CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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MEDICAL REVIEW(S)

CLINICAL REVIEW

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Reviewer Name(s)	Hyon J. Kwon, PharmD, MPH
Review Completion Date	February 8, 2013
Established Name	Canagliflozin
(Proposed) Trade Name	Invokana
Therapeutic Class	Sodium glucose co-transporter 2 (SGLT2) inhibitor
Applicant	Janssen Research & Development, LLC
Formulation(s)	Oral tablets
Dosing Regimen	100 mg or 300 mg once daily
Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Intended Population(s)	Adults with type 2 diabetes mellitus

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1 Recommendations/Risk Benefit Assessment

Canagliflozin (Invokana™) is an orally active, competitive, reversible sodium glucose co-transporter 2 inhibitor, proposed for the treatment of adults with type 2 diabetes (T2DM) as an adjunct to diet and exercise. The proposed dose is 100 mg and 300 mg to be taken once daily. For subjects at risk for volume depletion (e.g., on loop diuretic, moderate renal impairment [e.g., eGFR 30 to <60 mL/min/1.73m^2], and ≥75 years of age), 100 mg dose is proposed as the starting dose, and the dose may be increased to 300 mg if additional glycemic control is needed. If approved, canagliflozin would be a first-in-class agent.

1.1 Recommendation on Regulatory Action

I recommend approval of canagliflozin for the proposed indication, as there is substantial evidence of effectiveness from nine pivotal Phase 3 trials that are adequate and well-controlled.

However, given the available information related to efficacy and safety submitted in this NDA, I do not recommend:

- Canagliflozin for use in patients with moderate renal impairment who are Chronic Kidney Disease (CKD) Stage 3b and below (e.g., eGFR <45 mL/min/1.73m^2).
- Canagliflozin 300 mg dose in elderly (e.g., ≥75 years) and in patients who are CKD Stage 3a (e.g., eGFR ≥45 to <60 mL/min/1.73m^2).

I have summarized my rationale for this recommendation in section 1.2 below.

1.2 Risk Benefit Assessment

Despite the number of antidiabetic agents that are currently available for the treatment of type 2 diabetes (see section 2.2), there is a need for new agents that can safely and effectively be used either alone or added on to the current therapies as type 2 diabetes is a progressive disease. Canagliflozin offers unique benefit for the treatment of type 2 diabetes, since its glycemic efficacy is independent of insulin unlike other currently approved non-insulin oral antidiabetic agents. The applicant has demonstrated efficacy of canagliflozin in monotherapy and combination therapy settings for treatment of type 2 diabetes.

In the Phase 3 program, the applicant chose to study two doses of canagliflozin, 100 mg and 300 mg, and both doses were studied in all Phase 3 trials except in one active-control trial (DIA3015). In nine Phase 3 trials, the efficacy and safety of canagliflozin was evaluated both as monotherapy and in combination with other approved antidiabetic agents, and both doses of canagliflozin demonstrated glycemic efficacy of HbA1c lowering, as discussed in detail under the efficacy section (see section 6). The HbA1c reductions with canagliflozin 100 mg and 300 mg relative to placebo were: -0.91 and -1.16% as monotherapy, -0.62 and -0.77% as add-on to metformin, -0.74 and -0.83% as add-on to sulfonylurea (SU), -0.65 and -0.74% as add-on to

insulin, -0.71 and -0.92 as add-on to metformin and SU, -0.62 and -0.76% as add-on to metformin and pioglitazone.

The applicant also conducted trials in special populations of interest (DIA3010 and DIA3004), where the HbA1c lowering was modest compared to other placebo-controlled trials. DIA3010 was a trial in Older Adults that enrolled subjects who were 55 to 80 years of age (mean baseline age of 63.6 years), and demonstrated HbA1c reduction of 0.57 and 0.70% with canagliflozin 100 mg and 300 mg relative to placebo. DIA3004 was a trial in Moderate Renal Impairment that enrolled subjects with eGFR of 30 to 50 mL/min/1.73m^2 (mean baseline eGFR of 39.4 mL/min/1.73m^2), and demonstrated HbA1c reduction of 0.29 and 0.42% with canagliflozin 100 mg and 300 mg relative to placebo. Benefit-risk considerations for subjects with moderate renal impairment and in elderly are discussed separately below.

In two active-control trials, the efficacy of canagliflozin was assessed relative to other therapies; the active controls were glimepiride and sitagliptin. In DIA3009, addition of canagliflozin 100 mg and 300 mg to metformin background therapy was non-inferior to glimepiride, and canagliflozin 300 mg was also statistically superior to glimepiride, althought the treatment difference was modest (-0.12%). In DIA3015, addition of canagliflozin 300 mg to metformin and SU was non-inferior to sitagliptin 100 mg, and was statistically superior with treatment difference of -0.37% ($p<0.001$).

The two doses of canagliflozin showed a modest dose-response in HbA1c reduction, with the incremental HbA1c reduction with 300 mg relative to 100 mg ranging from 0.09 to 0.25% across placebo-controlled Phase 3 trials. The incremental HbA1c reduction with 300 mg compared to 100 mg in placebo-controlled trials were: 0.25% as monotherapy, 0.15% as add-on to metformin, 0.21 as add-on to metformin and SU, and 0.14% as add-on to metformin and pioglitazone. The additional HbA1c reduction with 300 mg compared to 100 mg was lower in special population studies: 0.13% in Older Adults trial, 0.12% in Moderate Renal Impairment trial, and 0.09% in 3008 substudies where canagliflozin was added to SU and insulin background therapy.

The proportion of subjects achieving ADA HbA1c target of <7% was significantly greater with both doses of canagliflozin compared to placebo in all trials except for special population studies. In support of modest dose-response seen with HbA1c reduction, there was also a modest dose response when evaluating proportion of subjects achieving HbA1c goals. About 13 to 18% additional subjects with canagliflozin 300 mg relative to 100 mg achieved HbA1c of <7% when canagliflozin was used as monotherapy, add-on to metformin, or add-on to dual combination therapies (metformin and SU or pioglitazone).

Given that a large proportion of diabetic patients are obese and hypertensive, other non-glycemic benefits demonstrated with canagliflozin appear to be favorable, which include modest reduction in body weight and blood pressure. Reductions in body weight and blood pressure could in theory offer meaningful benefit in reducing cardiovascular (CV) risk in these patients. Therefore, canagliflozin has demonstrated its glycemic efficacy even in diabetic patients who are already receiving maximum doses of other antihyperglycemic agents, and offers the benefit of an

oral formulation, convenient once-daily dosing, weight and blood pressure reduction, and low risk for hypoglycemia.

However, its effect on lipids, another CV risk factor, show conflicting trend for CV benefit. Although there was a trend for an increase in HDL-C with canagliflozin, which would be beneficial, there was also a dose-dependent increase in LDL-C, which has been associated with increasing CV risk. The result of CV meta-analysis conducted in order to evaluate the CV risk with canagliflozin did not show an increase in CV risk, with the upper bound of 95% confidence interval less than 1.8, meeting the FDA's Guidance[1] for ruling out an unacceptable cardiovascular risk. The hazard ratio for one of the MACE-plus composite endpoint in the CV meta-analysis, stroke, was greater than 1, but the 95% confidence interval was wide and crossed 1 due to low number of total events. Most of the observed strokes were ischemic, which is a concern since canagliflozin can cause volume depletion and hemoconcentration. However, an increased incidence of thromboembolic events with canagliflozin was not seen in the safety database at this time.

Although the overall hazard ratio for CV events did not show an increased CV risk with canagliflozin, an imbalance in the early CV events not favoring canagliflozin in DIA3008 was noted by the FDA statistical reviewer. DIA3008 was a CV outcomes trial and enrolled patients at a higher background CV risk compared to other trials. Review of available data of these early CV events did not provide sufficient details to determine whether this imbalance is a real risk that may be attributable to canagliflozin or occurred by the play of chance. The applicant provided data to support this theory by showing that the expected rate of event in the comparator arm was unusually low for this time period. It is thus possible to dismiss that the increased CV risk observed in the first 30 days of canagliflozin use is just a chance finding, especially since it would seem that the overall CV risk of canagliflozin is not elevated. However, we need to consider that the hemodynamic effect of canagliflozin is almost immediate, which was reflected in changes in blood pressure, electrolytes, renal function, as well as increased incidence of volume depletion events with canagliflozin that appear to be related to this hemodynamic changes and occur within 6 weeks of initiating canagliflozin. It is highly plausible that the early cardiovascular event may have been precipitated by one of these hemodynamic changes. In addition, this increase in early CV events was not observed in other Phase 3 trials where subjects did not have a high cardiovascular disease burden at baseline. As mentioned in safety discussions (see section 7.3), the incidence and/or pattern of adverse events, especially those related to hemodynamic changes (i.e., volume depletion, renal function), were different in different patient population. Therefore, it would seem plausible that the CV risk of canagliflozin may be different in different patient population, where patients who are at a high CV risk may potentially be more sensitive to the volume contraction related-effect of canagliflozin. However, I do not believe that this putative early CV risk, which has a lot of uncertainties, outweigh the benefits associated with canagliflozin at this time. I would recommend that the long-term consequence of increase in LDL-C with canagliflozin, as well as early CV events seen in those at

[1] FDA Guidance entitled Diabetes Mellitus: Evaluating Cardiovascular Risk in New Antidiabetic Therapeits to Treat Type 2 Diabetes, December 2008.

higher risk for CV events be evaluated as a postmarketing requirement, as discussed in section 1.4.

Aside from early cardiovascular events and increase in LDL-C, several other safety issues have been identified with canagliflozin (section 7.3). These include volume depletion-related events (i.e., hypotension), renal changes (i.e., decrease in eGFR) and related adverse events (i.e., renal failure), electrolyte changes, genital mycotic infections, urinary tract infections, skin and hypersensitivity reactions, pancreatitis, and bone fractures. In addition to increase in LDL-C, two other safety issues are clearly dose-dependent and are of significant concern: volume depletion and renal-related events.

Because canagliflozin increases urinary glucose excretion, it acts as an osmotic diuretic with an increase in urine output, and there was an increased incidence of adverse events related to intravascular volume depletion with canagliflozin (e.g., postural dizziness and hypotension). Related to these hemodynamic changes, canagliflozin was also associated with marked changes in renal function, electrolytes, and renal-related events such as renal failure. The incidence of volume depletion and renal-related events were dose-dependent and notably increased in subjects with moderate renal impairment. Subgroup analyses also showed that elderly (≥75 years of age) and concomitant use of loop diuretics were at an increased, dose-related risk for volume depletion events. I do not recommend the higher dose (300 mg) of canagliflozin in subjects with low baseline eGFR (<60 mL/min/1.73m^2) and elderly (≥75 years of age) [see separate discussion below].

I considered recommending approval of only the lower dose of canagliflozin, 100 mg, because of the increased incidences of volume depletion events and renal-related changes with the higher dose of canagliflozin (300 mg), as well as dose-dependent increase in LDL-C. The additional incremental HbA1c lowering with 300 mg relative to 100 mg was about 0.1 to 0.15% with a couple of trials showing difference of 0.2%, and this additional HbA1c lowering may not be beneficial in the context of increased safety issues with 300 mg dose. But about an additional 20% of subjects achieved ADA goal of <7% with 300 mg dose compared to 100 mg dose, and I believe this is a clinically meaningful additional benefit with 300 mg dose. The higher dose of canagliflozin would offer additional benefit in patients who need further HbA1c lowering to achieve ADA goal without having to add another antidiabetic therapy, and both doses of canagliflozin should be made available as an option to these patients. Since I will not be recommending the use of 300 mg dose of canagliflozin in patients with moderate renal impairment and elderly where the incidences of volume depletion and renal-related events were notably elevated, I believe prescribers can monitor for and manage volume depletion events, renal-related changes, and LDL-C increase in patients with normal to mild renal impairment. I agree with the applicant that in patients at risk for volume depletion (other than moderate renal impairment and elderly, as discussed below), canagliflozin 100 mg dose can be the starting dose, and the dose may be increased to 300 mg if additional glycemic control is needed, with appropriate monitoring in place.

Other safety issues related to canagliflozin, such as genital mycotic infections, urinary tract infections, skin and hypersensitivity reactions, and pancreatitis were not dose-dependent and can be mitigated by appropriate labeling. The slight imbalance in fractures, although cannot be ignored, does not appear to outweigh the observed benefit for canagliflozin at this time, and I believe the bone safety can be further reassessed with more data when the final clinical study report of DIA3010, a dedicated bone safety trial, becomes available with 104-week data. Lastly, although we did not see an imbalance in any malignancies with canagliflozin during this NDA, given the rarity of these cancers, we can continue to follow up on these nonclinical malignancy signal for mechanistically-related cancers (e.g., pheochromocytoma, Leydig cell tumors, and renal tubule carcinoma) in the postmarketing setting.

Benefit-Risk in Moderate Renal Impairment

Based on the observed efficacy and safety with canagliflozin, a separate benefit risk assessment is needed for patients with moderate renal impairment. Given its mechanism of action, the glycemic efficacy of canagliflozin was expected to decline with declining renal function. Compared to other placebo-controlled Phase 3 trials where subjects had normal to mild renal impairment, a modest glycemic efficacy was observed in a dedicated Moderate Renal Impairment trial as discussed above (DIA3004, baseline eGFR ≥30 to <50 mL/min/1.73m^2). In addition, a pooled population of subjects with moderate renal function (baseline eGFR ≥30 to <60 mL/min/1.73m^2) showed modest HbA1c change of -0.38 and -0.47% with 100 mg and 300 mg respectively compared to placebo. This data from the pooled population of subjects with moderate renal impairment showed minimal incremental HbA1c reduction with the higher dose of canagliflozin compared to the lower dose (-0.09%).

A subgroup analysis of HbA1c lowering efficacy by baseline eGFR in this pooled population of subjects with moderate renal impairment showed that the glycemic efficacy was further attenuated in the subgroup of subjects at the lower half of moderate renal function (e.g., baseline eGFR ≥30 to <45 mL/min/1.73m^2) compared to the upper half of moderate renal function (e.g., baseline eGFR ≥45 to <60 mL/min/1.73m^2). This subgroup analysis is appropriate since Chronic Kidney Disease (CKD) Stage 3 can be further divided into CKD Stage 3a (eGFR ≥45 to <60 mL/min/1.73m^2) and CKD Stage 3b (eGFR ≥30 to <45 mL/min/1.73m^2). In the subgroup of subjects with CKD Stage 3b, the HbA1c change relative to placebo was -0.23% with the lower dose of canagliflozin (100 mg), which barely reached statistical significance (95% CI:-0.45,-0.01); the HbA1c change relative to placebo was -0.39% with the higher dose of canagliflozin (300 mg).

In the context of this modest benefit in those with moderate renal impairment, we need to consider the risk. In Phase 3 trials, an early and dose-dependent decrease in eGFR was observed, and the pattern and persistence of eGFR decrease over time appear to vary depending on the population. Compared to normal to mild renal impairment, where the decline in eGFR appear to return to near baseline levels during treatment, the decline in eGFR in those with moderate renal impairment appear to persist over time (e.g., subjects in DIA3004). Also, in DIA3004 (Moderate Renal Impairment trial), there was a significant difference in the magnitude of eGFR decline by

the end of 26 weeks with both doses of canagliflozin compared to placebo. The incidence of subjects with marked eGFR decrease, accordingly, was higher in subjects with moderate renal impairment compared to normal to mild renal function. In the Moderate Renal Impairment (DS2), 9.3%, 12.2%, and 4.9% of canagliflozin 100 mg, 300 mg, and placebo groups respectively had eGFR decrease of >30% baseline at anytime. This compares to 2.0%, 4.1%, and 2.1% of canagliflozin 100 mg, 300 mg, and placebo groups respectively who had eGFR decrease of >30% baseline at any time in the Placebo-controlled Studies Dataset (DS1), which included subjects with normal to mild renal function.

Also, subjects with moderate renal impairment had a higher risk for renal-related adverse events (i.e., acute renal failure): 8.9% and 9.3% of canagliflozin 100 mg and 300 mg groups compared to 3.7% of placebo group had renal-related adverse events in the Moderate Renal Impairment Dataset (DS2). This data suggest that the adverse consequences of renal-related changes were elevated with both doses of canagliflozin in subjects with moderate renal impairment. This compares to relatively lower overall incidence of renal-related events in patients with normal to mild renal impairment, where 0.6%, 1.7%, and 0.6 % of canagliflozin 100 mg, 300 mg, and placebo groups respectively reported renal-related adverse events in the Placebo-controlled Studies Dataset (DS1).

Subjects with moderate renal impairment were also at a higher risk for volume depletion-related events such as hypotension after treatment with canagliflozin, and this was dose-dependent. The incidence of volume depletion events was 3-fold higher with 300 mg (8.5%) and 2-fold higher with 100 mg dose (5%) compared to placebo (2.6%) in subjects with moderate renal impairment (DS2). This compares to the incidence of volume depletion events of 1.2%, 1.3%, and 1.1% in canagliflozin 100 mg, 300 mg, and placebo groups respectively in DS1.

The applicant also conducted univariate subgroup analyses to identify risk factors for volume depletion events with canagliflozin and showed that there was about 2-3 fold increase in volume depletion events with canagliflozin 300 mg compared to non-canagliflozin in subjects with moderate renal impairment, elderly (≥75 years of age), and those who are on loop diuretics. Based on this subgroup analyses, the applicant propose initiating canagliflozin at 100 mg dose and increasing the dose to 300 mg if additional glycemic control is needed in these patients whose risk for volume depletion events appear to be dose-dependent. Although it is possible that the volume depletion-related events may be lessened by initiating treatment with the lower dose of canagliflozin, canagliflozin 100 mg achieved 0.23% HbA1c reduction relative to placebo in subjects at the lower end of moderate renal function (e.g., CKD Stage 3b, eGFR ≥30 to <45 mL/min/1.73m^2). Therefore, I believe that the increased risk of renal-related events, which are elevated in subjects with moderate renal impairment even at 100 mg dose, outweigh the small benefit that these patients (e.g., eGFR ≥30 to <45 mL/min/1.73m^2) may derive from treatment with canagliflozin, and do not recommend 100 mg dose in this patient population.

It may be argued that perhaps 300 mg dose could still be used in subjects at the lower half of moderate renal function (e.g., eGFR ≥30 to <45 mL/min/1.73m^2) since there was a modest glycemic efficacy with the HbA1c change of -0.39% relative to placebo with 300 mg dose.

However, starting these patients at the higher dose would expose them to a higher risk of volume depletion and renal-related events, and it would seem that the possible benefit do not outweigh this increased risk in this patient population without much kidney reserve. The long term renal consequences of chronic exposure with canagliflozin are unknown, and as Dr. Thomson pointed out, the risk of potentially meaningful episodes of acute kidney injury may be magnified in the postmarketing setting as canagliflozin is used in the general type 2 diabetic patients who already have declining renal function and will not be as carefully monitored as subjects who participated in a clinical trial. I believe this risk is particularly applicable in patients with CKD Stage 3b (e.g., eGFR ≥30 to <45 mL/min/1.73m^2), and this was also expressed by some panel members during the Advisory Committee meeting (see section 9.3). This population was significantly underrepresented in the overall development program for canagliflozin, and I believe the potential consequences of canagliflozin use in this patient population needs to be further evaluated.

In patients with renal function ≥45 to <60 mL/min/1.73m^2, the glycemic efficacy with canagliflozin was similar with both doses of canagliflozin (about -0.5% HbA1c change compared to placebo). Since the higher dose of canagliflozin did not demonstrate any incremental glycemic benefit over the lower dose, there is no benefit to justify the increased risk of volume depletion with the higher dose of canagliflozin in this patient population. Therefore, I believe the benefit outweighs the risk with the lower dose (100 mg), but not with the higher dose of canagliflozin (300 mg) in patients with CKD Stage 3a (e.g., eGFR ≥45 to <60 mL/min/1.73m^2).

Benefit-Risk in Elderly

In addition to subjects with impaired renal function, elderly were observed to have less efficacy compared to younger patients. In particular, subgroup analysis with age cutoff of 75 years demonstrated that the higher dose of canagliflozin (300 mg) did not offer additional glycemic benefit from the lower dose (100 mg). Dr. Wei Liu's subgroup analysis showed that the placebo-adjusted HbA1c change was -0.46% with 100 mg and -0.48% with 300 mg in those who were ≥75 years of age. This is in comparison to -0.66% and -0.81% with 100 mg and 300 mg of canagliflozin relative to placebo in subjects who were <75 years old. Although this is a post-hoc subgroup analysis and the number of subjects ≥75 years of age was small, this minimal increase (0.02%) in HbA1c reduction with 300 mg must be balanced against the observed risk. The subgroup analyses to identify risk factors for volume depletion events with canagliflozin showed that elderly patients who were ≥75 years of age had 2-3 fold increase in volume depletion events with the higher dose of canagliflozin (see Table 49). Therefore, I believe that the risk outweighs the benefit for canagliflozin 300 mg dose in ≥75 years of age.

1.3 Recommendations for Postmarket Risk Evaluation and Mitigation Strategies

I recommend that the risks identified with canagliflozin in this review be managed through appropriate labeling and a Medication Guide, and require postmarketing studies as discussed in

section 1.4. REMS such as a Communication Plan and/or elements to assure safe use are not warranted at this time.

1.4 Recommendations for Postmarket Requirements and Commitments

I recommend a dedicated cardiovascular study as a required postmarketing study to further evaluate the overall cardiovascular risk prospectively, not only to rule out the upper bound of hazard ratio of 1.3, but also to address the observed increase in cardiovascular risk during the early course of treatment with canagliflozin (within 30 days) in those at a high CV risk, and to further evaluate the clinical significance of increase in LDL-C levels with canagliflozin treatment. I also recommend that the following be included as secondary objectives in this trial: 1) evaluate the long-term consequences of renal changes, and 2) evaluate the incidence of fractures.

In nonclinical studies, canagliflozin led to pheochromocytoma, Leydig cell tumors, and renal tubule carcinoma. Pheochromocytoma or Leydig cell tumors have not been reported thus far, and the incidence of renal tubule carcinoma was very low and balanced between treatment groups in the clinical program. However, given that the clinical database of canagliflozin is not large or long enough to fully evaluate any malignancy risk in an NDA, a postmarketing follow up or assessment for these cancers is warranted. Based on our internal discussion with the Office of Surveillance and Epidemiolgy (OSE), given the rarity of these malignancies, OSE recommended that we monitor for and thoroughly follow-up any postmarketing cases of malignancies via enhanced pharmacovigilance.

In addition to malignancies, I recommend that the following adverse events of interest be monitored through enhanced pharmacovigilance: fatal pancreatitis, hemorrhagic/necrotizing pancreatitis, severe hypersensitivity reactions (angioedema, anaphylaxis, Stevens-Johnson syndrome), photosensitivity reactions, thromboembolic events, and hepatic abnormalities.

2 Introduction and Regulatory Background

2.1 Product Information

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

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

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

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

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

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

2.2 Currently Available Treatments for Proposed Indications

Type 2 diabetes mellitus can be treated with a combination of proper diet, exercise, and the following drug therapies, either alone or in combination:

- Biguanides: metformin (i.e., Glucophage)
- Sulfonylureas: glyburide (Micronase), glipizide (Glucotrol), glimepiride (Amaryl), chlorpropamide (Diabinese), tolazamide (Tolinase)
- Insulin
- GLP-1 agonist: exenatide (Byetta), liraglutide (Victoza)
- Thiazolidinediones (TZDs): rosiglitazone (Avandia), pioglitazone (Actos)

- Dipeptidyl peptidase 4 (DPP-4) inhibitor: sitagliptin (Januvia), saxagliptin (Onglyza), linagliptin (Tradjenta), and alogliptin (Nesina)
- Meglitinides: repaglinide (Prandin), nateglinide (Starlix)
- α-Glucosidase inhibitor: acarbose (Precose), miglitol (Glyset)
- Pramlintide (Symlin)
- Dopamine agonist: bromocriptine mesylate (Cycloset)
- Bile acid sequestrants: colesevelam (WelChol)
- Various fixed dose combinations of oral therapies (i.e., Janumet, ActoPlus Met, Kombiglyze XR, Oseni, Kazano)

2.3 Availability of Proposed Active Ingredient in the United States

Canagliflozin is not currently approved for marketing in the US. It is only available for use under the applicant's Investigational New Drug Applications.

2.4 Important Safety Issues With Consideration to Related Drugs

There are no currently marketed SGLT2 inhibitor in the US. Canagliflozin will be a first-in-class drug, if approved. An NDA for another SGLT2 inhibitor, dapagliflozin, was previously submitted and reviewed by this Division, and was not approved due to safety concerns, which included breast and bladder cancer and potential liver injury. Due to its mechanism of action of urinary glucose excretion and diuresis, SGLT2 inhibitors have mechanism-related safety concerns such as urinary tract infection, genital infections, volume depletion, hemoconcentration and thombosis, and renal-related events and laboratory changes were of concern. Animal studies with SGLT2 inhibitors have shown hyperostosis in rats, and bone safety is an important consideration with this class of agent. Rodent carcinogenicity studies have revealed renal, adrenal and leydig cell tumors for several members of the class. Sponsors have attributed this findings to intestinal carbohydrate malabsorption specific to animals (rats) and have questioned the human relevance of these findings.

2.5 Summary of Presubmission Regulatory Activity Related to Submission

The End-of-Phase 2 meeting occurred on April 28, 2009. The clinical discussion centered around the applicant's cardiovascular meta-analysis plan to assess the cardiovascular risk for canagliflozin to rule out the hazard ration 1.8 and 1.3, collection and reporting adverse events, study in patients with renal impairment, and clinical plan to evaluate bone safety with canagliflozin. The Division recommended that the applicant study 50 mg dose in addition to their proposed 100 mg and 300 mg dose in the Phase 3 program.

At the pre-NDA meeting on April 13, 2012, the applicant proposed to provide laboratory results for pooled safety dataset 3 in the NDA, and not for Dataset 4, and provide the laboratory results for Dataset 4 with the 4-Month Safety Update (4MSU). The Division recommended that in their ISS, section on hepatic events should include the incidence of serum alanine aminotransferase (ALT) elevations >3, >5, >10, and >20x the upper limite of normal for canagliflozin and non-

canagliflozin groups. Division also requested submission of narratives for all cases of biochemical Hy's law and all cases with serum ALT >10x ULN regardless of outcome.

2.6 Other Relevant Background Information

Dapagliflozin, another SGLT2 inhibitor, was approved by the European Commission on November 14, 2012.

3 Ethics and Good Clinical Practices

3.1 Submission Quality and Integrity

The nine Phase 3 trials in the canagliflozin development program were multinational studies. No one study site enrolled large numbers of subjects for any one of these studies. Most investigators randomized less than 10 subjects per protocol. Investigators who participated in more than one protocol, who enrolled relatively large number of subjects, and who did not have recent inspection records were selected for inspection. Five sites (3 US, 2 foreign) that enrolled subjects in DIA3005, DIA3006, DIA3015, DIA3009, DIA3010, and DIA3008 were requested for inspection. A sub-investigator for one of the requested inspection site (001002) had financial conflict (see Table 1 in section 3.3).

At the time of this review, no major protocol violations were noted that may affect the integrity of the NDA. Review from the Division of Scientific Investigations for requested site inspection is still pending at the time of this review. In addition, the Establishment Inspection Report for the relevant manufacturing and testing facilities is still pending.

3.2 Compliance with Good Clinical Practices

The applicant stated that the development program for canagliflozin was conducted in full compliance with Good Clinical Practices.

Protocol violations were small (<1%) and balanced between treatment groups across trials, and was unlikely to have affected the results. In addition, for efficacy, a per-protocol analysis was done as supportive efficacy analysis for individual Phase 3 trials in subjects who completed the trial without major protocol violations.

3.3 Financial Disclosures

The applicant submitted FDA Form 3455 for investigators with financial disclosures, which are summarized in Table 1 below. Any potential bias from these investigators will have minimal, if any, affect on the efficacy and safety conclusions for canagliflozin since the number of subjects

enrolled by these investigators was a small fraction of the total number of subjects in the clinical development program. In addition, DIA1011, DIA1019, and DIA1020 were randomized, subject-blind, placebo controlled studies. DIA3002, DIA3004, DIA3005, DIA3008, DIA3012, DIA3015 and DIA3009 were large Phase 3 multicenter, multinational trial that were randomized, double-blind, and placebo-controlled in design with an objective primary efficacy endpoint (HbA1c).

Table 1: Summary of Investigators with Financial Interests for Canagliflozin Program

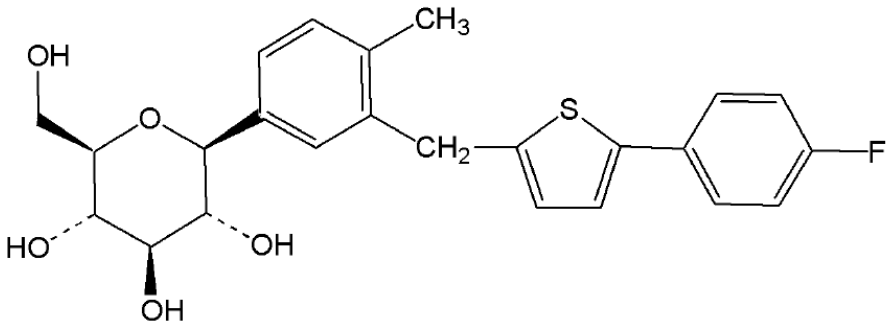
Protocol	Site	Investigator	Financial interests or arrangements	Enrolled
DIA1011, DIA1019, DIA1020	044001	(b) (6)	During the time of study and for 1 year following completion, received $28,199 in consulting fees from Johnson & Johnson for consultation on phototoxicity related issues and for being a potential principal investigator for clinical studies of canagliflozin	(b) (6)
DIA3002	001145		Reported significant equity interest in Johnson & Johnson in the amount of $60,000	
DIA3004, DIA3005	001190, 001017		Reported significant equity interest in Johnson & Johnson in excess of $50,000	
DIA3004, DIA3008	049002	(b) (6)	Received individual reimbursement from Johnson & Johnson in excess of $25,000 during the conduct of DIA3004 and DIA3008 including $15,000 in honoria	(b) (6)
DIA3005	001002		Reported a significant equity interest in Johnson & Johnson in excess of $50,000	
DIA3005	001029		Reported a significant equity interest in Johnson & Johnson in excess of $50,000	
DIA3008	049021		During the study and for 1 year following completion, received $53,188 in individual reimbursement for her work on DIA3008	
DIA3008	049022		During the study and for 1 year following completion, received $41,282 in individual reimbursement for his work on DIA3008	
DIA3008	049005		During the study and for 1 year following completion, received $44,840 in individual reimbursement for his work on DIA3008	
DIA3008	049008		During the study and for 1 year following completion, received $36,085 in individual reimbursement for his work on DIA3008	
DIA3009, DIA3012	001044, 001391		Reported a significant equity interest in Johnson & Johnson in excess of $50,000	
DIA3009	001053		Reported a significant equity interest in Johnson & Johnson in excess of $50,000	
DIA3012	049023		Received individual compensation of $65,672 for his work on DIA3009	
DIA3015	001805		Reported a significant equity interest in Johnson & Johnson in excess of $50,000	

4 Significant Efficacy/Safety Issues Related to Other Review Disciplines

4.1 Chemistry Manufacturing and Controls

Canagliflozin is a hemihydrate, but the strength is based on the anhydrous form. The commercial drug product is a film-coated immediate release tablet for oral administration, proposed to be marketed in 100 mg and 300 mg strengths.

The chemical structure of canagliflozin is presented here:



Dr. Sheldon Markofsky found that the stability studies provided support for an expiration-dating period of 24 months for both strengths of canagliflozin when stored at controlled room tempearture (25°C [77°F]), with excursions permitted to 15 to 30°C (59 to 86°F).

Dr. Markofsky recommends approval from CMC perspective, and noted that the Establishment Inspection work for the relevant manufacturing and testing facilities has not been completed. See Dr. Markofsky's CMC review (dated February 8, 2013) for full details.

4.2 Clinical Microbiology

Not applicable.

4.3 Preclinical Pharmacology/Toxicology

Drs. Fred Alavi and Daniel Minck, the primary nonclinical reviewers, concluded that the pharmacology and toxicology data support approval of canagliflozin. Relevant important nonclinical findings related to bone health, carcinogenicity, and pregnancy and lactation are briefly discussed below. Please see their reviews for full details.

Bone Health

In short and long-term toxicology studies in rats, clinically relevant doses of canagliflozin resulted in hyperostosis (increased trabecular bone) and decreased bone turnover. The bone mineralization and strength were not changed at clinically relevant drug exposure. The effect of canagliflozin on trabecular bone was likely due to disrupted calcium homeostasis, since canagliflozin reduced serum 1,25-OH vitamin D and parathyroid hormone levels, and increased urinary excretion of calcium in rats. Decrease in markers of bone resorption (urinary deoxypyridinoline) and bone formation (osteocalcin) also suggested decreases in bone turnover. Serum calcium levels were minimally changed due to compensatory mechanisms. Hyperostosis was not seen in dogs or mice. The applicant proposed that carbohydrate malabsorption due to SGLT1 inhibition led to increased calcium absorption in rats, which in turn disrupted calcium homeostasis and increased trabecular bone as downstream events of excess calcium. Dr. Alavi agreed, but also cautioned that although clinical risk appear to be minimal, slight carbohydrate malabsorption under chronic conditions may potentially imbalance calcium metabolism with potential long-term adverse effects on bone health in humans.

There was also decreased compact bone density and strength at high doses of canagliflozin (≥12x the MRHD) in both rats and dogs, associated with decreases in bone biomarkers. The most notable correlate was decrease in body weight in both rats and male dogs. As a result, Dr. Alavi stated that body weight loss with canagliflozin appeared to have played a role.

Carcinogenicity

Carcinogenicity of canagliflozin was studied in 2-year mice and rat studies. Canagliflozin administration in Sprague Dawley rats led to pheochromocytoma, Leydig cell adenoma, and renal tubule neoplasms. Testicular Leydig cell tumors increased at all tested doses of canagliflozin, with the lowest dose approaching clinical drug exposure. Renal tubule neoplasms and adrenal pheochromocytoma occurred at ≥12x clinical exposure. Dr. Alavi accepted carbohydrate malabsorption (which leads to disrupted calcium homeostasis) as the mechanism of action for the observed renal and adrenal tumors in rats. Testicular Leydig cell tumors in rats were linked to increase in luteinizing hormone (LH). Other investigational SGLT2 inhibitors have also shown similar signal for neoplasms of renal tubules, adrenal, or testicular Leydig cells.

Canagliflozin was not found to be genotoxic.

Pregnancy and Lactation

Dr. Daniel Minck recommends Pregnancy Category C.

A study conducted in juvenile rats led to an increased incidence of renal tubule and pelvic dilatation with canagliflozin during a susceptible window in juvenile rats. The susceptible time period for renal toxicity observed in young rats would correlate to the last half of gestational period and up to the first 2 years after birth in humans. Based on this study, Dr. Minck

recommends that canagliflozin use should be discontinued during the second and third trimesters of pregnancy and during nursing.

4.4 Clinical Pharmacology

Please see the Office of Clinical Pharmacology's (OCP) review dated February 6, 2012 for full details. OCP's recommendations are:

- In type 2 diabetic patients with normal (eGFR>90 mL/min/1.73m^2) and mild renal impairment (eGFR 60-90 mL/min/1.73m^2), canagliflozin should be started at 100 mg daily dose and titrated to 300 mg daily dose based on individual patient's tolerability and need of further glycemic control;
- In moderate renal impaired patients with eGFR of ≥40-60 mL/min/1.73m^2, starting dose of 100 mg and cautioning on the use of 300 mg dose;
- In moderate renal impaired patients with eGFR of <40 mL/min/1.73m^2, do not recommend because of unfavorable benefit-to-risk ratio;
- Renal function, volume status, and electrolyte imbalance should be closely monitored in elderly and other patients with high risk of volume depletion (e.g., on loop diuretics) especially when dose is increased from 100 mg daily to 300 mg daily.
- A higher dose of canagliflozin be considered in patients when a potent UGT inducer (such as rifampin) is initiated in patients well managed on 100 mg dose, since canagliflozin exposure is significantly lowered with rifampin.

4.4.1 Mechanism of Action

Canagliflozin is an orally active inhibitor of sodium-glucose co-transporter 2 in the proximal renal tubule, which reabsorbs the majority of filtered glucose from the tubular lumen. By inhibiting SGLT2, canagliflozin reduces reabsorption of filtered glucose, lowers the renal threshold for glucose (RT_G), and increase urinary glucose excretion (UGE). This glycosuric effect of canagliflozin leads to lowering plasma glucose levels, loss of calories and weight reduction, and reduction in systolic blood pressure through osmotic diuresis.

4.4.2 Pharmacodynamics

Canagliflozin lowers the RT_G, leading to UGE and decrease in plasma glucose concentration. In healthy individuals, the mean 24-hour UGE increased dose-dependently, with saturation of UGE at >200 mg daily dose. Canagliflozin 100 mg provided about 70% of UGE over 24-hours seen with >200 mg doses.

Canagliflozin doses of ≥200 mg provide near-maximal RT_G reduction over 24-hour period, and 100 mg dose provide near-maximal RT_G reduction during the first 13 hours after administration, with a modest rise in RT_G during 13-24 hours.

Canagliflozin 300 mg given before a meal reduced the postprandial glucose excursion, which was not seen with 150 mg dose. This may be due to increased SGLT1 inhibition in the intestinal lumen with the higher dose, before the drug gets absorbed.

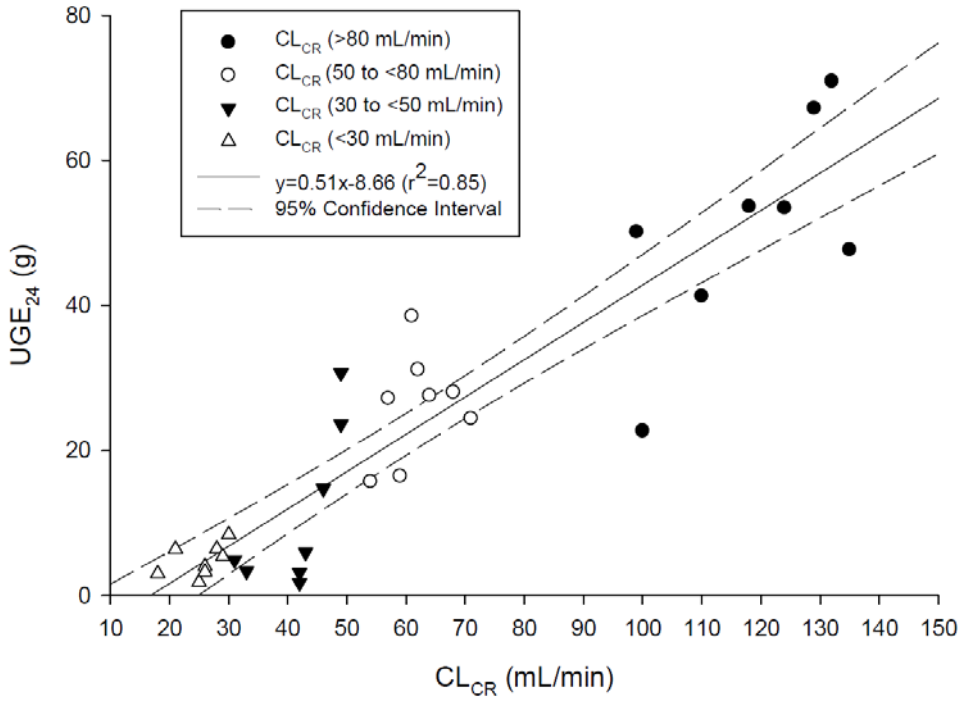
4.4.3 Pharmacokinetics

After ingestion, canagliflozin is rapidly absorbed, with the median time to reach maximal concentration (t_{max}) of 1 to 2 hours post-dose. The oral bioavailability is about 65% and coadministration of high-fat meal did not have an effect on the pharmcokinetics of canagliflozin. Canagliflozin demonstrates dose-proportional pharmacokinetics (plasma C_{max} and AUC) from 50 to 300 mg dose. Steady state is reached after 4 to 5 days of daily dose with canagliflozin 100 mg to 300 mg. Canagliflozin is metabolized to two inactive glucuronide metabolites, M7 and M5; CYP3A4-mediated metabolism of canagliflozin is minimal in humans. Canagliflozin is extensively bound to plasma proteins (98 to 99%), mainly to albumin (97%), and as a result is negligibly removed by dialysis. In healthy individuals, 33% of canagliflozin after ingestion gets excreted in urine as glucuronide metabolites and 60% is excreted in feces. The mean terminal plasma half-life ($t_{1/2}$) of canagliflozin was 10.6 and 13.1 hours with 100 mg and 300 mg dose respectively.

Renal Impairment

A single-dose, open-label study (DIA1003) evaluated the pharmacokinetic and pharmacodynamic in nondiabetic subjects with varying levels of renal function and in subjects with ESRD requiring hemodialysis. C_{max} of canagliflozin was not affected by renal impairment. The mean plasma AUC of canagliflozin increased with declining renal function: 15%, 29%, and 53% in those with mild, moderate, and severe renal impairment. The change in urinary glucose excretion over 24 hours demonstrated that with declining renal function, the total amount of glucose excreted in urine decreased over a 24-hour period, as shown in Figure 1.

Figure 1: Effect of Renal Impairment on Urinary Glucose Excretion



Source: CSR DIA1003, Attachment 2.38

Canagliflozin was negligibly removed by hemodialysis.

Hepatic Impairment

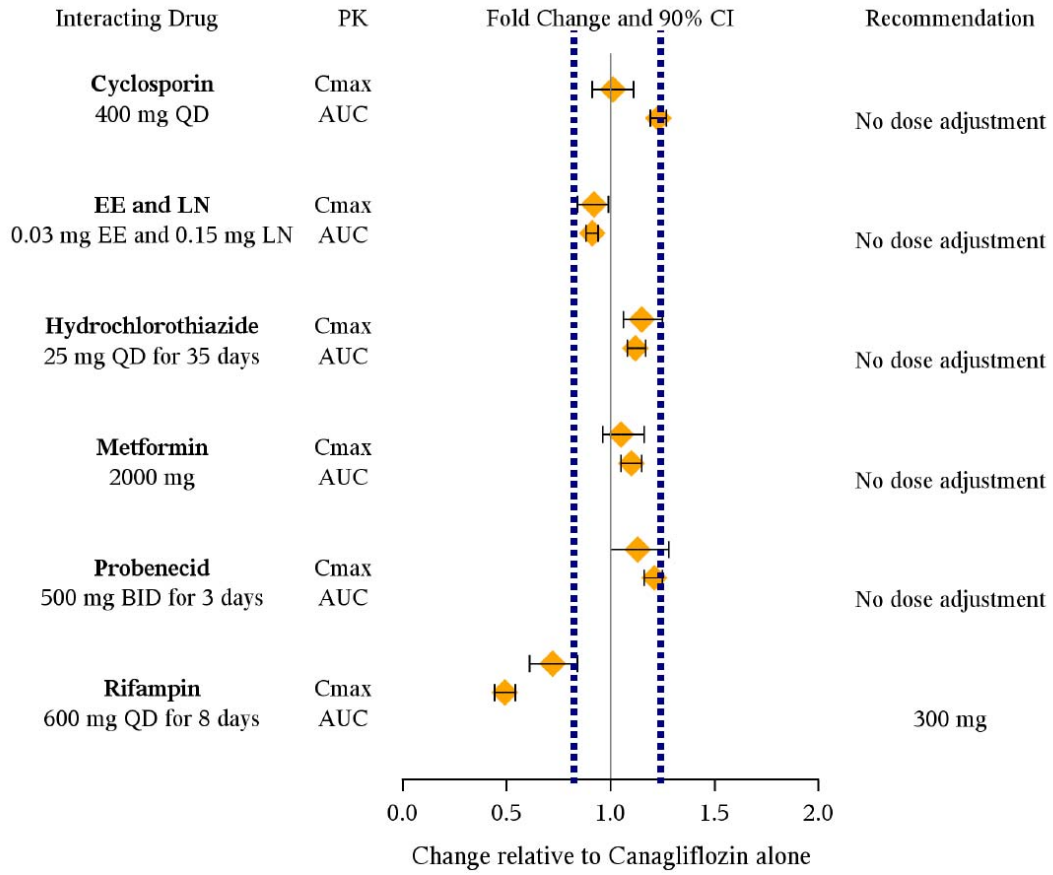
There was only a slight increases in the mean Cmax (7%) and AUC (11%) of canagliflozin in subjects with mild and moderate hepatic impairment after 300 mg dose of canagliflozin. No dose adjustment is necessary in patients with mild or moderate hepatic impairment.

Drug-drug interaction

The most significant drug-drug interactions with canagliflozin was with rifampin and digoxin.

As shown in Figure 2, there was a 52% reduction in the systemic exposure of canagliflozin with rifampin, due to induction of UGT enzymes responsible for the metabolism of canagliflozin. But the metabolites (M7 and M5) increased only 36%, possibly due to induction of biliary excretion. OCP recommends that due to potential loss of efficacy with 100 mg dose, 300 mg dose should be given to patients when rifampin is co-administered with canagliflozin.

Figure 2: Effect of Other Drugs on the Canagliflozin Pharmacokinetics



Source: OCP review, Figure 5

The mean digoxin trough levels were 18% higher when given with canagliflozin. The AUC_{0-24} of digoxin was about 20% higher and C_{max} of digoxin was 36% higher when given with canagliflozin, but no subjects exceeded the upper limit of therapeutic range of digoxin beyond 6 hours. OCP agrees with the applicant's recommendation to monitor digoxin levels when given concomitantly with canagliflozin.

5 Sources of Clinical Data

The NDA 204042 was submitted in an electronic Common Technical Document format, with the following link: \\CDSESUB5\EVSPROD\NDA204042\204042.enx

Canagliflozin is being developed globally by Janssen Research & Development, LLC (JRD), except in Japan, Taiwan, and Indonesia, where the sponsor's partner, Mitsubishi Tanabe Pharma Corporation (MTCP), is conducting an independent development program. Studies conducted by MTPC are preceded by a "TA" identifier, and all the other studies are conducted by JRD. For

trials sponsored by MTCP, the sponsor provided brief summary of the primary efficacy and safety results in the ISE and ISS respectively and a copy of the translated Clinical Study Reports.

The clinical program for canagliflozin consisted of:

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

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

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

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

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

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

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

5.1 Tables of Studies/Clinical Trials

Table 2 describe 35 clinical pharmacology trials of canagliflozin. Table 3 summarizes the key characteristics of the design, study population, treatment allocation and duration for the Phase 2b and 3 trials in the canagliflozin program.

Table 2: Clinical Pharmacology Trials of Canagliflozin

Study ID	Objective(s)	Subjects	Dose of Study Drug	Route	Formulation of Canagliflozin (Drug Product Batch Number) [a]	Included in Pop PK	Label [b]
Mass Balance					(b) (4)		
NAP1006	Mass balance	Healthy	192 mg, s.d.	p.o.		-	X
Absolute Bioavailability							
DIA1021	Absolute BA	Healthy	300 mg, s.d.; 10 µg, s.d.	p.o.; i.v.		-	X
Single-Dose PK in Healthy Subjects							
NAP1001 (Part 1) [c]	PK and PD of single escalating doses	Healthy	10, 30, 100, 200, 400, 600, or 800 mg qd, 400 mg bid, or placebo, s.d.	p.o.		-	-
DIA1001	PK and PD of single escalating doses	Healthy	800, 1,200, or 1,600, or placebo, s.d.	p.o.		X	-
DIA1015	PK of single escalating doses	Healthy	50, 100, or 300 mg, s.d.	p.o.		-	X
Multiple-Dose PK in Healthy Subjects							
NAP1008	PK and PD of single and multiple escalating doses	Healthy, obese	30, 100, 300, or 600 mg qd or 300 bid, or placebo for 2 weeks	p.o.		-	-
DIA1030	Single- and multiple-dose PK and PD	Healthy	50, 100, or 300 mg qd, or placebo for 6 days	p.o.		X	X
DIA1032	Steady-state PK and PD of qd vs. bid dosing	Healthy	50 or 150 mg bid, or 100 or 300 mg qd for 5 days	p.o.		-	-
Multiple-Dose PK and PK/PD Relationships of Canagliflozin in Subjects with T2DM							
NAP1002	PK and PD of single and multiple escalating doses	T2DM	30, 100, 200, 400 mg qd, or 300 mg bid, or placebo for 2 weeks	p.o.		-	-
DIA1007	Multiple-dose PK, PD, and PK/PD	T2DM	100 mg qd, 300 mg bid, or placebo for 4 weeks 1,000 mg acetaminophen on Days −3 and 25	p.o.		X	-
DIA1023	Multiple-dose PK and PD	T2DM	50, 100, or 300 mg qd, or placebo for 1 week	p.o.		X	X

					(b) (4)		
Intestinal Glucose Absorption and Renal Threshold Studies							
DIA1022	Glucose absorption and metabolism	Healthy	Part 1: none; Part 2: 300 mg or placebo, s.d. 960 mg acetaminophen on Day 1	p.o.		-	X
DIA1025	Comparison of 2 methods for determining RT_G	T2DM	Part 1: none; Part 2: 100 mg qd for 8 days	p.o.		-	X
DIA1045	Effect of canagliflozin on postmeal glucose	T2DM	Days 1 + 2: placebo + placebo, 300 mg + placebo, 300 + 300 mg, and 300 + 150 mg	p.o.		-	X
Effects of Intrinsic Factors							
DIA1013	Effect of mild or moderate hepatic impairment on PK	Nondiabetic; mild or moderate hepatic impairment	300 mg, s.d.	p.o.		-	X
DIA1003	Effect of varying degrees of renal function on PK and PD	Nondiabetic, varying degrees of renal function	200 mg, s.d.	p.o.		X	X
TA-7284-01 (Part 1) [c]	PK and PD of single escalating doses	Healthy, Japanese	30, 100, 200, 400, 800 mg, or placebo, s.d.	p.o.		-	-
TA-7284-02	Multiple-dose PK and PD	T2DM, Japanese	25, 100, 200, 400 mg, or placebo for 2 weeks	p.o.		X	-
DIA1008	Single-dose PK and PI	Healthy, Indian	200 or 300 mg, s.d.	p.o.		X	-
Effects of Extrinsic Factors							
NAP1004	DDI with metformin	Healthy	Canagliflozin: 100 mg qd (Days 4 to 8); metformin: 1,000 mg (s.d., Days 1 and 8)	p.o.		-	X
DIA1028	DDI with metformin	Healthy	Canagliflozin: 300 mg qd (Days 4 to 8); metformin: 2,000 mg (s.d., Days 1 and 8)	p.o.		-	X
DIA1002	DDI with ethinyl estradiol and levonorgestrel	Healthy	Canagliflozin: 200 mg qd (Days 4 to 9); ethinyl estradiol/levonorgestrel: 0.03/0.15 mg (s.d., Days 1 and 9)	p.o.		X	X
DIA1004	DDI with glyburide	Healthy	Canagliflozin: 200 mg qd (Days 4 to 9); glyburide: 1.25 mg (s.d., Days 1 and 9)	p.o.		-	X

DIA1006	DDI with HCTZ	Healthy	Canagliflozin: 200 mg qd (Days 1 to 7 in Period 1 and Days 29 to 35 in Period 2); HCTZ: 25 mg qd (Days 1 to 35 in Period 2)	p.o.	(b) (4)	-
DIA1034	DDI with HCTZ	Healthy	Canagliflozin: 300 mg qd (Days 1 to 7 in Period 1 and Days 29 to 35 in Period 2); HCTZ: 25 mg qd (Days 1 to 35, Period 2)	p.o.		X
DIA1009	DDI with simvastatin	Healthy	Canagliflozin: 300 mg qd (Days 2 to 7); simvastatin: 40 mg (s.d., Day 1 and 7)	p.o.		X
DIA1014	DDI with digoxin	Healthy	Canagliflozin: 300 mg qd (Days 1 to 7; Treatment B); digoxin: 0.5 mg (s.d., Day 1) and 0.25 mg qd (Days 2 to 7; Treatments A and B)	p.o.		X
DIA1016	DDI with warfarin	Healthy	Canagliflozin: 300 mg qd (Days 1 to 12; Treatment A); warfarin: 30 mg (s.d., Day 1 in Treatment B, Day 6 in Treatment A)	p.o.		X
DIA1029	DDI with rifampin	Healthy	Canagliflozin: 300 mg (s.d., Days 1 and 10); rifampin: 600 mg qd (Days 4 to 12)	p.o.		X
DIA1031	DDI with cyclosporine	Healthy	Canagliflozin: 300 mg qd (Days 1 to 8); cyclosporine: 400 mg (s.d., Day 8)	p.o.		X
DIA1048	DDI with probenecid	Healthy	Canagliflozin: 300 mg qd (Days 1 to 17); probenecid: 500 mg bid (Days 15 to 17)	p.o.		X
Special Pharmacodynamic Studies						
DIA1010	Thorough QT	Healthy	300 or 1,200 mg, 400 mg moxifloxacin, or placebo, s.d.	p.o.		X
NAP1005	Photo-sensitivity	Healthy	200 or 400 mg, 500 mg bid ciprofloxacin, or placebo, s.d.	p.o.		-
DIA1011	Photo-sensitivity	Healthy	300 mg qd or 300 mg bid, 500 mg bid ciprofloxacin, or placebo for 6 days	p.o.		X
DIA1019	Photo-sensitivity	Healthy	100 or 300 mg qd, 500 mg bid ciprofloxacin, or placebo for 6 days	p.o.		X
DIA1020	Photo-sensitivity	Healthy	300 mg qd or 300 mg bid for 5 days	p.o.		X

(b) (4)

Source: Summary of Clinical Pharmacology, Appendix 1

Table 3: Phase 2b and 3 Trials of Canagliflozin

Trial	Trial Design	Trial Population	Treatment Groups[a] & Number of Subjects Randomized	Duration
Phase 2b Dose-Range Finding Trials				
DIA2001 Add-on to Metformin	Randomized, double-blind, placebo and active-controlled, double-dummy, parallel group, dose-	HbA1c 7 to 10.5% inclusive	Cana 50 mg QD: 64 Cana 100 mg QD: 64 Cana 200 mg QD: 65 Cana 300 mg QD: 64 Cana 300 mg BID: 65 Sitagliptin 100 mg	12 weeks

	ranging trial		QD: 65 Placebo QD: 65	
OBE2001	Randomized, double-blind, placebo-controlled, parallel group, dose ranging trial	Non-diabetic obese/overweight subjects (BMI 30 to 50 inclusive, or ≥27 to <50 kg/m^2 with hypertension and dyslipidemia)	Cana 50 mg: 98 Cana 100 mg: 93 Cana 300 mg: 96 Placebo: 89	12 weeks
TA-7284-04 Monotherapy	Randomized, double-blind, placebo-controlled, parallel group	HbA1c 6.5 to 9.5% inclusive	Cana 50 mg: 82 Cana 100 mg: 74 Cana 200 mg: 76 Cana 300 mg: 75 Placebo: 75	12 weeks
Phase 3 Glycemic Efficacy Trials				
DIA3005 Monotherapy **Main Study**[b]	Randomized, double-blind, placebo-controlled, 3-arm parallel group	HbA1c 7 to 10% inclusive	Cana 100 mg: 195 Cana 300 mg: 197 Placebo: 192	52 weeks [26-week placebo-controlled, core double-blind period plus a 26-week active-controlled (sitagliptin 100 mg), extension double-blind period]
High Glycemic Cohort	Randomized, double-blind, 2-arm parallel group	HbA1c >10% to ≤12%	Cana 100 mg: 47 Cana 300 mg: 44	26 weeks
DIA3006[b] Add-on to Metformin	Randomized, double-blind, placebo- and active-controlled, 4-arm parallel group	T2DM subjects on metformin; HbA1c 7 to 10 5% inclusive	Cana 100 mg: 368 Cana 300 mg: 367 Sitagliptin 100 mg: 366 Placebo: 183	52 weeks [26-week placebo-controlled, core double-blind period plus a 26-week active-controlled (sitagliptin 100 mg), extension double-blind period]
DIA3009 Add-on to Metformin	Randomized, double-blind, active-controlled, 3-arm parallel group	T2DM subjects on metformin; HbA1c 7 to 9.5% inclusive	Cana 100 mg: 483 Cana 300 mg: 485 Glimepiride: 482	104 weeks (52-week active-controlled, core double-blind period plus a 52-week active-controlled, extension double-blind period)
DIA3002 Add-on to Metformin + SU	Randomized, double-blind, placebo-controlled, 3-arm parallel group	T2DM subjects on metformin + SU therapy; HbA1c 7 to 10 5% inclusive	Cana 100 mg: 157 Cana 300 mg: 156 Placebo: 156	52 weeks (26-week placebo-controlled, core double-blind period plus a 26-week placebo-controlled, extension double-blind period)
DIA3012[b] Add-on to Metformin + Pioglitazone	Randomized, double-blind, placebo-controlled, 3-arm parallel group	T2DM subjects on metformin + pioglitazone therapy; HbA1c 7 to 10 5% inclusive	Cana 100 mg: 113 Cana 300 mg: 114 Placebo: 115	52 weeks [26-week placebo-controlled, core double-blind period plus a 26-week active-controlled (sitagliptin 100 mg), extension double-blind period]
DIA3015 Add-on to Metformin + SU	Randomized, double-blind, active-controlled, 2-arm parallel group	T2DM subjects on metformin + SU therapy; HbA1c 7 to 10 5% inclusive	Cana 300 mg: 377 Sitagliptin 100 mg: 378	52 weeks
Special Population Trials				
DIA3004 Moderate Renal Impairment Study	Randomized, double-blind, placebo-controlled, 3-arm parallel group	HbA1c 7 to 10 5% inclusive; eGFR ≥30 to <50 mL/min/1.73m^2	Cana 100 mg: 90 Cana 300 mg: 89 Placebo: 90	52 weeks (26-week placebo-controlled, core double-blind period plus a 26-week placebo-controlled, extension double-blind period)
DIA3010 Older Adults	Randomized, double-blind, placebo-controlled, 3-arm parallel group	T2DM subjects with 55 to 80 years of age, inclusive; HbA1c 7 to 10% inclusive	Cana 100 mg: 241 Cana 300 mg: 236 Placebo: 237	104 weeks (26-week placebo-controlled, core double-blind period plus a 78-week placebo-controlled, extension double-blind period)
DIA3008				

CV Study (Interim Safety)	Randomized, double-blind, placebo-controlled, 3-arm parallel group	T2DM subjects on currently available AHA; Have a history or high risk of CV disease; HbA1c 7 to 10 5% inclusive	Cana 100 mg: 1445 Cana 300 mg: 1441 Placebo: 1441	Event-driven
Glycemic Efficacy[c] Insulin Substudy	Randomized, double-blind, placebo-controlled, 3-arm parallel group	T2DM subjects on insulin ≥20 units/day as monotherapy or in combination with other AHA(s); HbA1c 7 to 10 5% inclusive	Cana 100 mg: 566 Cana 300 mg: 587 Placebo: 565	18 weeks
SU Substudy	Randomized, double-blind, placebo-controlled, 3-arm parallel group	T2DM subjects on SU monotherapy; HbA1c 7 to 10 5% inclusive	Cana 100 mg: 42 Cana 300 mg: 40 Placebo: 45	18 weeks

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

5.2 Review Strategy

The primary and secondary efficacy data from each nine pivotal Phase 3 trials were reviewed to assess consistency of findings in different settings of clinical use, since there were differences in patient population, duration of exposure, and/or comparators across Phase 3 trials with canagliflozin. The efficacy review focused on the designated primary endpoint. Confirmatory secondary endpoints related to glycemic efficacy and endpoints the applicant proposed in the labeling were also reviewed. Subgroup analyses in the pooled population of placebo-controlled studies were reviewed to assess the consistency of efficacy response in subjects with different baseline characteristics.

For safety, pooled datasets for Phase 3 trials were reviewed to evaluate the overall safety of canagliflozin. See Section 7.1.3 for pooling of datasets for safety analyses. In addition, case narrative for confirmed adjudicated hepatic events, and bladder, breast, and renal cancers were reviewed.

It is important to determine the efficacy and safety of canagliflozin is renally impaired subjects since it is dependent upon eGFR given its mechanism of action, where the extent of urinary glucose excretion is proportional to renal function. In addition to the efficacy and safety review of trial DIA3004 (Moderate Renal Impairment Study) to determine the benefit/risk of canagliflozin in subjects with moderate renal impairment, the glycemic efficacy and safety in a large pooled population of subjects with baseline eGFR ≥30 to <60 mL/min/1.73m^2 across all Phase 3 trials were also reviewed.

5.3 Discussion of Individual Studies/Clinical Trials

5.3.1 Phase 3 Trials

Nine pivotal, controlled Phase 3 trials provided efficacy of canagliflozin as monotherapy and in combination with other AHA to treat T2DM, in a range of clinical use. Three of nine Phase 3 trials evaluated canagliflozin in special populations with T2DM; one in elderly, one in moderate renal impairment, and one in subjects at high risk for CV disease. Nine Phase 3 trials can be grouped according to the use of canagliflozin as following:

Canagliflozin as Monotherapy:
- DIA3005: Placebo-controlled trial of canagliflozin as monotherapy. Also included a separate non-placebo-controlled substudy investigating canagliflozin in subjects with higher baseline HbA1c value (>10 and ≤12%; High Glycemic Substudy) who were not eligible for the Main Study.

Canagliflozin as Add-on to AHA Monotherapy:
- DIA3006: Placebo- and active (sitagliptin)-controlled trial of canagliflozin as add-on to metformin.
- DIA3009: Active comparator (glimepiride)-controlled trial of canagliflozin as add-on to metformin.
- DIA3008 Sulfonylurea (SU) substudy of DIA3008: Placebo-controlled substudy of canagliflozin as add-on to SU monotherapy.

Canagliflozin as Add-on to Dual Combination AHA Therapy:
- DIA3002: Placebo-controlled trial of canagliflozin as add-on to metformin and SU.
- DIA3012: Placebo-controlled trial of canagliflozin as add-on to metformin and pioglitazone.
- DIA3015: Active comparator (sitagliptin)-controlled trial of canagliflozin as add-on to metformin and SU.

Canagliflozin as Add-on to Insulin:
- DIA3008 Insulin Substudy of DIA3008: Placebo-controlled substudy of canagliflozin as add-on to insulin (given as monotherapy, in combination with metformin, or in combination with another AHA).

Canagliflozin in Special Populations:
- DIA3004 - Moderate Renal Impairment Study: Placebo-controlled trial in T2DM subjects with moderate renal impairment (estimated glomerular filtration rate of ≥30 to <50 mL/min/1.73 m^2, based on MDRD equation), canagliflozin as add-on to their current AHA treatment regimen.
- DIA3010 - Older Adults Study: Placebo-controlled trial in older subjects (55-80 years, inclusive) on AHA therapy (diet and exercise alone or in combination with oral AHAs including insulin). This trial included dual energy X-ray absorptiometry (DXA) bone density and bone biomarker assessments.

- DIA3008 - Cardiovascular Safety Study (CANVAS): Placebo-controlled trial to evaluate CV outcomes of canagliflozin compared to placebo in T2DM subjects on a wide range of current AHAs who have a history or are at high risk of CV disease.

5.3.1.1 Characteristics of Phase 3 Trials

The main design features for the Phase 3 trials were similar and are summarized in this section. Following sections (Sections 5.3.1.2 to 5.3.1.10) provide brief summary of unique design features for each Phase 3 trial.

Study Objectives:

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

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

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

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

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

Overview of Study Design:

All Phase 3 trials were multinational, randomized, double-blind, parallel-group trials. The 52-week placebo-controlled Phase 3 trials (DIA3002, DIA3004, DIA3005, DIA3006, and DIA3012) and 104-week placebo-controlled Phase 3 trial DIA3010 assessed the primary efficacy endpoint

at Week 26. The active comparator-controlled Phase 3 trials DIA3009 (104-week) and DIA3015 (52-week) assessed the primary efficacy endpoint at Week 52. The CV safety trial DIA3008 included two efficacy substudies evaluating canagliflozin as an add-on to sulfonylurea (SU) monotherapy and insulin with primary efficacy endpoint measured at Week 18. All the placebo-controlled trials were designed to show superiority of canagliflozin compared to placebo, whereas two active-controlled trials (DIA3009 and DIA3015) were designed to show non-inferiority to active comparator.

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

Trials in special population (DIA3004, DIA3008 and its substudies, and DIA3010) did not require subjects to be on a specific baseline regimen of AHA; canagliflozin was added to their background stable AHA(s). Two substudies of DIA3008 evaluated canagliflozin as add-on to subjects already on a stable dose of insulin and SU monotherapy.

In all trials except DIA3015, CV trial (DIA3008), and substudies (DIA3005 High Glycemic substudy and DIA3008 substudies), subjects who completed the primary assessment at the end of double-blind core period continued the trial in a double-blind extension period. In DIA3015 and DIA3005 High Glycemic substudy, the trials were completed after the primary assessment at Week 52 and Week 26 respectively. DIA3008 is an event-driven trial. The duration of the double-blind extension period was 26 weeks for DIA3002, DIA3004, DIA3005 (Main Study), DIA3006, and DIA3012, 52 weeks for DIA3009, and 78 weeks for DIA3010. Subjects received the same double-blind study treatment during subsequent double-blind extension period in all trials except for subjects assigned to the placebo group in trials DIA3005 (Main Study), DIA3006, and DIA3012 who were switched, in a blinded fashion, to sitagliptin 100 mg daily during the controlled extension period.

Randomization, Stratification, Treatments, and Blinding:

For all Phase 3 trials, subjects who met enrollment criteria at the end of the placebo run-in period were randomly assigned to double-blind treatment on Day 1. Randomization to double-blind treatment was stratified in all Phase 3 trials according to the stratification variables shown in Table 4. All trials included treatment arms for both proposed doses of canagliflozin, 100 mg and

300 mg daily except for one trial, DIA3015, which included only canagliflozin 300 mg daily dose group. Sitagliptin 100 mg daily was the active comparator group in DIA 3006 and DIA3015, and glimepiride (titrated to 6 mg daily) was the active comparator in DIA3009.

Table 4: Stratification Variables in Phase 2 and 3 Trials

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

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

Treatment allocation was blinded to investigators, center personnel, subjects, and sponsor staff involved in the trial. HbA1c, FPG, and PPG values were masked to study centers after randomization unless criterion for glycemic rescue therapy was met or glycemic rescue therapy had been started. To prevent unblinding, UGE results were also not given to the investigational centers, and the central laboratory urinalysis did not include the measurement of urine glucose.

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

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

Key Inclusion Criteria:

- Subjects were eligible if their T2DM was inadequately controlled at screening and at the start of placebo run-in period while on protocol-specified background AHA therapy, with HbA1c of 7 to 10.5% inclusive at screening (for those not requiring AHA adjustment period) or at the start of placebo run-in period (for those requiring AHA adjustment period to meet the protocol-specified diabetes therapy), except for:
    - DIA3005 (main monotherapy study) and DIA3010 (Older Adults Study), subjects were eligible if their HbA1c was 7 to 10% inclusive;
    - DIA3005 High Glycemic substudy, subjects were eligible if their HbA1c was >10% and ≤12%;
    - DIA3009, subjects were to have HbA1c 7 to 9.5% inclusive.
- FPG value <270 mg/dL at the start of placebo run-in period, except for DIA3015 and DIA3005 High Glycemic substudy which required FPG ≤300 mg /dL and ≤350 mg /dL respectively. At the time of randomization (Day 1), subjects were also required to have fasting fingerstick glucose of ≥110 mg/dL.
- Adults with 18 to 80 years of age inclusive, except for trials of canagliflozin in special populations:
    - For DIA3004 (Moderate Renal Impairment Study), the age requirement was ≥25 years without upper limit of age;
    - For DIA3008 (Cardiovascular Safety Study), the age requirement was ≥30 years with CV history or ≥50 years with CV risk factors without upper limit of age;
    - For DIA3010 (Older Adults Study), the age requirement was 55 to 80 years inclusive.
- Both men and women were eligible for enrollment in all Phase 3 trials. Women were excluded if they were pregnant or breastfeeding, but could participate if they were postmenopausal, surgically sterile, or practicing birth control.

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

Key Exclusion Criteria:

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

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

Study Visits and Efficacy Measurements: The schedule of efficacy measurements during the double-blind period up to the primary endpoint are summarized in Table 5 for the nine Phase 3 trials.

Table 5: Efficacy Time and Events Schedule for Phase 3 Trials

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

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

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

Glycemic Rescue:

Subjects in Phase 3 trials were to remain on stable doses of background antidiabetic treatment at the beginning of the run-in period throughout the double-blind treatment period, except for persistent hyperglycemia, which led to subjects receiving rescue therapy or withdrawing from the trial. Criteria for rescue were based on repeated and confirmed (within 7 days) FPG values through Week 18 in DIA3008 substudies or Week 26 in all other Phase 3 trials, and on HbA1c values thereafter. Subjects receiving rescue therapy continued on double-blind study drug treatment and trial procedures related to the protocol until completion of trial. The glycemic thresholds for rescue were largely similar across all the Phase 3 trials; the specific rescue therapy for each trials are listed in Table 6 below. Of note, there was no rescue therapy for DIA3015; subjects who met prespecified glycemic levels in DIA3015 were withdrawn from the trial.

Table 6: Protocol Specified Rescue Therapy Across Phase 3 Trials

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

Source: ISE, section 12.1 of attachment 1.1

Safety Evaluations:

Safety evaluations included collection of adverse events, safety laboratory tests (including serum hematology, chemistry, and urinalysis), 12-lead ECGs, vital signs (blood pressure and pulse rate), body weight, physical examinations, SMBG, and collection of potential hypoglycemic episodes (from the subject diary) at specified times during the trials.

When serum creatinine values were available, the central laboratory also reported the estimated glomerular filtration rate (eGFR), which was calculated according to the 4-variable Modification of Diet in Renal Disease Study (MDRD) equation.

In DIA3004, additional safety assessments included measures of renal safety including eGFR based on serum creatinine, creatinine clearance calculated using the Cockroft-Gault formula, and albumin-creatinine ratio (ACR) measured in the first morning urine collection. In a subset of 90 subjects who underwent 24-hour urine collections, ACR and directly measured creatinine clearance were evaluated.

In DIA3010, bone mineral density was measured at the lumbar spin, hip, and forearm using dual-energy X-ray absorptiometry (DXA) at baseline, Week 26, Week 52, and Week 104. Serum collagen type 1 carboxyl-telopeptide (CTx) and propeptide amino terminal of type I procollagen (P1NP) were also measured to assess bone formation at baseline and at Week 26. In a subset of subjects (about 50 per treatment group), quantitative computed tomography (CT) of the spine and hip were used to assess trabecular and cortical bone density changes, geometric properties and material properties.

For selected specific adverse events, which included vulvovaginal events, urinary tract infections, fractures, and skin-related adverse events (including photosensitivity-related), additional information was obtained from investigators via supplementary electronic case report form (eCRF) to support detailed assessments. For adjudicated adverse events which included venous thromboembolism/pulmonary embolism, fractures, hospitalized congestive heart failure, all deaths, and CV composite endpoint (including CV death, nonfatal MI, nonfatal stroke, or hospitalized unstable angina), additional information was obtained from investigators for detailed assessment of events and adjudication by the Endpoint Adjudication Committee. In addition, additional information was collected on hypoglycemic events during the trial as well as on other specific adverse events such as increased ALT [≥3-fold upper limit of normal (ULN)] or adverse events leading to discontinuation. A dedicated eCRF collected information on hypoglycemia episodes, and analyses for hypoglycemia used results from this hypoglycemia eCRF and not from adverse event eCRF.

There were several safety monitoring committees for Phase 3 trials:

- An independent Endpoint Adjudication Committee (EAC) reviewed blinded data for major adverse cardiovascular events plus unstable angina, hospitalized congestive heart failure, venous thromboembolism/pulmonary embolism, and all deaths.
- Independent assessment committees reviewed blinded data for fracture (Fracture Adjudication Committee [FAC]), hepatic (Hepatic Events Assessment Committee [HEAC]), and renal events (Clinical Events Committee [CEC]) meeting pre-specified criteria.
- An Independent Data Monitoring Committee (IDMC) reviewed at specific, regular intervals unblinded analyses of serious adverse events and CV events across the entire clinical development program for canagliflozin. IDMC included diabetologists, cardiologists, statisticians, and a consultant oncologist, and had the authority to recommend specific program-wide decisions to the applicant.
- A company internal Medical Safety Review Committee (MSRC) monitored all available safety information in a blinded fashion on an ongoing basis for all Phase 3 trials. MSRC may have requested, based on a review of blinded safety data, an unblinded evaluation of a specific safety issue by IDMC.

Statistical Analysis:

The primary efficacy endpoint for Phase 3 trials was the change in HbA1c from baseline to Week 26 for DIA3002, DIA3004, DIA3005, DIA3006, DIA3010, and DIA3012, and at Week 52

for DIA3009 and DIA3015. The change in HbA1c from baseline was assessed at Week 18 for DIA3008 Insulin and SU substudies.

For seven of nine Phase 3 trials with controlled extensions, two separate and independent database locks are to be performed during the trial for data analyses and corresponding clinical study reports: one at the end of core controlled period, which is the primary assessment timepoint, and one at the end of controlled extension period.

The analysis of the primary efficacy endpoint was done using an analysis of covariance (ANCOVA) model, which included terms for treatment and randomization stratification factor(s) as fixed effects and the corresponding baseline HbA1c as a covariate (baseline eGFR was an additional covariate for DIA3004). The least-squares (LS) means for the treatment differences between each canagliflozin group and the comparator and their two-sided 95% confidence intervals (CI) were estimated from ANCOVA. The p-values for superiority testing for the change in HbA1c were calculated by comparing the LS means between treatment groups. For two non-inferiority trials with active comparators, a non-inferiority margin of 0.3% was used to compare canagliflozin against sitagliptin in DIA3015 and against glimepiride in DIA3009 after 52 weeks of treatment. For each Phase 3 trial, a prespecified sequential testing procedure was used to test the treatment differences of the primary and major secondary efficacy endpoints, controlling the family-wise error rate at 5%. In some trials, the sequential testing used the Hochberg procedure for systolic blood pressure, fasting HDL-C and triglyerides (and HOMA2-%B in DIA3012 only) for concurrently testing the treatment difference between 300 mg vs placebo and 100 mg vs placebo, with each test controlling the type-1 error at 2.5%. The sequence varied for each trial.

Secondary efficacy endpoints included changes from baseline in FPG and 2-hour PPG (in selected studies where a standardized MMTT was performed), the proportion of subjects achieving an HbA1c target of <7%, the percent change from baseline in body weight, systolic blood pressure, and fasting triglycerides and HDL-C. For continuous secondary endpoints, an ANCOVA model similar to the primary efficacy endpoint was used for analyses. Categorical variables (e.g., proportion of subjects with HbA1c <7%) were analysis using a logistic regression model, with treatment and stratification factor(s) as fixed factors and baseline HbA1c as covariate (baseline eGFR was an additional covariate for DIA3004).

The primary efficacy analysis set for each individual Phase 2 and Phase 3 trials was the modified intent-to-treat (mITT) analysis set, which included all randomized subjects who took at least one dose of double-blind study drug. All primary and major secondary analyses were based on the mITT analysis set.

A per-protocol (PP) analysis population was used for each Phase 3 trials as supportive efficacy analysis, which included all mITT subjects who completed treatment through the primary assessment timepoint, did not receive rescue therapy through the primary assessment timepoint, and had no major protocol violations that could impact interpretation of the primary efficacy endpoint. A completer's analysis set was also used as supportive efficacy analysis, which

included all mITT subjects who completed double-blind treatment and did not receive rescue therapy through the primary assessment timepoint.

Missing data for efficacy variable was imputated using the last observation carried forward (LOCF) method in the mITT analyses. For analyses of the change in baseline for an efficacy measure, only subjects who had both baseline and at least one postbaseline measure were included. Baseline was the pre-dosing measure on Day 1. If a subject received rescue therapy, all efficacy data after initiation of rescue were censored for efficacy analyses, and the last postbaseline value before rescue was carried forward. In DIA3015, meeting protocol-specified glycemic criteria triggered discontinuation of subject, and the last available postbaseline value was carried forward for the endpoint assessment.

The primary safety analyses excluded data collected after initiation of glycemic rescue therapy. A secondary safety analyses including all data regardless of rescue therapy were performed. There was no imputed missing values for clinical safety laboratory tests, vital signs, or ECG results.

DIA3008 substudies had some modifications made to the data analysis plan before unblinding, as discussed below.

DIA3008 Insulin substudy included subjects on insulin ≥20 IU/day. The applicant received regulatory feedback from the EMA during initiation of DIA3008 suggesting (b) (4) In order to address this issue, the applicant included all subjects who were on insulin ≥30 IU/day at baseline as the primary analysis population in this substudy. The applicant also analyzed all subjects on insulin ≥20 IU/day at baseline, and a subset of subjects on ≥30 IU/day of insulin and ≥2000 mg of metformin at baseline. About 85% of subjects on insulin randomized into DIA3008 were taking ≥30 IU/day of insulin.

The recruitment in the DIA3008 SU substudy was lower than expected, and a blinded review of data before database lock identified errors in stratification of subjects on SU monotherapy with the majority of errors from subjects receiving monotherapy with SU at doses below specified in the protocol. Thus, the primary analysis population for this substudy included subjects on protocol-specified doses of SU monotherapy, regardless of stratification used for randomization. The applicant also conducted an additional population for analysis consisting of all subjects on SU monotherapy regardless of SU dose and regardless of stratification used for randomization.

For two non-inferiority trials (DIA3009 and DIA3015), a non-inferiority margin of 0.3% was used to compare canagliflozin to an active comparator (sitagliptin in DIA3015, glimepiride in DIA3009) after 52 weeks of treatment.

5.3.1.2 DIA3005 (Main Monotherapy Study)

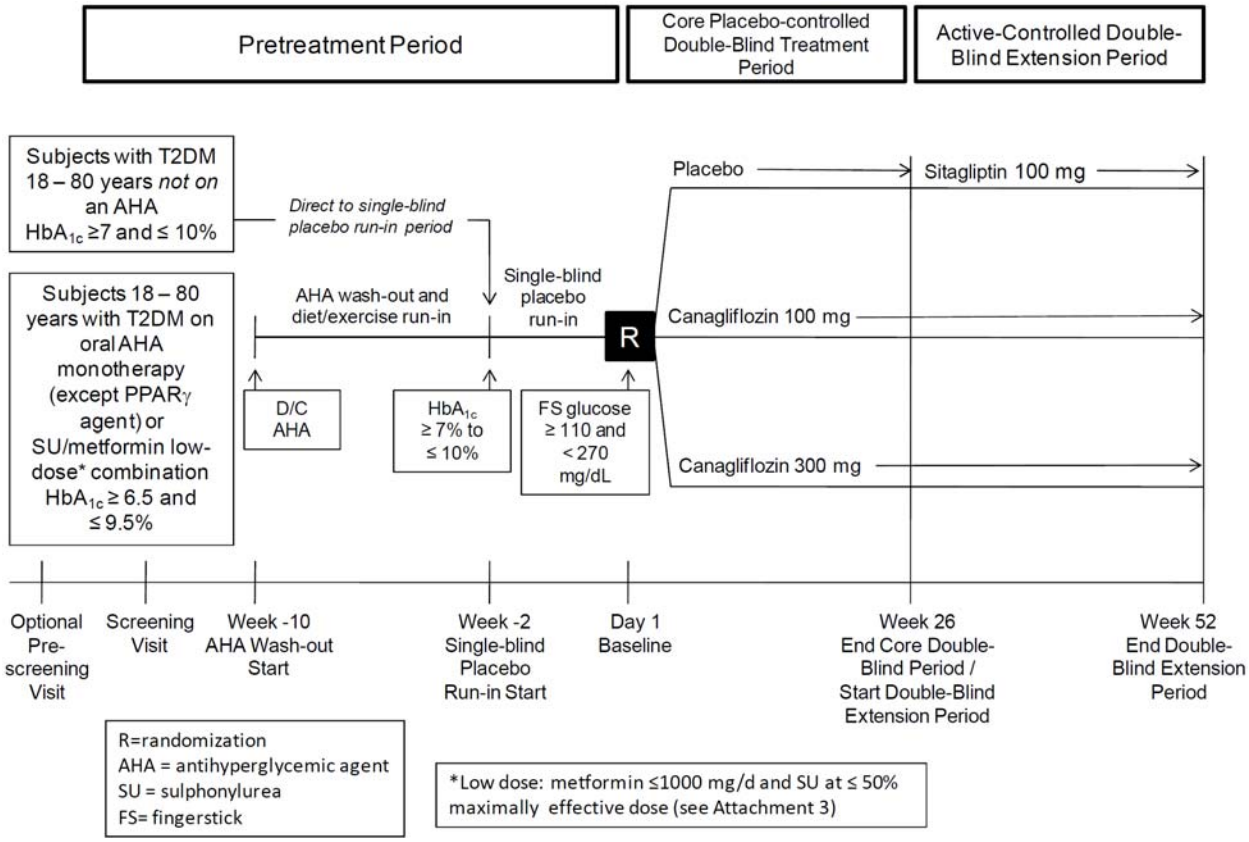
DIA3005 was a 52-week, randomized, double-blind, placebo-controlled, 3-arm parallel group, multicenter trial to investigate the efficacy and safety of canagliflozin monotherapy compared to placebo in T2DM subjects inadequately controlled with diet and exercise. Subjects were randomized in a 1:1:1 ratio to canagliflozin 100 mg, canagliflozin 300 mg, and matching placebo daily. Subjects who completed the 26-week core placebo-controlled, double-blind treatment period entered a 26-week active-controlled, double-blind extension period, where subjects in the canagliflozin treatment groups continued their treatment and subjects on placebo were switched to blinded active therapy (sitagliptin 100 mg).

T2DM subjects were eligible if they were either (1) not on an AHA for at least 12 weeks before screening with an HbA1c of 7-10% inclusive at screening, or (2) currently treated with an oral single AHA monotherapy (except PPARγ agonist) or on low-dose combination therapy with metformin (dose ≤1000 mg per day) and a SU dose of ≤50% of maximal or near-maximally effective doses with an HbA1c of 6.5-9.5% inclusive at screening.

Subjects not on an AHA directly entered a 2-week single-blind placebo run-in period. Subjects on AHA underwent an 8-week diet and exercise and AHA washout period before entering the 2-week single-blind placebo run-in period. All subjects were then randomized if they met all enrollment criteria. Figure 3 shows an overview of DIA3005 study design.

Subset of subjects participated in a FS-MMTT procedure on Day 1 and again at the end of the 26-week core double-blind treatment period.

Figure 3: Overview of DIA3005 Study Design



Source: 28431754DIA3005-Protocol and Protocol Amendments, Figure 1

DIA3005 High Glycemic Substudy

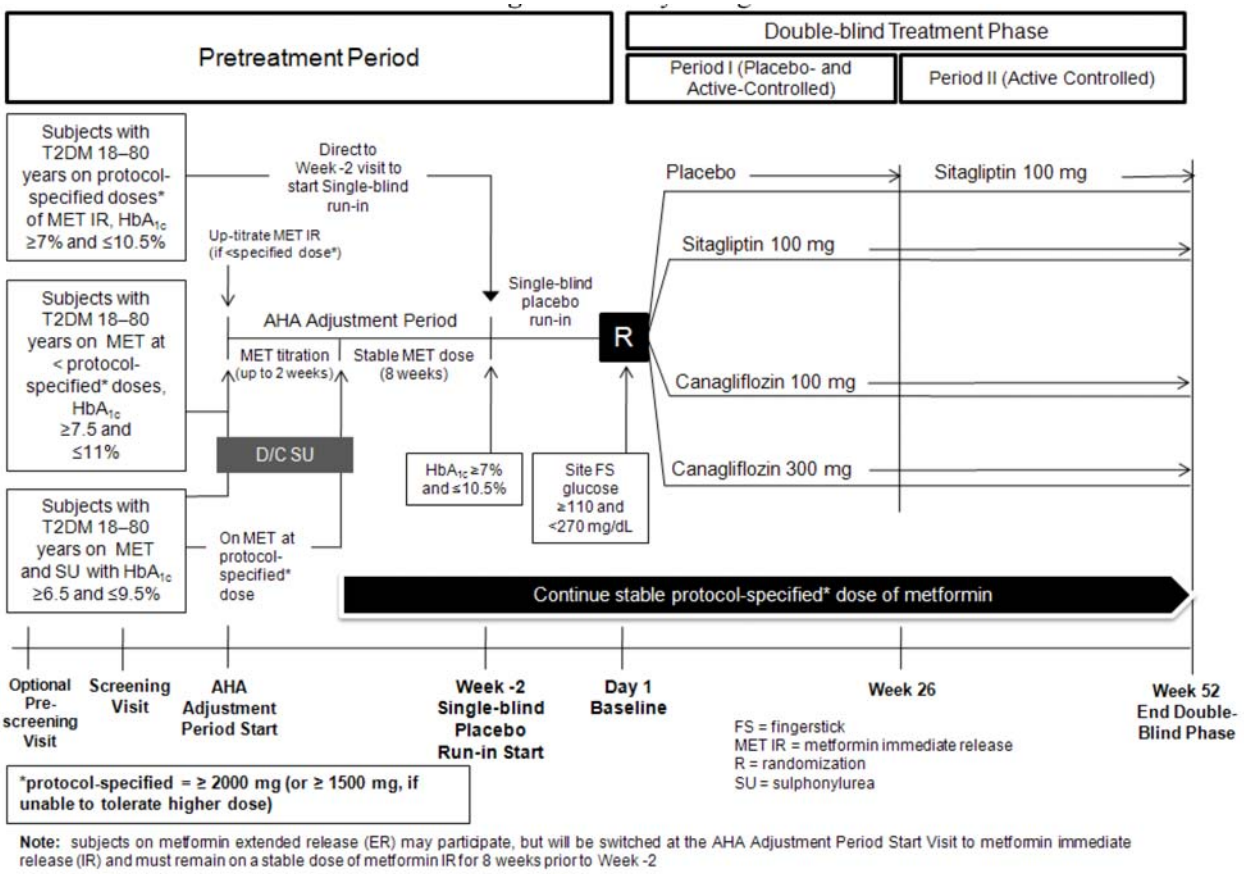
This was a 26-week high glycemic cohort substudy evaluating the efficacy and safety of canagliflozin in subjects with a baseline HbA1c value of >10% and ≤12% at screening or after the 8-week AHA washout period. The trial was not placebo-controlled, and subjects were randomized in a 1:1 ratio to double-blinded treatment of canagliflozin 100 mg or 300 mg daily. Subjects underwent 1-week single-blind placebo run-in period before entering the 26-week double-blind treatment period. There was no extension period for this substudy. Similar to the Main Study, subjects in the substudy received rescue therapy with metformin if they met the glycemic rescue criteria.

5.3.1.3 DIA3006 (Add-on to Metformin Monotherapy)

DIA3006 was a 52-week, randomized, double-blind, placebo- and active-controlled, 4-arm parallel group, multicenter trial to evaluate the efficacy and safety of canagliflozin when added to T2DM subjects who were inadequately controlled on a maximally (or near maximal) effective doses of metformin IR monotherapy. DIA3006 also had a secondary objective to evaluate the noninferiority of canagliflozin compared to sitagliptin after 52 weeks of therapy.

T2DM subjects who were already on metformin (IR or ER) monotherapy and on metformin in combination with an SU were eligible. Subjects already on metformin IR at maximally effective dose (MED, defined as ≥2000 mg/day, or ≥1500 mg/day if unable to tolerate higher doses) with an inadequate glycemic control (e.g., HbA1c of 7-10.5% inclusive) at screening directly entered a 2-week single-blind placebo run-in period. Other subjects entered an AHA adjustment period (e.g., SU wash-out period if applicable, and metformin IR dose titration and dose stable) of up to 10 weeks to modify their regimen to MED of metformin IR monotherapy, and if they had inadequate glycemic control after at least 8 weeks of MED of metformin IR monotherapy, entered a 2-week single-blind placebo run-in period. Subjects who met eligibility criteria at the end of placebo run-in period were then randomized in a 2:2:2:1 ratio to canagliflozin 100 mg, canagliflozin 300 mg, sitagliptin 100 mg, or matching placebo daily. Similar to DIA3005, subjects who completed the 26-week core placebo-and active-controlled, double-blind treatment period entered a 26-week active-controlled, double-blind extension period, where subjects in the active treatment groups (canagliflozin and sitagliptin) continued their treatment and subjects on placebo were switched to blinded active therapy (sitagliptin 100 mg). See Figure 4 for an overview of DIA3006 study design.

Figure 4: Overview of DIA3006 Study Design



Source: 28431754DIA3006-Protocol and Protocol Amendments, Figure 1

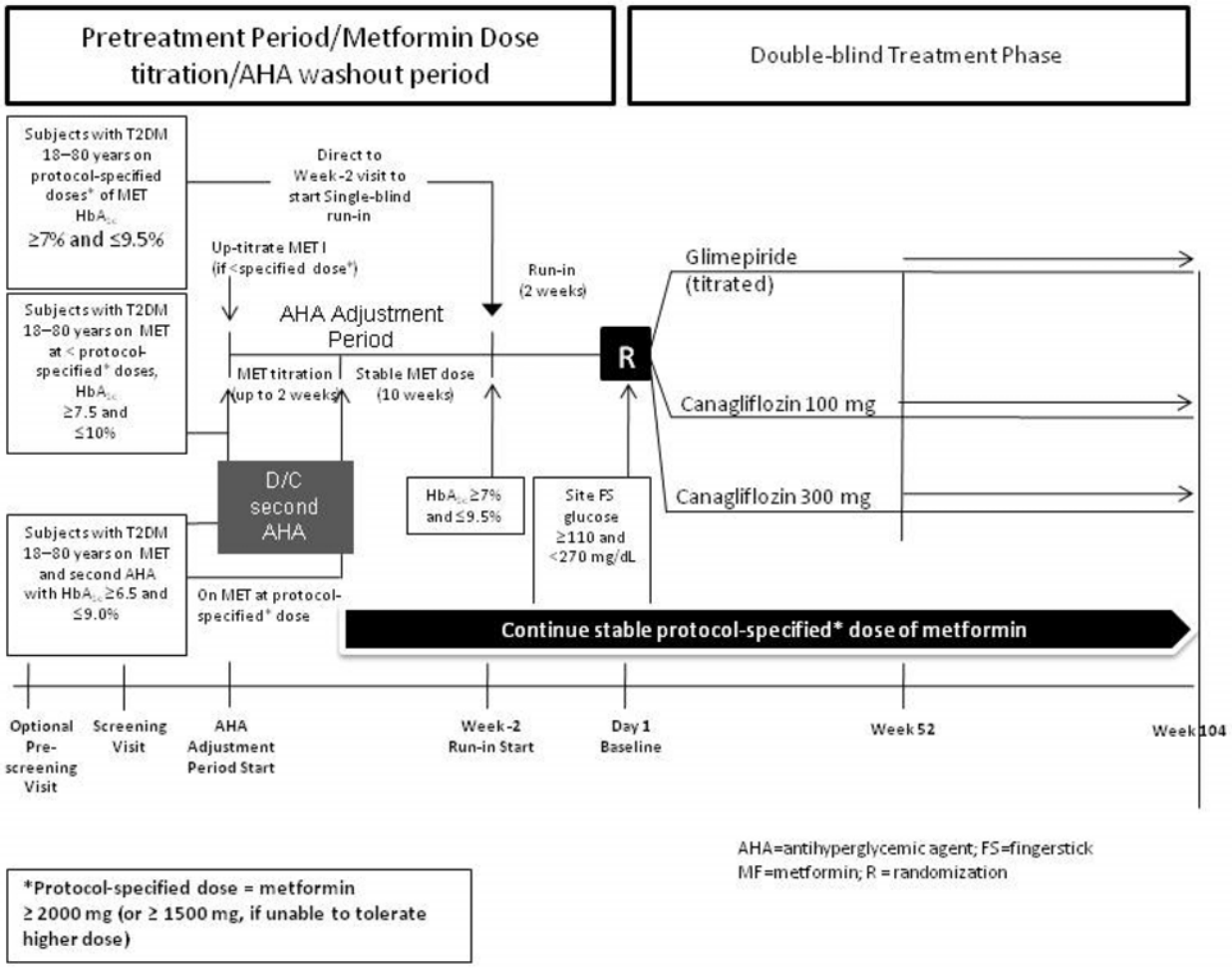
5.3.1.4 DIA3009 (Add-on to Metformin Monotherapy; Active comparator)

DIA3009 was a 104-week, randomized, double-blind, active-controlled, 3-arm parallel group, multicenter trial to evaluate the efficacy and safety of canagliflozin compared to glimepiride in T2DM subjects who were inadequately controlled on MED of metformin monotherapy. The trial included a 52-week core active-controlled double-blind treatment phase followed by a 52-week extension active-controlled, double-blind treatment period. The noninferiority of canagliflozin (both 100 mg and 300 mg dose) to glimepiride with respect to change in HbA1c from baseline was assessed at Week 52.

T2DM subjects on metformin monotherapy and subjects on metformin in combination with a second non-TZD AHA were eligible. Subjects on MED of metformin monotherapy for at least 12 weeks before screening with inadequate glycemic control (HbA1c 7 to 9.5% inclusive) directly entered a 2-week, single-blind, placebo run-in period. Subjects not on MED of metformin monotherapy entered an AHA adjustment period of up to 12-weeks, which consisted of up to a 2-week metformin dose titration and/or AHA washout period followed by a 10-week metformin dose stabilization period. These subjects were required to have HbA1c of 7 to 9.5%

inclusive after at least 10 weeks on a stable MED of metformin monotherapy before they entered the 2-week single-blind placebo run-in period. All subjects who met all eligibility criteria after placebo run-in period were then randomized in a 1:1:1 ratio to canagliflozin 100 mg, canagliflozin 300 mg, or glimepiride. See Figure 5 for an overview of DIA3009 study design.

Figure 5: Overview of DIA3009 Study Design



Source: CSR 28431754DIA3009, Figure 1

The starting dose for glimepiride was 1 mg daily, which was increased to a maximum dose of 6 or 8 mg daily based on the approved country specific label and based on protocol-specified criteria for increasing the dose of study drug. The dose of glimepiride was allowed to be lowered during the trial based on recurrent, unexplained severe or serious hypoglycemia. Since up- and down-titration of glimepiride dose was allowed during the trial, all study drugs were supplied in levels to allow for blinded increases and decreases in glimepiride dose. However, the dose of canagliflozin remained fixed throughout the trial, as shown below. In addition, the stable dose of metformin that was achieved during the titration period were continued during the double-blind treatment phase (unless clinically necessary).

Levels	Doses of canagliflozin 100 mg	Doses of canagliflozin 300 mg	Dose of glimepiride
1	canagliflozin 100 mg	canagliflozin 300 mg	glimepiride 1 mg
2	canagliflozin 100 mg	canagliflozin 300 mg	glimepiride 2 mg
3	canagliflozin 100 mg	canagliflozin 300 mg	glimepiride 4 mg
4	canagliflozin 100 mg	canagliflozin 300 mg	glimepiride 6 mg
5	canagliflozin 100 mg	canagliflozin 300 mg	glimepiride 8 mg

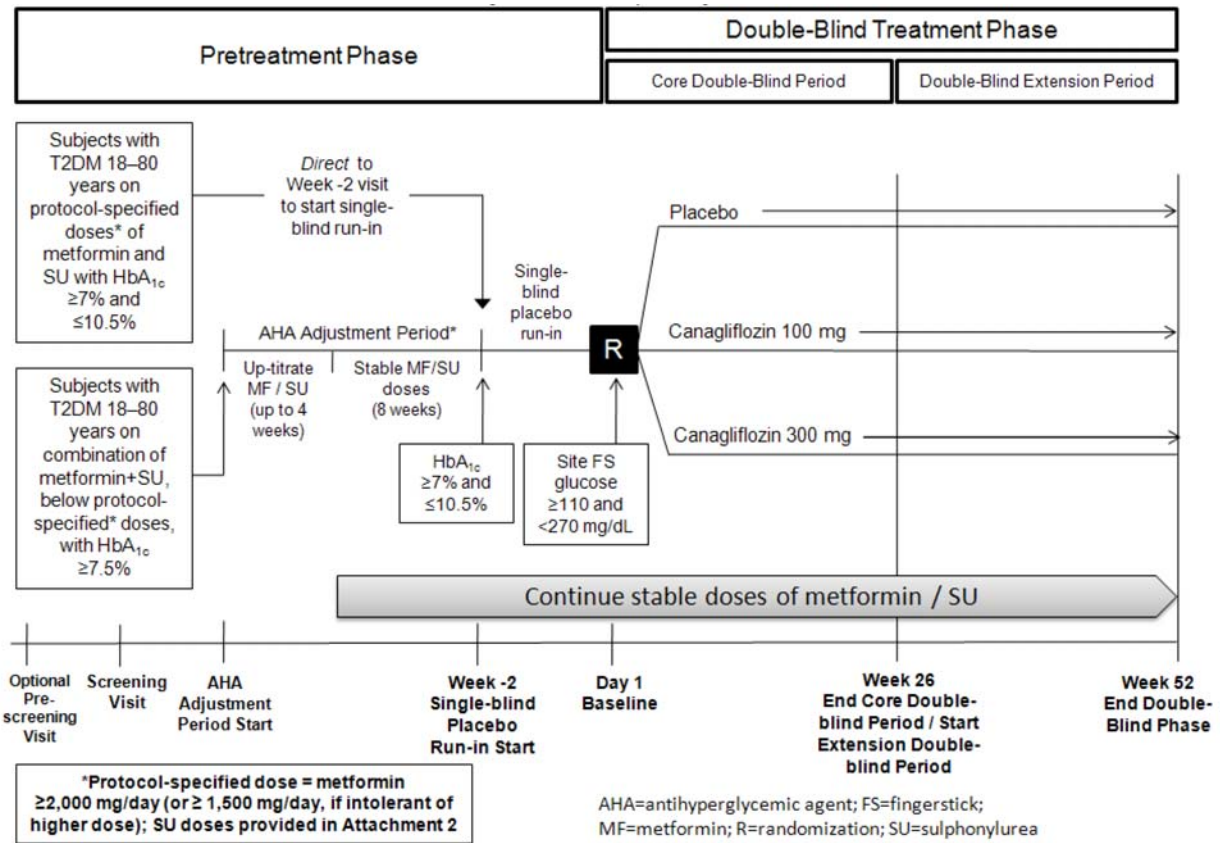
Rescue with pioglitazone was only initiated in subjects who were at Level 5 or Level 4 and met glycemic rescue criteria.

5.3.1.5 DIA3002 (Add-on to Metformin and SU)

DIA3002 was a 52-week, randomized, double-blind, placebo-controlled, 3-arm parallel-group, multicenter trial to evaluate the efficacy, safety, and tolerability of canagliflozin in the treatment of T2DM subjects with inadequate glycemic control (HbA1c 7 to 10.5% inclusive) on the combination of metformin and SU, with both agents at maximally or near-maximally effective doses. This trial also consisted of a 26-week core double-blind treatment period followed by a 26-week extension double-blind treatment period.

T2DM subjects were eligible if they were already on metformin and SU at protocol-specified doses, or on this combination with one or both at below protocol-specified doses. Similar to other trials with background metformin therapy, subjects were required to be at MED for metformin for randomization at ≥2000 mg/day, or ≥1500 mg/day if unable to tolerate a higher dose. The minimum daily dose of SU required for randomization was glipizide 20 mg, glipizide extended release 10 mg, glyburide/glibenclamide 10 mg, glimepiride 4 mg, gliclazide 160 mg, and gliclazide modified release 60 mg. Subjects already on metformin and SU at protocol-specified doses directly entered a 2-week single-blind placebo run-in period. Subjects with one or both metformin and SU below protocol-specified doses with HbA1c ≥7.5% underwent an AHA adjustment period of up to 12 weeks, which consisted of a 4-week metformin and/or SU dose titration period followed by a 8-week metformin and SU dose stable period (at protocol-specified doses of metformin and SU), before entering the 2-week single-blind placebo run-in period. All subjects who met all eligibility criteria after placebo run-in period were then randomized in a 1:1:1 ratio to canagliflozin 100 mg, canagliflozin 300 mg, or placebo. See Figure 6 below for an overview of DIA3002 study design.

Figure 6: Overview of DIA3002 Study Design



Source: Clinical Protocol 28431754DIA3002, Figure 1

A subset of subjects participated in a 3-hour frequently-sampled-MMTT (FS-MMTT) on Day 1 and again at the end of 26-week core double-blind period.

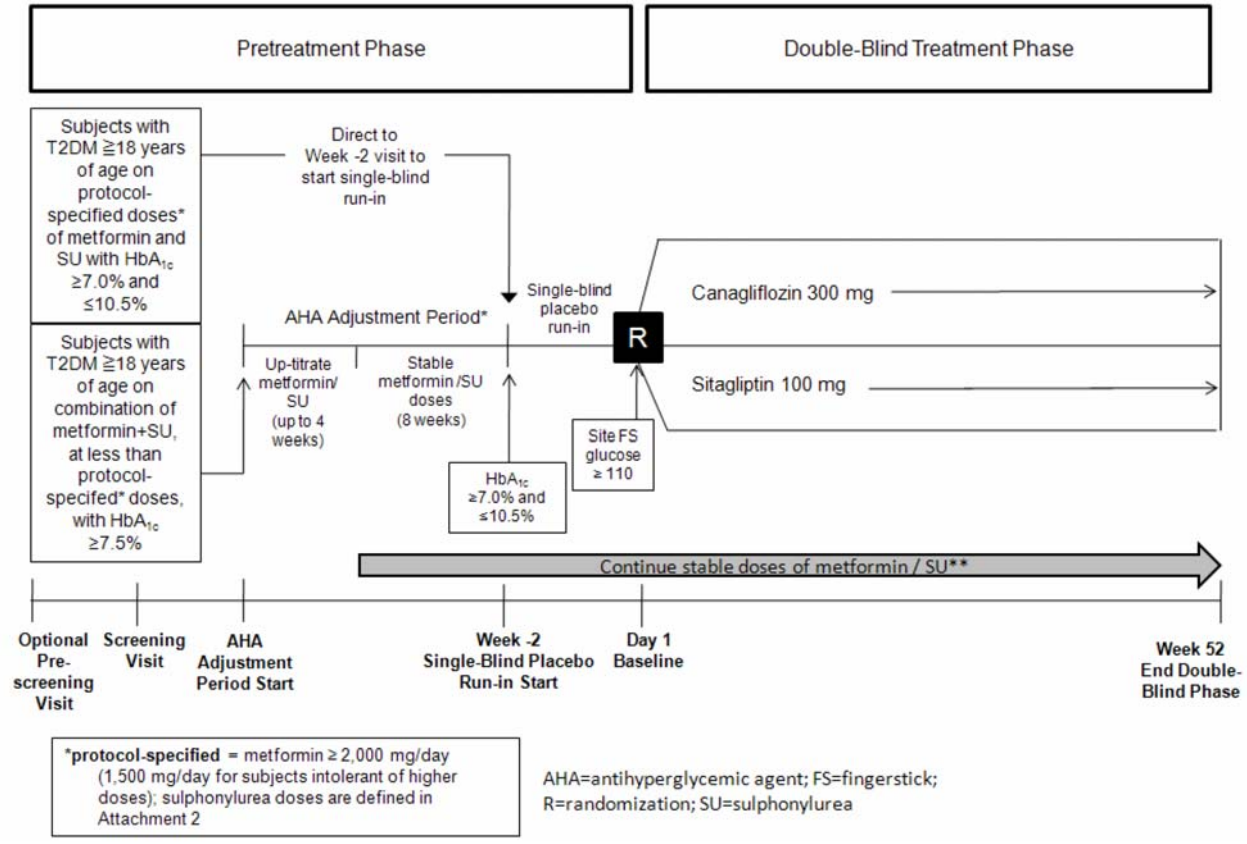
5.3.1.6 DIA3015 (Add-on to Metformin and SU; Active comparator)

DIA3015 was a 52-week randomized, double-blind, active-controlled, 2-arm parallel group, multicenter trial to evaluate the efficacy and safety of canagliflozin 300 mg compared to sitagliptin 100 mg in T2DM subjects with inadequate glycemic control (HbA1c 7 to 10.5% inclusive) on combination of metformin and SU, with both agents at maximally or near-maximally effective doses. Similar to other trials with background metformin therapy, subjects were required to be at MED for metformin for randomization at ≥2000 mg/day, or ≥1500 mg/day if unable to tolerate a higher dose. Similar to DIA3002, the minimum daily dose of SU required for randomization was glipizide 20 mg, glipizide extended release 10 mg, glyburide/glibenclamide 10 mg, glimepiride 4 mg, gliclazide 160 mg, and gliclazide modified release 60 mg.

T2DM subjects who were on metformin and SU were eligible to participate, even if one or both agents were below protocol-specified maximal doses of metformin and SU. Subjects already on

metformin and a SU at protocol-specified doses at screening with inadequate glycemic control directly entered the 2-week, single-blind placebo run-in period. Other subjects entered an AHA adjustment period of up to 12 weeks, which consisted of up to 4-week metformin and/or SU dose titration period and a 8-week metformin and SU dose stable period, after which they entered the 2-week single blind placebo run-in period if they had inadequate glycemic control. All subjects who met all enrollment criteria after the placebo run-in period were randomized in a 1:1 ratio to canagliflozin 300 mg daily or sitagliptin 100 mg daily, added to their current metformin/SU regimen. This trial had no extension period, and did not have canagliflozin 100 mg treatment group. The primary objective of this trial was to demonstrate the noninferiority of canagliflozin (300 mg daily) compared to sitagliptin (100 mg daily) with respect to change in HbA1c from baseline after 52 weeks of treatment. See Figure 7 below for an overview of DIA3015 Study Design.

Figure 7: Overview of DIA3015 Study Design



Source: 28431754DIA3015 Protocols and Amendments, Figure 1

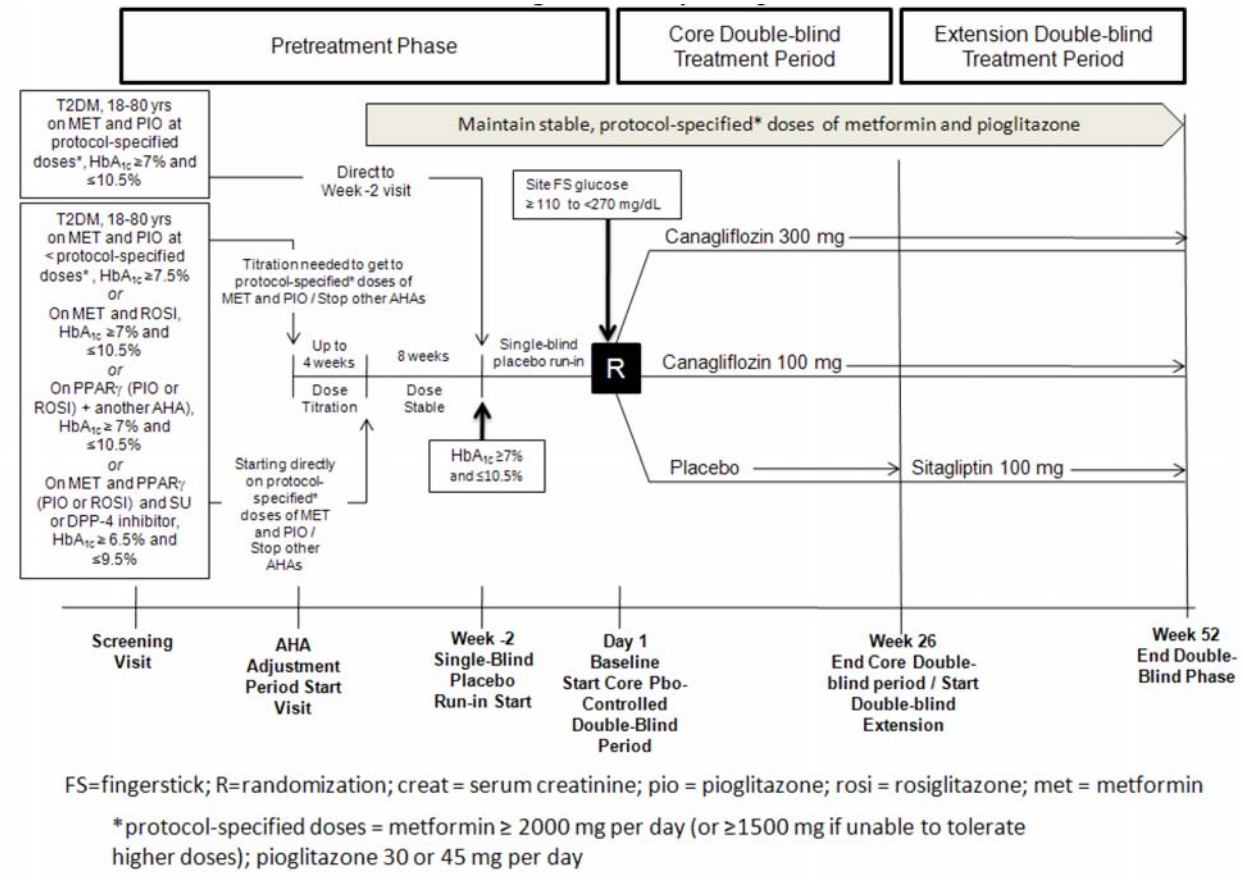
A subset of subjects participated in FS-MMTT procedure on Day 1 and again at the end of the 52-week treatment period.

5.3.1.7 DIA3012 (Add-on to Metformin and Pioglitazone)

DIA3012 was a 52-week, randomized, double-blind, placebo-controlled, 3-arm parallel-group, multicenter trial to evaluate the efficacy and safety of canagliflozin in T2DM subjects who were inadequately controlled (HbA1c of 7 to 10.5%, inclusive) on maximally (or near maximal) effective doses of metformin and pioglitazone. Subjects were to be on MED dose of metformin and on pioglitazone dose of 30 or 45 mg daily. The trial consisted of a 26-week core placebo-controlled, double-blind treatment period followed by a 26-week active-controlled, double-blind extension period where subjects in the active treatment group continued their canagliflozin therapy and subjects in the placebo group were switched to blinded active therapy (sitagliptin 100 mg daily onverencapsulated to match double-blind canagliflozin and placebo capsules).

T2DM subjects were eligible to participate if they were on a PPARγ agonist (pioglitazone or rosiglitazone) in combination with either metformin or an oral AHA other than metformin, or on a PPARγ agonist in combination with metformin and either a SU (or meglitinide) or a DPP-4 inhibitor. Subjects already on metformin and pioglitazone at protocol-specified doses for at least 16 weeks with inadequate glycemic control at screening directly entered the 2-week, single-blind placebo run-in period. Other subjects entered an AHA adjustment period of up to 12 weeks, which included up to 4-weeks of metformin/pioglitazone dose titration period and SU/meglitinide/DPP-4 inhibitor washout period followed by a 8-week metformin/pioglitzone dose-stable period, after which they entered the 2-week, single-blind placebo run-in period if they had inadequate glycemic control. If they met all other enrollment criteria after the placebo run-in period, they were randomized 1:1:1 ratio to canagliflozin 100 mg, canagliflozin 300 mg, or matching placebo daily. See Figure 8 for an overview of DIA3012 study design.

Figure 8: Overview of DIA3012 Study Design



Source: 28431754DIA3012 Protocol and Protocol Amendments, Figure 1

5.3.1.8 DIA3004 (Moderate Renal Impairment Study)

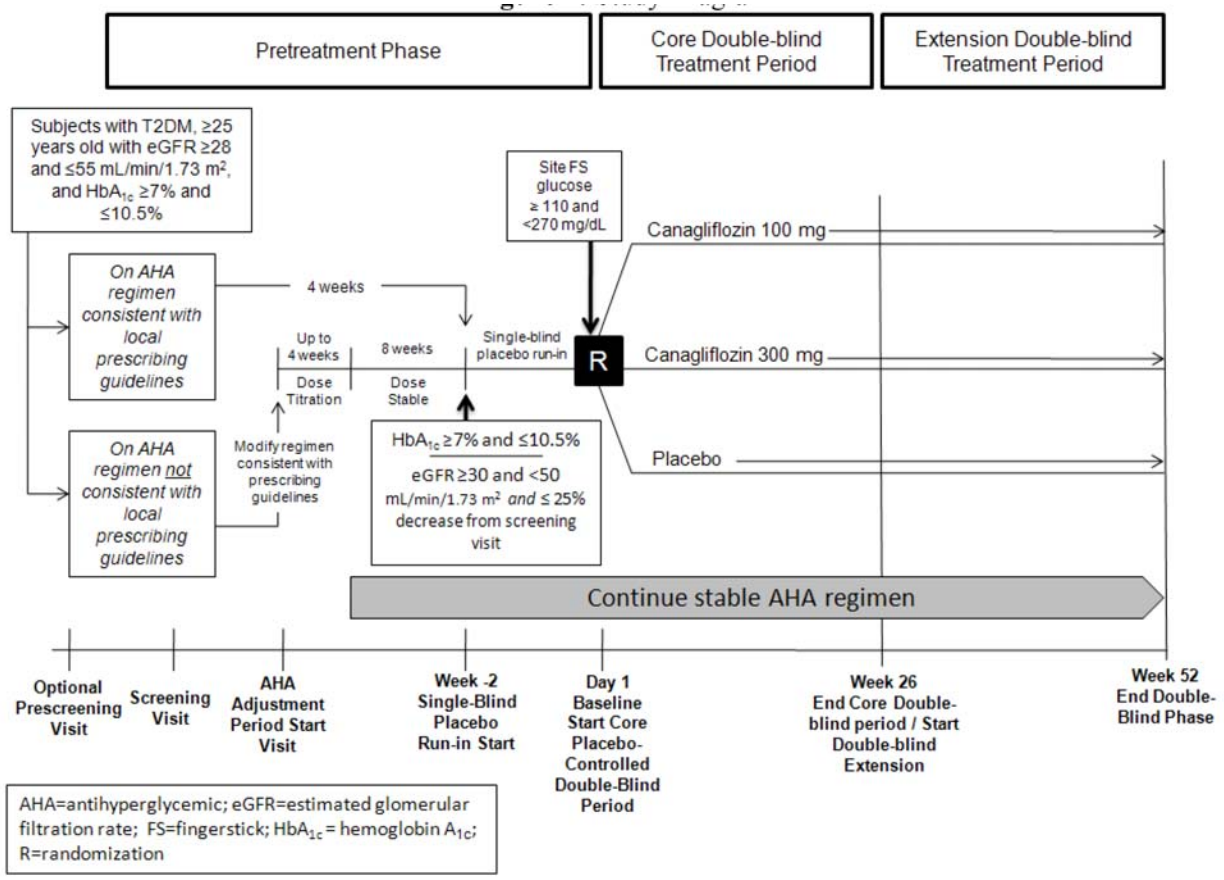
DIA3004 was a 52-week, randomized, double-blind, placebo-controlled, 3-arm parallel-group, multicenter trial in T2DM subjects who were ≥25 years of age with inadequate glycemic control (HbA1c 7 to 10.5% inclusive), had moderate renal impairment (eGFR ≥30 and <50 mL/min/1.73m^2, based on MDRD equation), and were either not on an AHA or on a stable AHA regimen (monotherapy or combination therapy with any approved agent) for at least 8 weeks (12 weeks for pioglitazone) before the start of the 2-week single-blind placebo run-in period (Week -2). Subjects also needed to have stable renal function, with a 4-week period between (pre)screening and Week -2, and by demonstrating that there was ≤25% decrease in eGFR values at Week -2 compared to the (pre)screening visit value.

Subjects were permitted on background AHA therapy with any approved agent, being used in accordance with local prescribing information for patients with T2DM and moderate renal impairment (i.e, metformin in subjects with moderate renal function), except for rosiglitazone, colesevelam, and bromocriptine. Subjects not meeting this criterion at screening had their AHA regimen appropriately adjusted during the AHA adjustment period. Subjects not requiring AHA

adjustment directly entered the 2-week single-blind placebo run-in period. Subjects who were on metformin or any other AHA not indicated in subjects with moderate renal insufficiency (according to local label) entered the single-blind placebo run-in period after background AHA was washed out and an alternative agent allowed to be used in subjects with moderate renal impairment was added as their AHA. These subjects entered up to 12-weeks of AHA adjustment period that included up to 4-weeks of washout/dose titration period and an 8-week dose stable period before entering the placebo run-in period.

After the 2-week single-blind placebo run-in period, subjects meeting all eligibility criteria were randomized in a 1:1:1 ratio to canagliflozin 100 mg, canagliflozin 300 mg, or placebo daily, which was added to the subject's stable diabetes regimen (diet, exercise, and medication therapy) for 52 weeks of double-blind treatment, which consisted of a 26-week core double-blind treatment period followed by a 26-week double-blind extension period. See Figure 9 for an overview of DIA3004 study design.

Figure 9: Overview of DIA3004 Study Design



Source: 28431754DIA3004 Protocol and Protocol Amendments, Figure 1

To assess the effect of canagliflozin on calcium homeostasis in these subjects with moderate renal impairment, serum PTH and 1,25-dihydroxyvitamin D and 25-hydroxyvitamin D were measured in this trial. Also, in order to assure complete evaluation of renal safety, investigators were also asked to provide additional information such as laboratory studies, results of imaging or other diagnostic studies, hospital records, and follow-up information on adverse events with terms indicating worsening renal function (e.g. acute renal failure) and on subjects discontinued due to meeting eGFR discontinuation criteria. In addition, the urinary ACR was evaluated in all subjects from the first morning void during the trial. To obtain additional information on urinary albumin excretion and renal function, a 24-hour urine collection substudy was performed in a subset of about 90 subjects to measure creatinine, albumin, and glucose. Other measures of renal function (such as creatinine, BUN, and electrolytes) were collected on a regular basis, with a routine analysis obtained at baseline, Week 26, and Week 52.

5.3.1.9 DIA3010 (Older Adults Study)

DIA3010 was a 104-week, randomized, double-blind, placebo-controlled, 3-arm parallel group trial designed to evaluate the efficacy and safety of canagliflozin compared to placebo in older subjects (55 to 80 years of age, inclusive) with inadequate glycemic control (HbA1c 7 to 10% inclusive) on their current diabetes treatment. This trial also had a secondary goal of assessing the effects of canagliflozin on bone safety in older adults who are at a higher risk for bone loss and resultant fractures. To achieve this goal, the trial evaluated changes in bone density, bone turnover, and bone strength.

Subjects either not currently on an AHA or on a stable regimen of AHA(s) for at least 8 weeks before screening were eligible for participation if they met other eligibility criteria. Subjects were allowed to be on any background AHA in monotherapy or combination therapy with any approved agent (including metformin, SU, DPP-4 inhibitor, alpha glucosidase inhibitor, GLP-1 analogue, or insulin for at least 12 weeks, or on pioglitazone for at least 6 months) if they were used in accordance with local prescribing information. Subjects receiving rosiglitazone were not eligible. After screening, all subjects entered a 2-week single-blind placebo run-in period. Eligible subjects were randomized in a 1:1:1 ratio to canagliflozin 100 mg, canagliflozin 300 mg, or matching placebo daily to their background stable AHA(s), and entered a 26-week core placebo-controlled, double-blind treatment period followed by a 78-week extension, placebo-controlled, double-blind treatment period. Subjects remained on their background stable AHA(s) from the screening visit to the Week 104 visit, unless down-titration was needed for safety or they met glycemic criteria for rescue therapy.

Assessments of the bone safety included bone mineral density at the lumbar spine, hip (including femoral neck and total hip), and distal forearm using DXA. Bone turnover markers including serum collagen type 1 carboxy-telopeptide (CTx) and propeptide amino terminal type I procollagen (P1NP) were also measured in this trial. Serum calcium and phosphorus were measured to assess calcium homeostasis.

Quantitative computed tomography of the spine and hip was used to assess trabecular and cortical bone density changes, geometric properties and material properties in a subset of subjects (about 50 per treatment group) after 52 weeks of treatment, the result of which will be available in the final CSR after completion of 104-week double-blind period, which is still ongoing.

5.3.1.10 DIA3008 (Cardiovascular Safety and Outcome Study)

DIA3008 (Canagliflozin Cardiovascular Assessment Study, or CANVAS) is an ongoing, event-driven trial with the study duration based upon the occurrence of sufficient events to evaluate the trial hypothesis and objectives. This is a randomized, double-blind, placebo-controlled, 2 sequential-cohort, 3-arm parallel group multicenter trial to evaluate the CV benefit, safety, and tolerability with canagliflozin compared to placebo in T2DM subjects with inadequate glycemic control on a wide range of current AHAs, and had either a history or high risk of CV disease. Subjects were allowed to be either not on AHA, or on an oral AHAs, insulin therapy, and other parenteral agents such as GLP-1 agonists. The primary hypothesis for this CV trial is that treatment with canagliflozin would reduce CV risk compare to placebo as measured by the HR for a composite CV endpoint including CV death, nonfatal MI, and nonfatal stroke.

T2DM subjects with inadequate glycemic control (HbA1c 7 to 10.5% inclusive) who were not on an AHA or on an AHA in monotherapy or combination therapy, and who had known CV disease or at high risk of CV disease were eligible, as following:

- Aged ≥30 years with documented symptomatic atherosclerotic CV disease (stroke, MI), hospital admission for unstable angina, coronary artery bypass graft, percutaneous coronary intervention, peripheral revascularization, symptomatic with hemodynamically-significant carotid or peripheral vascular disease, or amputation secondary to vascular disease;
- Aged ≥50 years with two or more of the following CV risk factors at screening: duration of T2DM of ≥10 years, SBP >140 mmHg while on at least one BP-lowering treatment, current daily cigarette smoker, documented micro- or macro-albuminuria, or documented HDL-C of <1 mmol/L (<39 mg/dL).

The applicant targeted enrollment ratio of 70% of subjects with known CV disease (minimum of 60%) to 30% of subjects at high risk of CV disease (maximum of 40%).

After screening visit, subjects entered a 2-week single-blind placebo, diet/exercise, and CV risk factor (e.g., blood pressure and lipids) management optimization period. All subjects, at entry to the 2-week single-blind placebo period, received diet/exercise counseling, counseled on hypoglycemia recognition and management, and were given a monitor and material for SMBG measurements. Subjects may extend this for an additional 2-weeks if additional time in run-in was required to adjust/optimize lipid- or blood-pressure-lowering drugs.

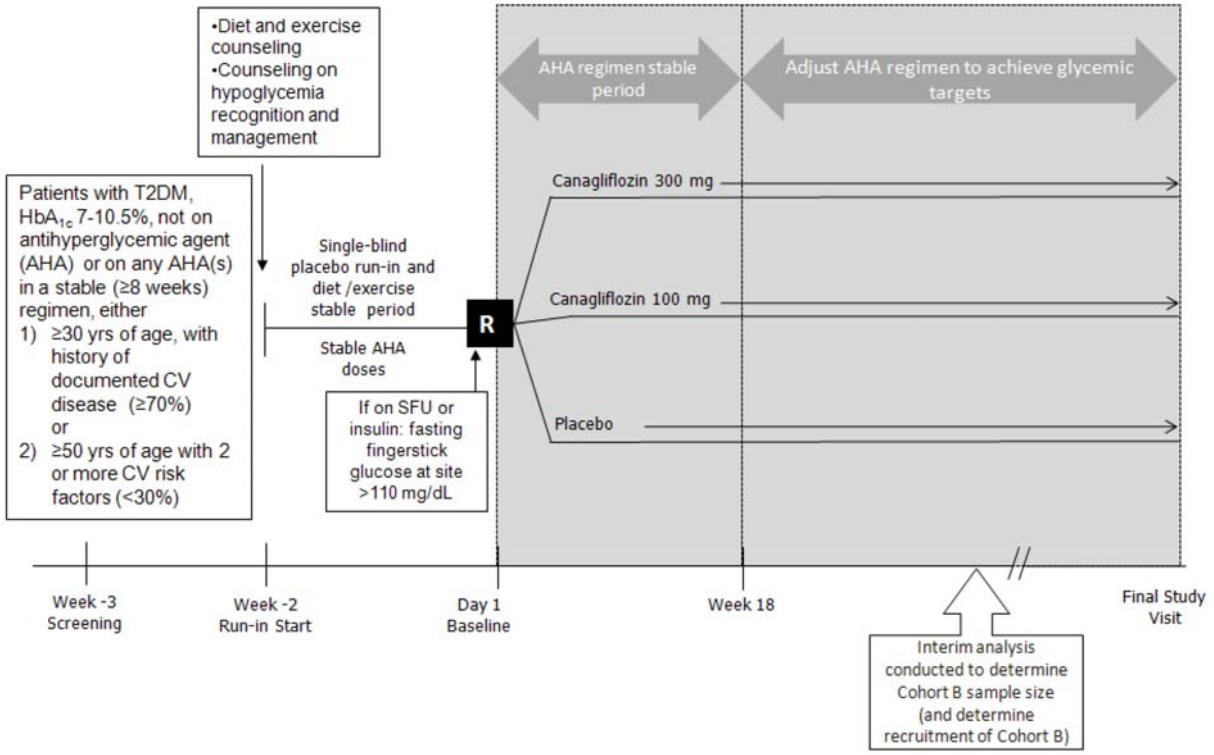
For the initial cohort (Cohort A), subjects who met all eligibility criteria and completed the placebo run-in period were randomized in a 1:1:1 ratio to canagliflozin 100 mg, canagliflozin

300 mg, or matching placebo. Randomization of subjects in Cohort A was stratified according to six strata, based on the background AHA the subject was receiving at the run-in visit:

1) Insulin ≥20 units/day on a stable dose at least 10 weeks
2) Insulin ≥20 units/day + metformin on stable doses at least 10 weeks
3) Insulin ≥20 units/day + any other AHA(s) on stable doses at least 10 weeks
4) SU monotherapy at stable, protocol-specified dose for at least 10 weeks
5) Pioglitazone ≥30 mg/day + metformin ≥2000 mg/day (or ≥1500 mg if intolerant) for at least 10 weeks
6) Any other AHA not specified above

Subjects were to remain on a stable regimen of their current AHA regimen from screening until Week 18 visit of the double-blind treatment phase, unless down-titration was necessary for hypoglycemia management. After 18 weeks, investigators were allowed to individualize AHA regimen consistent with standard diabetes guidelines to achieve good glycemic control, with up-titration or stepwise addition of AHA therapies. See Figure 10: Overview of DIA3008 Study Design below.

Figure 10: Overview of DIA3008 Study Design (Cohort A)



Source: Clinical protocol 28431754DIA3008 (CANVAS), Figure 1

The trial included two sequential cohorts, with the decision to recruit further subjects (e.g., re-open enrollment into Cohort B) dependent upon a protocol-specified interim analysis of results

from the initial cohort (Cohort A). An interim analysis was planned 4 years after trial initiation by an IDMC in order to assess the study feasibility in achieving the primary hypothesis of CV benefit, and to recommend that study recruitment be re-opened if the intermediate outcome was positive. If the recruitment was not re-opened, the initial cohort of subjects were to be continued to be followed to assess the long-term safety and tolerability of canagliflozin. Subjects in Cohort A are to have a minimum duration of 4-years of follow-up.

Reviewer's comment: At the pre-NDA meeting, the applicant stated that they unblinded data for DIA3008 at the interim analysis due to concerns over increase in LDL-C observed with canagliflozin therapy, and will not conduct Cohort B. The applicant plans to follow the current Cohort A to provide the needed events to support the next CV HR meta-analysis in appropriate time.

In DIA3008, all deaths and events for CV composite endpoints (e.g., CV deaths, nonfatal MI, nonfatal stroke, or hospitalized unstable angina) were captured on eCRF for these endpoints. With the exception of CV deaths, these events were not reported as adverse events (e.g., not recorded in the adverse event or serious adverse event eCRF page).

DIA3008 Substudies: These substudies were conducted in the initial cohort of subjects (Cohort A) of DIA3008 in order to assess the efficacy, safety, and tolerability of canagliflozin compared to placebo in T2DM subjects with inadequate glycemic control for the following subgroups: (1) subjects receiving insulin ≥20 units/day monotherapy or in combination with other AHA(s), (2) sulfonylurea monotherapy at protocol-specified doses, or (3) pioglitazone ≥30 mg/day plus metformin ≥2000 mg/day (or ≥1500 mg/day if intolerant) and no other AHA. However, there was inadequate enrollment in the pioglitazone substudy. All the subjects in these substudies followed the same procedures and assessments as the overall trial.

Subjects in the insulin substudy were those within one of the three strata of the main trial involving a stable dose of insulin. A stable dose of insulin was defined as no change in the insulin regimen and ≤15% change in the average total daily dose of insulin. Subjects in the SU substudy were those stratified to the SU monotherapy stratum in the main trial.

5.3.2 Phase 2 Trials

The development program for canagliflozin included two Phase 2 trials conducted by JRD:

- DIA2001 was a 12-week placebo-controlled, Phase 2b dose-ranging trial in T2DM subjects with inadequate glycemic control on metformin. This trial demonstrated efficacy and safety of canagliflozin as add-on therapy for treatment of T2DM and supported selection of doses for Phase 3 trials.
- OBE2001 was a 12-week placebo-controlled, Phase 2b dose-ranging trial in non-diabetic, overweight or obese subjects with hypertension and dyslipidemia. This trial provided supportive safety for canagliflozin and demonstrated weight loss response in non-diabetic subjects.

In addition, a 12-week placebo-controlled, Phase 2 dose-finding MTPC-sponsored trials conducted in T2DM adults from Japan, TA-7284-04, investigated canagliflozin as monotherapy (50, 100, 200, 300 mg QD).

The trial design, randomization, and pretreatment periods in the Phase 2 trials in T2DM (DIA2001 and TA-7284-04) were similar to Phase 3 trials. Both DIA2001 and TA-7284-04 were randomized, double-blind, placebo-controlled, parallel group multicenter trials. DIA2001 also had an active-control treatment group with sitagliptin. The duration of Phase 2 trials were 12 weeks with no extension period. Subjects in DIA2001 were maintained on background therapy of metformin (≥1500 mg/day) throughout the run-in and double-blind treatment periods. Subjects in TA-7284094 did not receive any background AHA other than diet and exercise during the trial. Subjects in these two Phase 2 trials who experienced poor glycemic control during the double-blind treatment period were discontinued from the trial.

6 Review of Efficacy

Efficacy Summary

In the clinical development program for canagliflozin, its efficacy was evaluated both as monotherapy and in combination with approved anti-diabetic agent(s), where canagliflozin was given as an add-on to metformin, metformin+sulfonylurea, metformin+pioglitazone, sulfonylurea and insulin. In addition, the efficacy and safety of canagliflozin in T2DM with moderate renal function (DIA3004) and older adults (DIA3010) were also evaluated. The glycemic efficacy of canagliflozin compared to placebo, as measured by the change in HbA1c from baseline, was observed in all placebo-controlled Phase 3 trials and achieved statistical significance. The placebo-adjusted mean reduction in HbA1c was dose-dependent, and ranged from -0.29 to -0.91% with canagliflozin 100 mg and -0.42 to -1.16% with canagliflozin 300 mg. Canagliflozin resulted in near-maximal HbA1c reduction by Week 12.

The largest HbA1c reduction associated with canagliflozin was see in monotherapy trial (DIA3005), where canagliflozin 100 mg and 300 mg achieved -0.91% and -1.16% difference from placebo. The following points summarize the range of glycemic efficacy across other Phase 3 trials:

- Canagliflozin 100 mg and 300 mg, when added to metformin background therapy, achieved a range of -0.62 to -0.77% difference from placebo in HbA1c reduction (DIA3006)
- Canagliflozin 100 mg and 300 mg, when added to sulfonylurea background therapy, achieved a range of -0.74 to -0.83% difference from placebo in HbA1c reduction (DIA3008 SU substudy)
- Canagliflozin 100 mg and 300 mg, when added to metformin and SU background therapy, achieved a range of -0.71 to -0.92% difference from placebo in HbA1c reduction (DIA3002)

- Canagliflozin 100 mg and 300 mg, when added to metformin and pioglitazone background therapy, achieved a range of -0.62 to -0.76% difference from placebo in HbA1c reduction (DIA3012)
- Canagliflozin 100 mg and 300 mg, when added to background insulin therapy, achieved a range of -0.65 to -0.74% difference from placebo in HbA1c reduction (DIA3008 Insulin substudy)

Canagliflozin showed a modest dose response in HbA1c reduction, and the incremental HbA1c reduction from 100 mg to 300 mg ranged from -0.09 to 0.26% across Phase 3 trials.

In two active-controlled trials (DIA3009, DIA3015), the applicant showed that canagliflozin was non-inferior when compared to glimepiride (both doses) and sitagliptin (only 300 mg dose). In addition, canagliflozin 300 mg was statistically superior to both glimepiride and sitagliptin, although the treatment difference between canagliflozin 300 mg and glimepiride was modest (-0.12%). The treatment difference for canagliflozin 300 mg compared to sitagliptin was -0.37% ($p<0.001$).

The applicant also conducted a study in Older Adults (DIA3010), which included subjects who were 55 to 80 years of age (mean age of 63.6 years), and showed that canagliflozin 100 mg and 300 mg achieved a range of -0.57 to -0.70% difference from placebo in HbA1c reduction. The FDA statistician's subgroup analysis of age from a large pool of placebo-controlled studies (including DIA3004 and DIA3010) showed a statistically significant interaction between age and treatment. The glycemic efficacy was relatively smaller in elderly compared to the younger age subgroup, especially in those ≥75 years (placebo-subtracted LS mean HbA1c of -0.46 and -0.48% for 100 mg and 300 mg respectively) compared to < 75 years old (placebo-subtracted LS mean HbA1c of -0.66 and -0.81% for 100 mg and 300 mg respectively).

In addition, the applicant conducted a dedicated trial in subjects with moderate renal impairment (DIA3004), with baseline eGFR range of 30 to 50 mL/min/1.73m^2 (mean 39.4 mL/min/1.73m^2), and canagliflozin achieved -0.29 and -0.42% difference from placebo in HbA1c reduction with 100 mg and 300 mg respectively. To further evaluate glycemic efficacy in subjects with moderate renal impairement, a population of subjects with moderate renal function, defined as baseline eGFR of ≥30 to <60 mL/min/1.73m^2 (mean 48.2 mL/min/1.73m^2), was pooled across Phase 3 trials. Canagliflozin achieved -0.38 and -0.47% difference from placebo in HbA1c reduction with 100 mg and 300 mg respectively in this pooled population, which was numerically larger compared to the results from DIA3004. This was most likely due to baseline differences in eGFR between two population.

The major secondary glycemic efficacy endpoints included changes in fasting plasma glucose (FPG), 2-hour postprandial glucose, and proportion of subjects achieving HbA1c <7%.

Except for canagliflozin 300 mg group in DIA3004 (and canagliflozin 100 mg due to testing sequence), statistically significant reductions in FPG were observed with canagliflozin in all placebo-controlled Phase 3 trials. Also, consistent with HbA1c reduction, DIA3004 had the

smallest numerical reduction in the LS mean FPG with canagliflozin compared to placebo among the placebo-controlled trials.

The change in 2-hour postprandial glucose was only studied in DIA3005 and DIA3006 using a Mixed Meal Tolerance Test, where a statistically significant reduction was seen with canagliflozin relative to placebo by Week 26, and this appeared to be dose-dependent.

All study groups in placebo-controlled trials, except for 100 mg dose group in DIA3004, had a statistically significant proportion of subjects who achieved HbA1c of <7% compared to placebo. However, due to pre-specified sequential testing to adjust for multiplicity, comparison of canagliflozin dose groups in DIA3004 and 100 mg dose group in DIA3008 SU substudy should be considered nominal.

Aside from special population studies, the percentage of subjects achieving ADA HbA1c target was significantly greater in the canagliflozin group compared to the placebo group. There was a modest dose response when evaluation proportion of subjects achieving HbA1c goals. A larger proportion of subjects with canagliflozin 300 mg (13 to 18%) achieved ADA target of <7% compared to 100 mg dose of canagliflozin when canagliflozin was used as monotherapy, add-on to AHA monotherapy, or add-on to dual combination AHA therapy.

Other major secondary non-glycemic efficacy endpoints included change in body weight and systolic blood pressure.

A dose-dependent and statistically significant reductions in body weight was achieved with canagliflozin compared to placebo, except with 100 mg dose group in DIA3008 SU substudy. The 300 mg dose of canagliflozin in DIA3008 SU substudy also showed modest body weight reduction compared to other 300 mg dose groups in other placebo-controlled trials. Similarly, the body weight reduction was modest in another trial where SU was a background AHA therapy (DIA3002) compared to other placebo-controlled trials. This result suggest that weight gain associated with SU may attenuate the weight reduction with canagliflozin.

The body weight reduction in subjects with moderate renal impairment (DIA3004) was also modest; the placebo-subtracted LS mean % body weight reduction was 1.6% with 100 mg and 1.8% with 300 mg dose of canagliflozin. In the remaining placebo-controlled trials, the placebo-subtracted LS mean reduction of percent body weight with canagliflozin ranged from 1.9 to 2.7% with 100 mg and 1.8 to 3.8% with 300 mg dose.

There was a dose-dependent and statistically significant placebo-subtracted LS mean reduction in systolic blood pressure (SBP) from baseline to the primary endpoint, except for trials where canagliflozin was studied as an add to SU (DIS3002 and DIA3008 SU substudy). In the remaining placebo-controlled trials, the placebo-subtracted LS mean reduction in SBP ranged from 2.6 to 5.7 mmHg and 3.5 to 7.9 mmHg with 100 mg and 300 mg respectively.

Canagliflozin was associated with non-dose dependent increases in HDL-C with canagliflozin in Phase 3 trials, although the treatment difference compared to placebo did not always reach statistical significance. Canagliflozin did not show a consistent trend with the change in triglycerides, and the observed changes were small. Any observed treatment difference compared to placebo was due to increased triglycerides in the placebo group.

6.1 Indication

The applicant proposed the following indication: "TRADENAME (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus."

6.1.1 Methods

Nine Phase 3 Trials, summarized in Table 3, provided the pivotal efficacy for the applicant's proposed indication of treatment of type 2 diabetes.

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

In addition to evaluating glycemic efficacy in each Phase 3 trials, a pooled population of subjects with baseline eGFR of ≥30 to <60 mL/min/1.73m^2 from Phase 3 trials was used to evaluate glycemic response in subjects with moderate renal impairment. Most Phase 3 trials only included subjects with eGFR of ≥55 mL/min/1.73m^2 except for DIA3004 (eGFR of ≥30 to <50 mL/min/1.73m^2) and DIA3008 (eGFR of ≥30 mL/min/1.73m^2). Subjects with eGFR ≥50 mL/min/1.73m^2 were eligible for trial in DIS3005 and DIA3010.

The applicant also pooled population from the following placebo-controlled studies to conduct subgroup analyses: DIA3005 Main Study, DIA3006 (excluding sitagliptin group), DIA3008 SU substudy (Population 1), DIA3002, DIA3012, and DIA3008 Insulin substudy (Population 2). At my request, the FDA statistician, Dr. Wei Liu, conducted analysis of another pooled dataset, which included all the applicant's pool and trials DIA3004 and DIA3010, to further assess the glycemic efficacy by baseline age.

6.1.2 Demographics

The baseline demographic, anthropometric, and diabetic characteristics for each Phase 3 trial are summarized in Table 7, Table 8, and Table 9; the data shows the demographic characteristics combining all treatment groups within each Phase 3 trial. Baseline characteristics between treatment groups within each trial were balanced (data not shown here; see Dr. Wei's statistical review for details of baseline characteristics for each treatment group for each Phase 3 trial).

The median age of subjects in most Phase 3 trials was 55 to 60 years of age, and was older in subjects in DIA3004 (Moderate Renal Impairment Study), DIA3008 (Cardiovascular Safety Study), and DIA3010 (Older Adults Study), which was anticipated based on the study entry criteria. Whites represented the most common racial group in all studies. Participation of Hispanics ranged from 7 to 30%, and Asians were modestly represented in the canagliflozin trials. African-American subjects were underrepresented in the canagliflozin program, with most Phase 3 trials having <10% of total subjects.

A large proportion of subjects were overweight and the majority of subjects were obese (baseline BMI ≥30 kg/m^2). There were slightly more obese subjects in the add-on to metformin and sulfonylurea trial (DIA3002) and in the add-on to basal insulin trial (DIA3008 Insulin substudy).

The mean baseline HbA1c ranged from 7.7 to 8.4%, and varied as expected by the inclusion criteria. Subjects in the monotherapy trial (DIA3005) had the shortest diabetes duration (median 3 years) and subjects in DIA3004 and DIA3008 had the longest duration of diabetes (median 15 years). Baseline estimated GFR (eGFR) was reflective of diabetes duration and subject median age. The mean baseline eGFR was lower in DIA3004 and DIA3008 compared to the other Phase 3 trials as per entry criteria.

Table 7: Baseline Demographic Characteristics by Phase 3 Trial

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

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

Table 8: Baseline Anthropometric Characteristics by Phase 3 Trial

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

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

Table 9: Baseline Diabetes Characteristics by Phase 3 Trial

Characteristic	Monotherapy	Dual Therapy			Triple Therapy			Add-on to Insulin	Special Populations	
	DIA3005	DIA3006 Add-on to Metformin	DIA3009 Add-on to Metformin	DIA3008 SU Substudy[a]	DIA3002 Add-on to Metformin + SU	DIA3015 Add-on to Metformin + SU	DIA3012 Add-on to Metformin + PIO	DIA3008 Substudy[b]	DIA3004 Renal Impairment	DIA3010 Older Adults
Baseline HbA_{1c} (%)										
N	584	1283	1450	127	469	755	342	1716	269	714
Mean (SD)	8.0 (0.97)	7.9 (0.90)	7.8 (0.79)	8.4 (1.00)	8.1 (0.92)	8.1 (0.91)	7.9 (0.96)	8.3 (0.90)	8.0 (0.87)	7.7 (0.78)
Category, n (%)										
<7.0%	68 (11.6)	161 (12.5)	195 (13.4)	3 (2.4)	33 (7.0)	64 (8.5)	43 (12.6)	59 (3.4)	29 (10.8)	108 (15.1)
7 - <8%	242 (41.4)	536 (41.7)	683 (47.1)	53 (41.7)	193 (41.2)	295 (39.1)	148 (43.3)	629 (36.6)	110 (40.9)	350 (49.0)
8 - <9%	177 (30.3)	402 (31.3)	441 (30.4)	33 (26.0)	152 (32.4)	247 (32.7)	91 (26.6)	642 (37.4)	94 (34.9)	202 (28.3)
9 - ≤10%	80 (13.7)	161 (12.5)	125 (8.6)	28 (22.0)	78 (16.6)	133 (17.6)	52 (15.2)	318 (18.5)	36 (13.4)[c]	53 (7.4)
>10%	17 (2.9)	23 (1.8)	6 (0.4)	10 (7.9)	13 (2.8)	16 (2.1)	8 (2.3)	68 (4.0)		1 (0.1)
Baseline FPG (mmol/L)										
N	583	1282	1450	126	469	755	342	1713	268	714
Mean (SD)	9.5 (2.31)	9.4 (2.32)	9.2 (2.06)	10.0 (2.55)	9.5 (2.20)	9.3 (2.56)	9.2 (2.22)	9.4 (2.78)	9.1 (2.75)	8.7 (2.12)
Duration of diabetes (years)										
N	584	1284	1450	127	469	755	342	1718	269	714
Mean (SD)	4.3 (4.40)	6.9 (5.35)	6.6 (5.33)	10.2 (6.37)	9.6 (6.26)	9.6 (6.16)	10.6 (7.00)	16.6 (7.49)	16.3 (8.52)	11.7 (7.45)
Median	3.0	5.7	5.0	9.0	8.6	8.0	9.7	15.0	15.0	10.0
Baseline eGFR-(mL/min/1.73m^2)										
N	584	1284	1449	125	469	755	342	1716	269	714
Mean (SD)	87.1 (20.28)	88.6 (18.47)	90.2 (18.74)	69.3 (18.55)	89.4 (19.65)	87.5 (19.14)	86.4 (18.59)	74.9 (19.02)	39.4 (6.88)	77.5 (16.57)
Median	85.0	87.0	88.2	69.0	88.0	86.0	84.0	74.0	39.0	76.0
Range	(38,227)	(44,169)	(33,181)	(32,116)	(26,163)	(50.0;164.0)	(48,144)	(27,159)	(24,61)	(37,153)
Category, n (%)										
<60	32 (5.5)	40 (3.1)	38 (2.6)	44 (35.2)	15 (3.2)	41 (5.4)	25 (7.3)	348 (20.3)	268 (99.6)	94 (13.2)
60 - <90	324 (55.5)	665 (51.8)	715 (49.3)	65 (51.2)	235 (50.1)	382 (50.6)	184 (53.8)	1014 (59.0)	1 (0.4)	456 (63.9)
≥90	228 (39.0)	579 (45.1)	696 (48.0)	16 (12.6)	219 (46.7)	332 (44.0)	133 (38.9)	354 (20.6)		164 (23.0)
Subjects with microvascular complications										
N	584	1284	1450	127	469	755	342	1718	269	714
n (%)	40 (6.8)	286 (22.3)	269 (18.6)	55 (43.3)	124 (26.4)	251 (33.2)	66 (19.3)	1026 (59.7)	216 (80.3)	212 (29.7)
Baseline SBP (mmHg)										
N	584	1284	1450	127	469	755	342	1718	269	714
Mean (SD)	127.7 (12.95)	128.2 (12.99)	129.8 (13.22)	136.2 (12.93)	130.5 (13.52)	130.7 (13.57)	127.2 (12.21)	137.8 (16.65)	134.9 (14.01)	131.1 (13.32)
Baseline TG (mmol/L)										
N	584	1284	1449	127	469	755	342	1715	269	714
Mean (SD)	2.09 (1.236)	2.09 (1.395)	2.05 (1.611)	2.00 (1.061)	2.22 (1.471)	1.98 (1.347)	1.64 (1.064)	1.96 (1.421)	1.98 (1.049)	1.76 (1.148)

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

6.1.3 Subject Disposition

Across the Phase 3 clinical trials, a total of 7803 subjects were randomized and received at least one dose of study drug (mITT analysis set); from DIA3008, only those subjects who participated in the insulin and sulfonylurea sub-studies are included. Of 7803 subjects receiving study drug, 4994 subjects were treated with canagliflozin (2302 subjects with 100 mg and 2692 subjects with 300 mg), 1583 subjects were treated with placebo, and 1226 subjects were treated with active comparator (744 with sitagliptin and 482 with glimepiride). Table 10 presents mITT population for each Phase 3 trial.

Table 10: Number of Subjects in Modified Intent-to-Treat (mITT) Analysis Set by Phase 3 Trial

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

[a] Data for DIA3008 SU substudy presented for Population 1 (subjects on protocol-specified doses of SU monotherapy regardless of stratification).
[b] Data for DIA3008 Insulin substudy presented for Population 2 (subjects receiving insulin dose ≥30 IU/day).
Key: CANA = canagliflozin, mITT = modified Intent-to-Treat, PIO = pioglitazone, SU = sulfonylurea.

Source: ISE, Table 18

The overall mean duration of subject exposure before rescue was slightly greater in the canagliflozin groups compared to placebo for each Phase 3 trials, as shown in Table 11, except for DIA3008 SU substudy.

Table 11: Duration of Exposure to Study Drug Prior to Rescue by Phase 3 Trial (mITT)

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

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

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

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

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

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

Source: ISE, Table 19

The completion rates for canagliflozin treatment groups for trials with a primary endpoint at Week 26 ranged from 80 to 90% in DIA3005, DIA3006, DIA3002, DIA3012, DIA3004, and DIA3010, which was higher than the corresponding completion rates in the placebo group which ranged from 62 to 72%, as shown in Table 12. The lower completion rates in the placebo group may be due to lack of efficacy, as reflected by a higher proportion of subjects receiving placebo needing glycemic rescue compared to canagliflozin, which would not be unexpected.

Discontinuations due to adverse event were either balanced or slightly higher with canagliflozin compared to placebo across Phase 3 trials.

In two active-comparator trials with the primary assessment at Week 52 (DIA3009 and DIA3015), the completion rates for canagliflozin groups ranged from 67 to 76%; the completion rate was higher with canagliflozin compared to the active comparator (glimepiride and sitagliptin). In DIA3015, rescue therapy was not allowed and subjects who met pre-specified glycemic levels were withdrawn from the trial, which contributed to the lower completion rate in DIA3015 compared to other Phase 3 trial: 10.6% (40/377) and 22.5% (85/378) of subjects in canagliflozin 300 mg and sitagliptin 100 mg group respectively discontinued due to meeting glycemic withdrawal criteria.

Table 12: Subject Disposition (N[%]) of All Randomized Subjects in Phase 3 Trials

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

SU=sulfonylurea;*Population 1
Source: Tables 2 and 3 from Clinical Study Report for each trial

6.1.4 Analysis of Primary Endpoint(s)

The primary efficacy endpoint in all nine Phase 3 trials was the change in HbA1c from baseline to the end of study, which is summarized in Table 13. The mean baseline HbA1c ranged from 7.76 to 8.49% (except for DIA3005 High Glycemic substudy), with the a slightly higher baseline HbA1c observed in two substudies of DIA3008 (Insulin and Sulfonylurea substudy).

Except for two active-comparator trials DIA3009 and DIA3015, other placebo-controlled Phase 3 trials were superiority comparisons of two doses of canagliflozin to placebo. In the 7 placebo-controlled, pivotal Phase 3 trials of canagliflozin, both the 100 mg and 300 mg doses, achieved statistically significant LS mean reductions in HbA1c from baseline to Week 26 (or Week 18 in 3008 substudies) compared to placebo, regardless of add-on therapy. The placebo-adjusted mean reductions in HbA1c ranged from 0.29 to 0.91% with canagliflozin 100 mg and 0.42 to 1.16% with canagliflozin 300 mg.

Not surprisingly, the greatest efficacy was observed in DIA3005 (Monotherapy), since subjects in this trial were relatively healthy diabetic subjects compared to other trials, enrolling T2DM subjects who had inadequate glycemic control only with diet and exercise. A modest efficacy was observed in DIA3004 compared to other Phase 3 trials, with placebo-subtracted mean reductions of -0.3% and -0.4% with 100 mg and 300 mg doses respectively. DIA3004 included subjects with moderate renal impairment with baseline eGFR of ≥30 to <50 mL/min/1.73m^2. As discussed in section 2.1, the efficacy results of canagliflozin in a pooled dataset with moderate renal impairment with eGFR criteria of ≥30 to <60 mL/min/1.73m^2 was evaluated and is discussed further in section 6.1.10.

In the active-comparator (glimepiride) trial DIA3009 (add-on to metformin), the LS mean change in HbA1c from baseline at Week 52 was -0.82 and -0.93% with canagliflozin 100 mg and 300 mg respectively compared to -0.82% with glimepiride. The observed treatment difference was -0.01 for canagliflozin 100 mg (95% CI:-0.11,0.09) and -0.12% for canagliflozin 300 mg (95% CI:-0.22,-0.02) when compared to glimepiride. In the active-comparator (sitagliptin) trial of DIA3015 (add-on to metformin and SU) which only studied canagliflozin 300 mg dose, the LS mean change in HbA1c from baseline at Week 52 was -1.03% with canagliflozin 300 mg and -0.66% with sitagliptin. In both active-controlled non-inferiority trial, the non-inferiority (NI) margin was 0.3% and the upper limits of both 95% CIs for between-group difference were below the NI margin in all canagliflozin groups, meeting the pre-specified criteria of non-inferiority.

In protocol-specified assessments (to be done after establishing noninferiority), canagliflozin 300 mg was also shown to be statistically superior to glimepiride with treatment difference of -0.12% ($p=0.016$) and sitagliptin with treatment difference of -0.37% ($p<0.001$) in DIA3009 and DIA3015 respectively.

According to the statistical reviewer, Dr. Wei Lu, supportive analyses using mixed model repeated measures (MMRM) was very similar to the primary analysis using the LOCF method presented in Table 13.

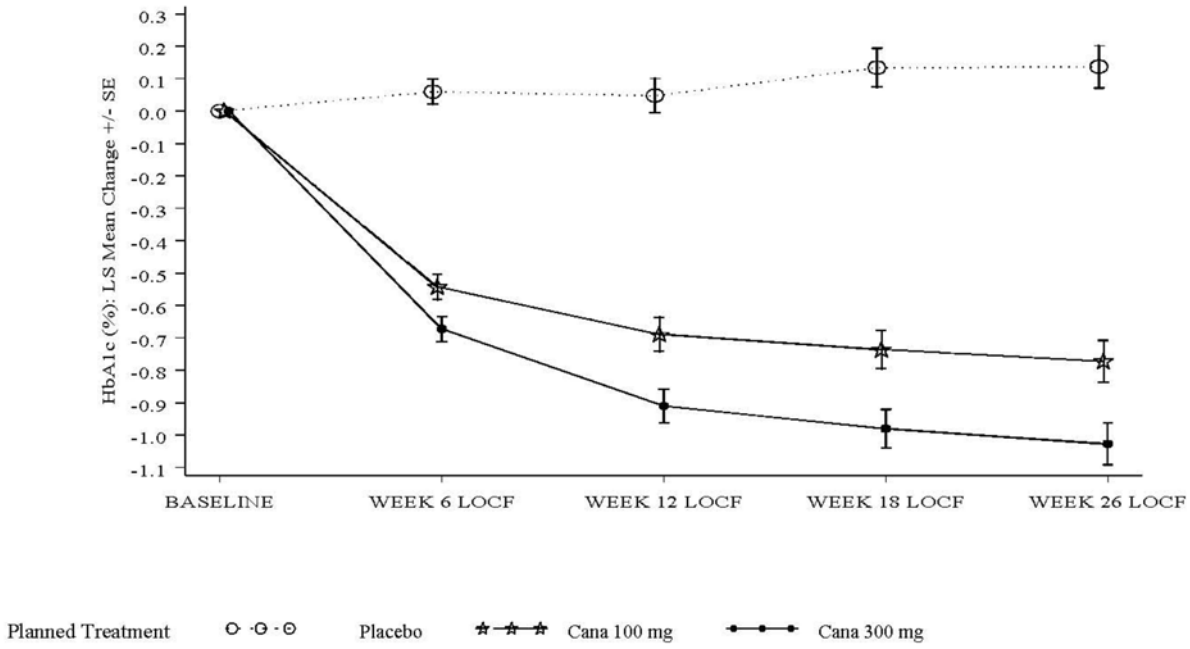
Table 13: Summary of Change in HbA1c From Baseline to Endpoint - mITT (LOCF)

Study (Weeks)	Treatment Arm	N	Baseline Mean ± SE	LS Mean Change ± SE	LS mean difference (95% CI)	Diff* bw Cana	p-value
Monotherapy							
DIA3005 (26) Main study	Cana 300 mg	193	8.01 ± 0.07	-1.03 ± 0.06	-1.16 (-1.34, -0.99)	0.25	<.0001
	Cana 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	Cana 300 mg	43	10.62 ± 0.15	-2.56±0.22		0.43	
	Cana 100 mg	46	10.59 ± 0.13	-2.13±0.22			
Add-on to AHA Monotherapy							
DIA3006 (26) Add-on to metformin	Cana 300 mg	360	7.95 ± 0.05	-0.94 ± 0.04	-0.77(-0.91,-0.64)	0.15	<.0001
	Cana 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) Add-on to metform	Cana 300 mg	474	7.79 ± 0.04	-0.93 ± 0.04	-0.12 (-0.22, -0.02)	0.11	0.0158
	Cana 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 AHA Therapy							
DIA3002 (26) Add on to metformin+SU	Cana 300 mg	152	8.13 ± 0.08	-1.06 ± 0.08	-0.92 (-1.11, -0.73)	0.21	<.0001
	Cana 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) Add on to metformin+PIO	Cana 300 mg	112	7.84 ± 0.09	-1.03 ± 0.07	-0.76 (-0.95, -0.57)	0.14	<.0001
	Cana 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) Add on to metformin+SU	Cana 300 mg	365	8.13 ± 0.05	-0.66 ± 0.05	-0.37 (-0.50, -0.25)	NA	<.0001
	Sitagliptin	374	8.12 ± 0.05	-1.03 ± 0.05			
Special Population							
DIA3010 (26) Older Adults	Cana 300 mg	229	7.69 ± 0.05	-0.73 ± 0.06	-0.70 (-0.84, -0.57)	0.13	<.0001
	Cana 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 Impairment	Cana 300 mg	89	7.97 ± 0.09	-0.44 ± 0.09	-0.42 (-0.65, -0.19)	0.12	0.0004
	Cana 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) SU substudy	Cana 300 mg	39	8.28 ± 0.16	-0.79 ± 0.15	-0.83 (-1.24, -0.42)	0.09	0.0001
	Cana 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	Cana 300 mg	572	8.27 ± 0.04	-0.72 ± 0.03	-0.74 (-0.82, -0.65)	0.09	<.0001
	Cana 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			

*LS mean difference between canagliflozin 300 and 100 mg; SU=sulfonylurea; PIO=pioglitazone;
Source: EMDAC Briefing, Statistical Review, Table 2

Review of plot of the LS mean change from baseline in HbA1c over time in mITT analysis set for Phase 3 trials showed that there was a rapid decrease in HbA1c through 12-18 weeks with canagliflozin, after which the HbA1c values remained stable until the primary assessment timepoint. The plot for DIA3005 is shown below as an example (Figure 11).

Figure 11: LS Mean Change in HbA1c From Baseline Over Time in DIA3005 (Main Study) - LOCF



Source: CSR DIA3005, Figure 4

Canagliflozin showed a modest dose response in HbA1c reduction, and the additional LS mean HbA1c reduction with 300 mg compared to 100 mg ranged 0.09 to 0.26% across placebo-controlled Phase 3 trials. The most significant HbA1c change between two canagliflozin doses was seen in DIA3005, Monotherapy trial, with 300 mg dose showing an additional 0.26% LS mean HbA1c reduction compared to 100 mg dose. In trials where canagliflozin was added to background metformin (DIA3006, DIA3009), 300 mg dose led to an additional 0.11 and 0.15% LS mean HbA1c reduction compared to 100 mg dose. In trials where canagliflozin was added to dual combination AHA therapy, 300 mg dose led to additional 0.21% (DIA3002; add-on to metformin+SU) and 0.14% (DIA3012; add-on to metformin+pioglitazone) LS mean HbA1c reduction compared to 100 mg dose. In special population trials DIA3004 (Moderate Renal Impairment) and DIA3010 (Older Adults), additional LS mean HbA1c reduction with canagliflozin 300 mg was 0.12 and 0.13 % respectively compared to 100 mg dose. DIA3008 substudies where canagliflozin was added to insulin and SU showed the least incremental HbA1c change; the incremental HbA1c reduction was 0.09% with 300 mg compared to 100 mg dose.

Please also refer to Dr. Wei Lu's statistical review.

6.1.5 Analysis of Secondary Endpoints(s)

The applicant seeks labeling references to the following major secondary endpoints: changes in fasting plasma glucose (FPG), 2-hour postprandial glucose (2-PPG), proportion of subjects achieving HbA1c <7%, body weight, and systolic blood pressure. Therefore, this section will focus on these secondary endpoints.

Fasting Plasma Glucose

The change in FPG from baseline to the primary endpoint was a major secondary glycemic efficacy endpoint for all Phase 3 trials except for DIA3009, and are summarized for each trial in Table 14.

Except for canagliflozin 300 mg group in DIA3004, statistically significant reductions in FPG were observed with canagliflozin by Week 26 (or 18 in 3008 substudies) compared to placebo in all placebo-controlled trials, and this appeared to be dose-dependent.

For DIA3004, the hierarchial testing sequence was prespecifiedto first examine FPG lowering for canagliflozin 300 mg, then for 100 mg. Based on this, the 300 mg dose of canagliflozin did not reach statistical significance in FPG lowering (p=0.07), and the subsequent statistical testing was considered nominal. Similarly, DIA3008 had prespecified hierarchial testing sequence, to first examine HbA1c lowering with 300 mg then 100 mg, then body weight reduction, FPG-lowering, proportion of HbA1c <7%, and SBP lowering. With canagliflozin 100 mg, weight loss did not reach statistical significance (p=0.557), and therefore subsequent p values are considered nominal (p<0.05).

Consistent with attenuation of HbA1c reduction, subjects in DIA3004 had smallest reduction in the LS mean FPG with canagliflozin relative to other placebo-controlled Phase 3 trials.

In the DIA3005 High Glycemic substudy, the LS mean reduction of FPG from baseline to Week 26 was 86 mg/dL and 82 mg/dL with canagliflozin 300 mg and 100 mg respectively.

Table 14: Summary of Change in Fasting Plasma Glucose (mg/dL) From Baseline to Endpoint - 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 AHA Monotherapy						
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 metform	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 AHA 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		

SU=sulfonylurea; PIO=pioglitazone; *p values are nominal based on testing sequence
Source: ISE, Table 25

2-hour Postprandial Glucose

The change in 2-hour PPG from baseline to the primary endpoint was a major secondary efficacy endpoint in DIA3005 and DIA3006. A Mixed Meal Tolerance Test was done in all randomized subjects at the primary endpoint timepoint, Week 26, and the results of this analysis are summarized in Table 15. In both DIA3005 and DIA3006, a statistically significant reduction in 2-hour PPG was seen with canagliflozin by Week 26 compared to placebo, and this appeared to be dose-dependent.

Table 15: Summary of Change in 2-hour Postprandial Glucose From Baseline to Endpoint in DIA3005 and DIA3006 - LOCF

Study (Weeks)	Treatment Arm	N	Baseline Mean (SD)	LS Mean Change ± SE	LS mean difference (95% CI)	p-value
Monotherapy						
DIA3005 (26)	Cana 300 mg	157	254 (72)	-59 ± 4	-64 (-75, -53)	<0.001
Main study	Cana 100 mg	154	250 (73)	-43 ± 4	-48 (-59, -37)	<0.001
	Placebo	126	229 (62)	5 ± 4		
Add-on to AHA Monotherapy						
DIA3006 (26)	Cana 300 mg	288	262 (74)	-57 ± 3	-47 (-58, -36)	<0.001
Add-on to	Cana 100 mg	298	258 (68)	-48 ± 3	-38 (-49, -27)	<0.001
metformin	Placebo	129	249 (65)	-10 ± 5		

Source: ISE, DEFF11X_SS

Proportion of subjects achieving HbA1c <7%

The proportion of subjects in each treatment group achieving HbA1c <7% by the primary endpoint for each Phase 3 trial are summarized in Table 16. Except for DIA3009, this was a major secondary efficacy endpoint. All canagliflozin treatment groups, except for canagliflozin groups in DIA3004 and 100 mg group in DIA3008 SU substudy due to pre-specified sequential testing, had a statistically significant number of canagliflozin subjects who achieved HbA1c level of <7% compared to placebo ($p<0.05$).

Also, significantly more subjects in the canagliflozin 300 mg group achieved <7% target than canagliflozin 100 mg. In the Monotherapy trial, DIA3005, an additional 17.8% of subjects achieved ADA goal of <7% with 300 mg compared to 100 mg dose of canagliflozin. In DIA3006, DIA3002, and DIA3012, where canagliflozin was add-on to metformin (with or without other AHA), an additional 12.3 to 17.4% subjects achieved ADA goal of <7% with 300 mg compared to 100 mg dose of canagliflozin. In DIA3010, an additional 10.8% achieved HbA1c <7% with 300 mg compared to 100 mg.

This difference between higher and lower dose of canagliflozin who reach HbA1c <7% was slightly less in DIA3008 substudies (8.3% in SU substudy and 4.9% in insulin substudy), although both doses of canagliflozin was statistically significant compared to placebo in DIA3008 insulin substudy. In DIA3008 SU substudy, due to pre-specified sequential statistical

testing strategy, comparison of canagliflozin 100 mg with placebo group was considered nominal (i.e., not controlled for multiplicity) because statistical significance for the canagliflozin 100 mg group relative to placebo was not shown for weight loss (see following Body Weight section).

In DIA3004, comparison of canagliflozin groups to placebo was also nominal because FPG-lowering was not demonstrated by statistical testing, and no further statistical hypothesis testing could be done because of pre-specified sequential testing. In DIA3004, consistent with attenuated HbA1c lowering efficacy of canagliflozin observed in this population of subjects with moderate renal impairment, the placebo-subtracted proportion of subjects who achieve HbA1c <7% was 10% with 100 mg and 15% with 300 mg, which was less than what was seen in other placebo-controlled studies. The p-value for comparison of canagliflozin 100 mg to placebo was 0.227.

Table 16: Proportion of Subjects Achieving HbA1c <7% at Primary Assessment Timepoint - LOCF: Study-by-Study Comparison

Study (Weeks)	Treatment Arm	N	% achieving target <7%	%Diff (minus comparator)	95% CI	p-value
Monotherapy						
DIA3005 (26)	Cana 300 mg	193	62.4	41.7	32.3;51.2	<0.001
Main study	Cana 100 mg	191	44.5	23.9	14.2;33.5	<0.001
	Placebo	189	20.6			
Add-on to AHA Monotherapy						
DIA3006 (26)	Cana 300 mg	360	57.8	27.9	19.2;36.8	<0.001
Add-on to	Cana 100 mg	365	45.5	15.6	24.5;6.8	<0.001
metformin	Placebo	181	29.8			
DIA3009 (52)	Cana 300 mg	474	60.1	4.3	-2.2;10.8	
Add-on to metform	Cana 100 mg	478	53.6	-2.3	-8.8;4.3	
	Glimepiride	473	55.8			
Add-on to Dual Combination AHA Therapy						
DIA3002 (26)	Cana 300 mg	152	56.6	38.6	27.9;49.2	<0.001
Add on to	Cana 100 mg	155	43.2	25.2	14.6;35.8	<0.001
metformin+SU	Placebo	150	18.0			
DIA3012 (26)	Cana 300 mg	112	64.3	31.8	18.6;45.1	<0.001
Add on to	Cana 100 mg	113	46.9	14.4	1.0;27.9	0.007
metformin+PIO	Placebo	114	32.5			
DIA3015 (52)	Cana 300 mg	365	47.6	12.3	4.9;19.6	
Add on to	Sitagliptin	374	35.3			
metformin+SU						
Special Population						
DIA3010 (26)	Cana 300 mg	229	58.5	30.5	21.5;39.5	<0.001
Older Adults	Cana 100 mg	239	47.7	19.7	10.7;28.7	<0.001
	Placebo	232	28.0			
DIA3004 (26)	Cana 300 mg	89	32.6	15.3	1.6;29.0	0.017
Moderate Renal	Cana 100 mg	88	27.3	10.0	-3.3;23.4	0.227
Impairment	Placebo	87	17.2			
DIA3008 (18)	Cana 300 mg	39	33.3	28.3	9.5;47.1	0.004
SU substudy	Cana 100 mg	40	25.0	20.0	2.5;37.5	0.014
	Placebo	40	5.0			
DIA3008 (18)	Cana 300 mg	572	24.7	17.0	12.6;21.4	<0.001
Insulin substudy	Cana 100 mg	551	19.8	12.1	7.8;16.3	<0.001
	Placebo	545	7.7			

SU=sulfonylurea; PIO=pioglitazone;
Source: ISE, Table 24

In the DIA3005 High Glycemic substudy, where subjects were required to have a baseline HbA1c >10% to enroll, 17.4% of subjects in 300 mg group and 11.6% of subjects in 100 mg achieved HbA1c <7% by 26 weeks. There was no placebo control in this trial.

Body Weight

The percent change in body weight from baseline to the primary endpoint was a major secondary endpoint that was associated with hypothesis testing in each Phase 3 trials, and the results are summarized in Table 17 below.

There was a dose-dependent and significant placebo-subtracted LS mean percent reduction in the body weight from baseline to the primary endpoint, except with the 100 mg dose of canagliflozin in DIA3008 SU substudy where it did not reach statistical significance. The placebo-subtracted LS mean percent body weight reduction with 300 mg dose of canagliflozin was also modest (-1.8%) in this substudy compared to other Phase 3 trials. Also, in another trial where SU was a background AHA therapy with metformin (DIA3002), although the change in percent body weight was statistically significant, the observed changes were modest compared to the other Phase 3 trials where SU was not a background AHA therapy.

Reviewer's comment: Treatment with sulfonylurea leads to weight gain. The change in body weight in trials where canagliflozin was added on to background SU (DIA3008 SU substudy, DIA3002) suggest that weight gain associated with SU may attenuate the weight reduction with canagliflozin.

In addition, body weight reduction in subjects with moderate renal impairment (DIA3004) was also modest; the placebo-subtracted LS mean % body weight reduction was 1.6% with 100 mg and 1.8% with 300 mg dose of canagliflozin.

In the remaining placebo-controlled trials, the placebo-subtracted LS mean reduction of percent body weight with canagliflozin ranged from 1.9 to 2.7% with 100 mg and 1.8 to 3.8% with 300 mg dose.

Table 17: Summary of Percent Change in Body Weight From Baseline to Endpoint - mITT, LOCF

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

SU=sulfonylurea; PIO=pioglitazone; *p values are nominal based on testing sequence
Source: ISE, Table 29

Blood Pressure

The change in systolic blood pressure (SBP) from baseline to primary endpoint was a major secondary efficacy endpoint in each of Phase 3 trials, and the results of this analyses using the LOCF approach are summarized in Table 18.

There was a dose-dependent and statistically significant placebo-subtracted LS mean reduction in systolic blood pressure (SBP) from baseline to the primary endpoint, except for trials where canagliflozin was studied as an add to SU (DIS3002 and DIA3008 SU substudy) where the changes in blood pressure did not reach statistical significance with both doses of canagliflozin. In these trials, the placebo-subtracted effect sizes with canagliflozin was smaller in these two trials because the placebo group had a larger reduction in SBP in comparison to other placebo-controlled trials.

In the remaining placebo-controlled trials, the placebo-subtracted LS mean reduction in SBP ranged from 2.6 to 5.7 mmHg and 3.5 to 7.9 mmHg with 100 mg and 300 mg respectively.

Reviewer's comment: This is a clinically relevant and significant blood pressure reduction, as studies have shown that a BP reduction of 10 mmHg systolic would result in 22% reduction in coronary events and 41% reduction in stroke.[2] In addition, observational data have demonstrated that patients with both hypertension and diabetes have about 2-fold greater risk of developing cardiovascular disease than patients with hypertension without diabetes.[3] However, recent evidence[4] have shown that intensive lowering of blood pressure did not translate into increased cardiovascular benefit and was associated with serious adverse events related to antihypertensive treatment. Therefore, the clinical relevance of this blood pressure lowering effect with canagliflozin should be studied in a cardiovascular outcome trial, especially given the effect of canagliflozin on other cardiovascular risk factors (e.g., lipids).

[2] Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomized trials in the context of expectations from prospective epidemiological studies. BMJ, 20009;338.b1665.
[3] Arauz-Pacheco C, Parrott MA, Raskin P. Hypertension management in adults with diabetes. Diabetes Care 2004; 27 Suppl 1: S65-7.
[4] Cooper-DeHoff RM, Gong Y, Hnadberg EM, et al. Tight blood pressure control and cardiovascular outcomes among hypertensive patients with diabetes and coronary artery disease. JAMA 2010;304:61--68.

Table 18: Summary of Change in Systolic Blood Pressure (mmHg) From Baseline to Endpoint - LOCF, mITT

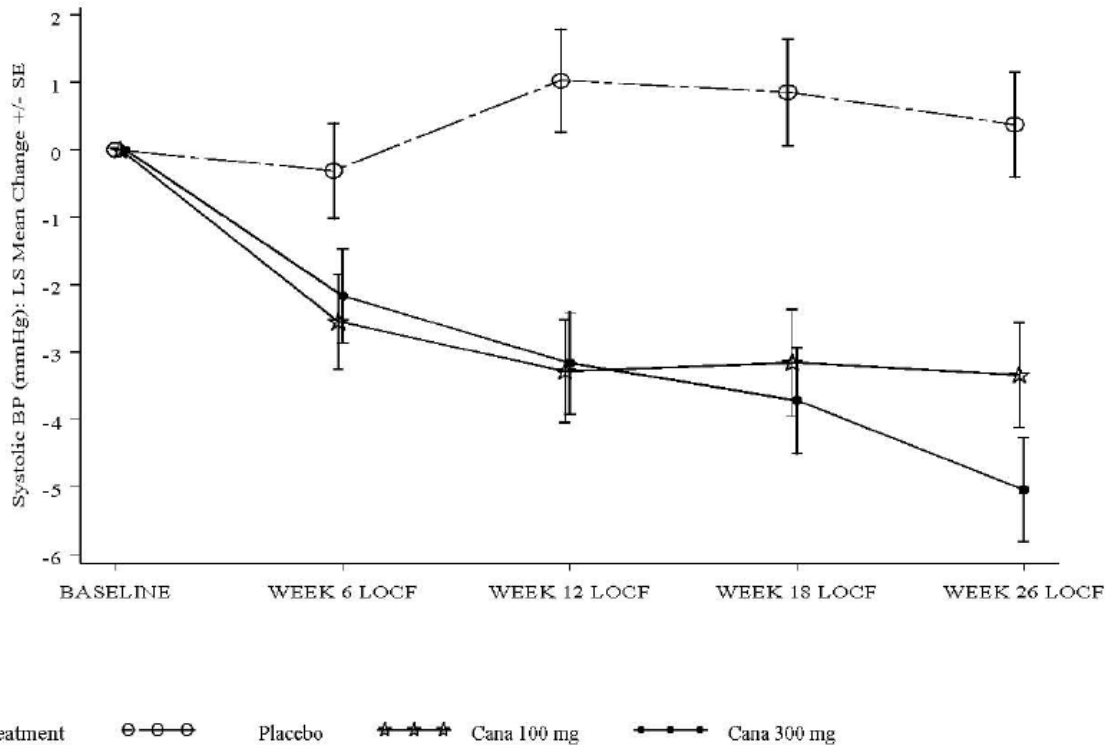
Study (Weeks)	Treatment Arm	N	Baseline Mean (SD)	Change from baseline ± SE	LS mean difference (95% CI)	p-value
Monotherapy						
DIA3005 (26)	Cana 300 mg	195	128.5 (12.7)	-5.0 ± 0.8	-5.4 (-7.6, -3.3)	<0.001
Main study	Cana 100 mg	192	126.7 (12.5)	-3.3 ± 0.8	-3.7 (-5.9, -1.6)	<0.001
	Placebo	190	127.7 (13.7)	0.4 ± 0.8		
Add-on to AHA Monotherapy						
DIA3006 (26)	Cana 300 mg	360	128.7 (13.0)	-5.1 ± 0.6	-6.6 (-8.5, -4.7)	<0.001
Add-on to	Cana 100 mg	365	128.0 (12.7)	-3.8 ± 0.6	-5.4 (-7.3, -3.4)	<0.001
metformin	Placebo	181	128.1 (12.7)	-1.5 ± 0.8		
DIA3009 (52)	Cana 300 mg	480	130.0 (13.8)	-4.6 ± 0.6	-4.8 (-6.2, -3.4)	
Add-on to	Cana 100 mg	479	130.0 (12.4)	-3.3 ± 0.6	-3.5 (-4.9, -2.1)	
metform	Glimepiride	478	129.5 (13.5)	0.20 ± 0.6		
Add-on to Dual Combination AHA Therapy						
DIA3002 (26)	Cana 300 mg	154	130.8 (12.8)	-4.3 ± 1.0	-1.6 (-4.1, -0.9)	0.201
Add on to	Cana 100 mg	156	130.4 (13.5)	-4.9 ± 1.0	-2.2 (-4.7, 0.2)	0.077
metformin+SU	Placebo	150	130.1 (13.7)	-2.7 ± 1.0		
DIA3012 (26)	Cana 300 mg	112	126.7 (12.0)	-4.7 ± 1.0	-3.5 (-6.3, -0.6)	0.016
Add on to	Cana 100 mg	113	126.4 (12.3)	-5.3 ± 1.0	-4.1 (-6.9, -1.3)	0.005
metformin+PIO	Placebo	114	128.2 (12.3)	-1.2 ± 1.0		
DIA3015 (52)	Cana 300 mg	375	131.2 (13.2)	-5.1 ± 0.7	-5.9 (-7.6, -4.2)	<0.001
Add on to	Sitagliptin	367	130.1 (14.0)	0.9 ± 0.7		
metformin+SU						
Special Population						
DIA3010 (26)	Cana 300 mg	234	131.1 (14.6)	-6.9 ± 1.1	-7.9 (-10.1, -5.6)	<0.001
Older Adults	Cana 100 mg	240	130.6 (13.2)	-3.5 ± 1.0	-4.6 (-6.9, -2.4)	<0.001
	Placebo	234	131.4 (12.2)	1.1 ± 1.0		
DIA3004 (26)	Cana 300 mg	89	136.7 (15.0)	-6.4 ± 1.5	-6.1 (-9.9, -2.3)	0.002
Moderate Renal	Cana 100 mg	90	135.9 (13.1)	-6.1 ± 1.5	-5.7 (-9.5, -1.9)	0.003
Impairment	Placebo	88	132.1 (13.6)	-0.3 ± 1.5		
DIA3008 (18)	Cana 300 mg	39	133.5 (13.9)	-5.2 ± 2.4	-1.8 (-8.2, -4.7)	0.588
SU substudy	Cana 100 mg	40	138.0 (10.2)	-3.5 ± 2.3	-0.1 (-6.5, 6.2)	0.975
	Placebo	44	137.3 (13.4)	-3.4 ± 2.2		
DIA3008 (18)	Cana 300 mg	576	138.2 (16.8)	-6.9 ± 0.5	-4.4 (-5.8, -2.9)	<0.001
Insulin substudy	Cana 100 mg	559	137.0 (16.8)	-5.1 ± 0.5	-2.6 (-4.1, -1.1)	<0.001
	Placebo	551	138.2 (16.1)	-2.5 ± 0.5		

SU=sulfonylurea; PIO=pioglitazone; *p values are nominal based on testing sequence
Source: ISE, Table 34

Review of graphs for the LS mean change in SBP from baseline over time for Phase 3 trials showed that there was a nearly full decrease at the first study visit after being randomized, which was Week 6 for most Phase 3 trials. The SBP reduction thereafter was smaller in comparison.

The plot for DIA3005 is shown below as an example to demonstrate this change in SBP with canagliflozin (Figure 12).

Figure 12: LS Mean Change in Systolic Blood Pressure From Baseline Over Time (Main Study) - LOCF



Source: CSR DIA3005, Figure 13

6.1.6 Other Endpoints - Plasma Fasting Lipid

Changes in fasting triglycerides and HDL-C levels were also major secondary endpoints except for DIA3009 and DIA3004. The placebo-subtracted LS mean percent changes in fasting HDL-C and triglyerides for each Phase 3 trial are summarized in Table 19.

HDL-C

Overall, there was a mean percent increases in HDL-C with canagliflozin in Phase 3 trials, but this increase was not dose-dependent. The placebo-adjusted LS mean percent increase in HDL-C with both doses of canagliflozin was statistically significant in four of eight placebo-controlled Phase 3 trials (DIA3005, DIA3006, DIA3012, and DIA3010).

In active-controlled trials, DIA3009 and DIA3015, canagliflozin was also associated with larger LS mean percent increases compared to its comparators, glimepiride and sitagliptin respectively. In DIA3009, the LS mean percent change in HDL-C was 7.5% with 100 mg and 8.6% with 300 mg compared to 0.3% with glimepiride, resulting in treatment difference of 7.5% with 100 mg dose and 8.6% with 300 mg dose. In DIA3015, the LS mean percent change in HDL-C was 7.6% with canagliflozin 300 mg and 0.6% with sitagliptin, with treatment difference of 7.0 ($p<0.001$).

Table 19: Placebo-Subtracted LS Mean Percent Change of HDL-C (95% CI) from Baseline to Endpoint in Placebo-Controlled Phase 3 Trials - LOCF, mITT

Trial	HDL-C (mg/dL)	
	Cana 100	Cana 300
DIA3005 - Monotherapy	6.7 (2.9;10.6)	6.0 (2.2;9.9)
DIA3006 - Add-on to metformin	6.7 (3.6;9.7)	8.5 (5.4;11.5)
DIA3008 - Add-on to SU substudy	2.5 (-5.5;10.5)	0.8 (-7.2;8.8)
DIA3002 - Add-on to metformin+SU	2.5 (-0.9;5.9)	3.4 (-0.1;6.8)
DIA3012 - Add-on to metformin+pio	4.8 (1.2;8.5)	6.5 (2.8;10.2)
DIA3008 - Add-on to insulin substudy	0.9 (-1.3;3.0)	4.7 (2.5;6.9)
DIA3004- Moderate renal impairment	2.6 (-1.9;7.0)	1.4 (-3.0;5.8)
DIA3010 - Older adults	5.3 (2.6;7.9)	4.7 (2.0;7.4)

Source: ISS, DEFF08X_SS, DEFF10X_SS

Triglycerides

The LS mean change in fasting triglycerides from baseline to the primary endpoint in each Phase 3 trials are summarized in Table 20. The mean percent changes in triglycerides during treatment with canagliflozin was small, and there was no consistent trend (i.e., increase or decrease) in triglycerides with canagliflozin. The treatment difference of canagliflozin against placebo showed mean percent change decrease due to a general increase in percent change with placebo. In fact, the placebo-adjusted decrease in mean percent change of triglycerides with canagliflozin reached statistical significance in only one of eight placebo-controlled trials (DIA3012) because there was a large increase in the LS mean percent change (15.2%) of triglycerides in the placebo group.

Table 20: Change in Mean Triglycerides (mg/dL) From Baseline to Endpoint - LOCF

	Placebo	Cana 100	Cana 300	Sitagliptin	Glimepiride
DIA3005	171	183	183		
Baseline	196.9	172.9	174.4		
LS mean % change	7.8	2.5	-2.4		
Diff of LS mean		-5.3	-10.24		
p-value		0.267	0.034		
DIA3006	171	358	341	338	
Baseline	188.9	191.9	188.-	175.5	
LS mean % change	3.2	1.6	-1.4	1.0	
Diff of LS mean		-1.6	-4.7		
p-value		0.702	0.274		
DIA3009		465	461		466
Baseline		186.0	189.6		170.0
LS mean % change		-3.7	2.3		9.5
Diff of LS mean		-13.2	-7.2		
95% CI		-19.4;-7.0	-13.4;-1.0		
DIA3008 SU substudy	35	38	39		
Baseline	160.2	212.3	159.6		
LS mean % change	-0.3	-13.2	11.9		
Diff of LS mean		-12.9	12.2		
p-value		0.105	0.113		
DIA3002	134	145	142		
Baseline	198.4	187.5	199.5		
LS mean % change	11.6	5.4	8.5		
Diff of LS mean		-6.2	-3.1		
p-value		0.256	0.571		
DIA3012	105	108	109		
Baseline	143.9	146.7	143.8		
LS mean % change	15.2	3.2	-1.7		
Diff of LS mean		-12.1	-16.9		
p-value		0.034	0.003		
DIA3015			365	353	
Baseline			182.7	168.2	
LS mean % change			9.6	11.9	
Diff of LS mean			-2.3		
95% CI			-9.8;5.3		
DIA3008 Insulin Substudy	476	513	528		
Baseline	171.5	177.7	168.9		
LS mean % change	6.7	6.9	4.7		
Diff of LS mean		0.2	-2.0		

p-value		0.941	0.440		
DIA3004	75	82	85		
Baseline	179.4	164.9	189.3		
LS mean % change	7.9	6.2	11.9		
Diff of LS mean		-1.7	4.0		
p-value		0.779	0.518		
DIA3010	206	227	222		
Baseline	151.3	158.5	152.7		
LS mean % change	7.7	2.8	8.4		
Diff of LS mean		-4.8	0.7		
p-value		0.194	0.846		

Source: ISE, DEFF10X_SS, DEFF10X_SS_3015

During the clinical development of canagliflozin, an increase in LDL-C levels was noted, which is further discussed in section 7.3.12. Overall, placebo-subtracted LS mean percent increase of LDL-C ranged 2 to 7.9% with 100 mg and 4.6 to 12.2% with 300 mg of canagliflozin. Changes in other fasting lipid parameters were also discussed in section 7.3.12.

6.1.7 Subpopulations

A pooled population of subjects from the placebo-controlled Phase 3 trials was used to conduct subgroup analyses to assess glycemic efficacy and weight changes across subjects with different characteristics. The trials and subjects from each trial contributing to this pool is summarized in Table 21. The LOCF method from individual studies was used for these pooled subgroup analyses.

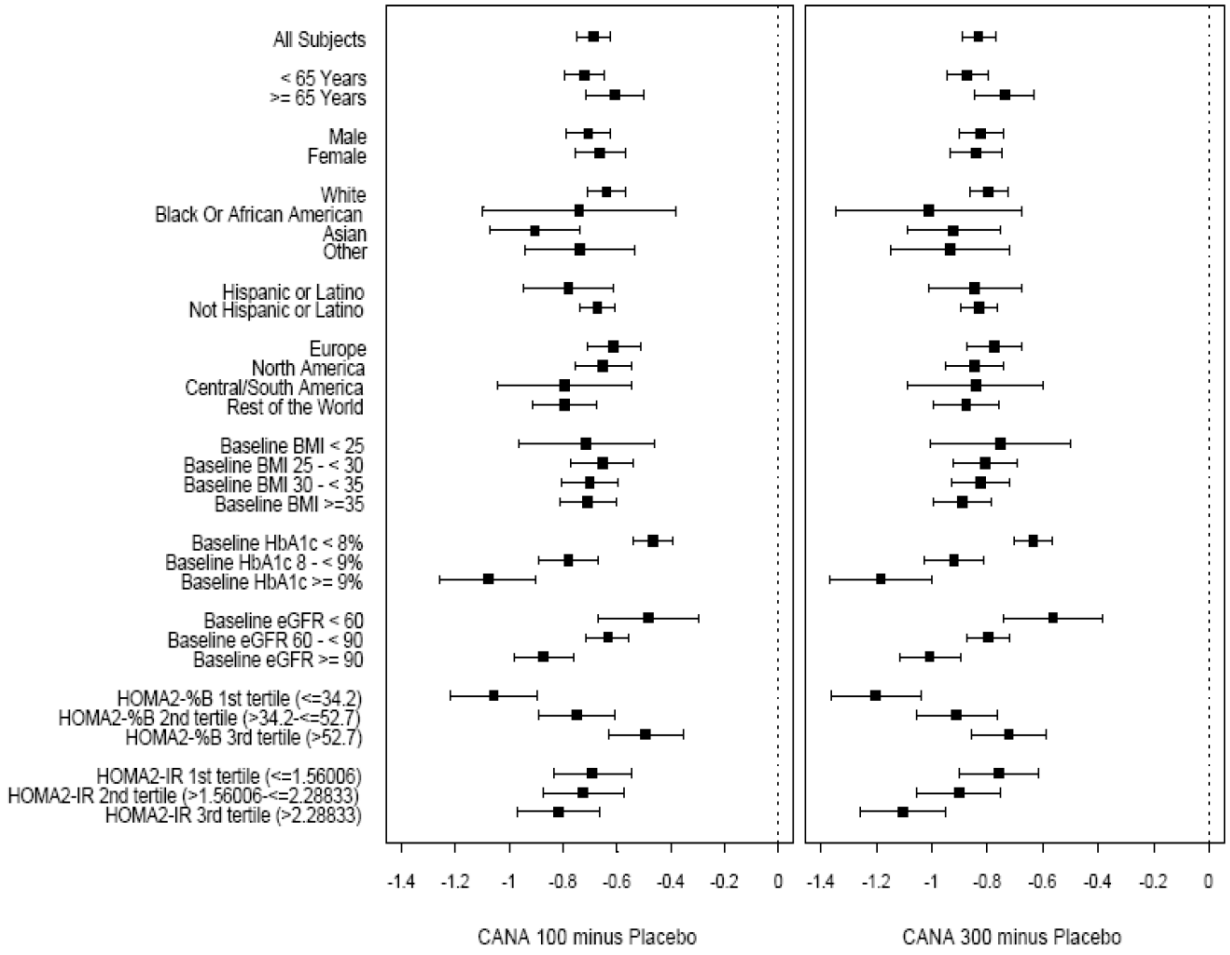
Table 21: Number of Subjects Contributing to Pooled Population of Placebo-Controlled Studies for Subgroup Analyses - mITT

Study Type/ Study ID	Timing of Primary Endpoint	Number of Subjects Contributing Data to Pooled Population			
		Placebo	CANA 100 mg	CANA 300 mg	Total
Monotherapy					
DIA3005 – Main Study	26 weeks	192	195	197	584
Dual therapy					
DIA3006 – Add-on to metformin	26 weeks	183	368	367	918
DIA3008 substudy – Add-on to SU	18 weeks	45	42	40	127
Triple therapy					
DIA3002 – Add-on to metformin + SU	26 weeks	156	157	156	469
DIA3012 – Add-on to metformin + PIO	26 weeks	115	113	114	342
Add-on to insulin					
DIA3008 substudy	18 weeks	565	566	587	1718
Overall total		**1256**	**1441**	**1461**	**4158**

Key: CANA = canagliflozin, PO = pioglitazone, SU = sulfonylurea.
Source: ISE, Table 45

The placebo-adjusted LS mean changes and its associated 95% confidence interval for the change in HbA1c from baseline to primary endpoint within each subgroups for the pooled placebo-controlled studies are presented in Figure 13 below. The placebo-adjusted LS mean change in HbA1c for this pool of placebo-controlled studies was -0.83% (95% CI:-0.89,-0.77) for 300 mg dose and -0.68 % (95% CI:-0.75,-0.63) for 100 mg dose.

Figure 13: Placebo-Subtracted LS Mean Change (95% CI) From Baseline to Endpoint - Pooled Placebo-Controlled Studies, mITT



Source: ISE, Figure 4-1

The subgroup analyses showed that five baseline characteristics had statistically significant interactions (alpha 0.10): HbA1c, eGFR, race, HOMA2-%B, and HOMA-IR. HOMA-IR and HOMA2-%B are likely to be influenced by baseline differences in HbA1c, indicating that these may not be an important subgroup factors. For baseline HbA1c, eGFR, and race, the following observations were noted:

- HbA1c: A greater placebo-adjusted LS mean HbA1c reductions were seen in subjects with higher baseline HbA1c values compared to those with lower values in both doses of canagliflozin groups.
- eGFR: A greater placebo-adjusted LS mean HbA1c reductions were seen in subjects with a baseline eGFR >90 mL/min/1.73m^2 compared to those with <60 mL/min/1.73 m^2. Discussion of eGFR as a factor impacting glycemic efficacy can be found in section 6.1.10.

- Race: A greater placebo-adjusted LS mean HbA1c reduction was seen in Asian with 100 mg dose, and a greater HbA1c reduction was seen in African-American with 300 mg dose of canagliflozin. Of note, most subjects were Caucasian.

Although subgroup analysis of age did not show a statistically significant interaction with treatment, the magnitude of the LS mean HbA1c reductions was relatively smaller for the older age subgroup compared to the younger age subgroup. When the age subgroups were defined at 75, the incremental HbA1c reduction at the higher dose of canagliflozin (300 mg) was not seen in those ≥75 years, as summarized in Table 22. The placebo-subtracted LS mean HbA1c response was actually less with the higher dose (-0.55%) compared to the lower dose (-0.65%). However, it is notable that the size of this subgroup (≥75 years) was very small.

Table 22: LS Mean Change in HbA1c from Baseline to Endpoint by Age Subgroup (<75 or ≥75 Years): Pooled Placebo-Controlled Studies, mITT, LOCF

Blood hemoglobin A_{1c} (%)	Placebo	CANA 100 mg	CANA 300 mg
Age group (years): <75			
Value at baseline			
N	1143	1345	1351
Mean (SD)	8.12 (0.910)	8.14 (0.923)	8.12 (0.945)
Change from baseline			
LS mean (SE)	-0.15 (0.024)	-0.84 (0.023)	-1.00 (0.023)
P value (minus placebo)[a]		<0.001	<0.001
Diff. of LS means (SE)		-0.69 (0.032)	-0.85 (0.032)
95% CI[a]		(-0.752;-0.627)	(-0.907;-0.783)
Age group (years): ≥75			
Value at baseline			
N	48	59	68
Mean (SD)	7.86 (0.842)	8.13 (0.924)	7.87 (0.736)
Change from baseline			
LS mean (SE)	-0.13 (0.139)	-0.77 (0.120)	-0.68 (0.124)
P value (minus placebo)[a]		<0.001	<0.001
Diff. of LS means (SE)		-0.65 (0.158)	-0.55 (0.151)
95% CI[a]		(-0.958;-0.334)	(-0.850;-0.255)

[a] Pairwise comparison: p values and CIs are based on the ANCOVA model with factor(s) treatment, study and baseline HbA_{1c}.
Key: CANA = canagliflozin, CI = confidence interval, Diff = difference, ISE = Integrated Summary of Efficacy, LOCF = last observation carried forward, LS = least squares, N = number, SD = standard deviation, SE = standard error.
Note: The table includes only the subjects who had both baseline and postbaseline HbA_{1c}.
Note: Predefined timepoint of primary endpoint: Week 18 (DIA3008 SU and Insulin substudies) or Week 26 (DIA3002, DIA3005, DIA3006, DIA3012).
Note: Studies include DIA3002, DIA3005 (excluding High Glycemic substudy), DIA3006 (excluding active comparator), DIA3008 SU and Insulin substudies, DIA3012
Source: ISE, Table 52

Per my request, Dr. Wei Liu, FDA statistician, conducted another pooled dataset, by adding results of DIA3004 and DIA3010 to the applicant's pool of placebo-controlled studies. The

results of Dr. Liu's analyses are summarized in Table 23. DIA3004 and DIA3010 included more elderly and more subjects with impaired renal function compared to the applicant's pooled data. Dr. Liu's analysis further demonstrated that the glycemic efficacy with canagliflozin is diminished in subjects who are ≥75 years, and that there is no additional glycemic benefit with the higher dose of canagliflozin. In addition, contrary to the applicant's analysis, the difference between subgroups by age were statistically significant in Dr. Liu's dataset (interaction p-values <0.01).

Table 23: Summary of HbA1c Change from Baseline to Endpoint - Pooled Data*

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

*Include DIA3005 Main Study, DIA3006, DIA3008 SU substudy (Population 1), DIA3002, DIA3012, DIA3008 Insulin substudy (Population 2), DIA3004, and DIA3010.
Source: FDA's EMDAC Background Package, Statistical Review, Table 5

Reviewer's comment: Although this is a post-hoc subgroup analysis and the overall number of subjects who are ≥75 years of age is small, data suggest that the higher dose of canagliflozin may not provide additional glycemic benefit in elderly who are ≥75 years of age. This should be weighed against the risks associated with canagliflozin, especially dose-dependent risks discussed in section 7.3.

6.1.8 Analysis of Clinical Information Relevant to Dosing Recommendations

For discussion of key pharmacodynamic effects of canagliflozin in increasing urinary glucose excretion and reducing renal threshold for glucose, see Clinical Pharmacologist review by Dr. Jaya Vaidyanathan.

In a 12-week Phase 2b dose-ranging trial in T2DM (DIA2001), all canagliflozin doses studied (50, 100, 200, 300 mg daily, and 300 mg twice daily) significantly reduced FPG, and the maximal reductions in FPG was seen at doses of 200 mg daily and higher. In addition, all doses significantly reduced HbA1c, with the maximal reduction in HbA1c seen with 300 mg daily and 300 mg twice daily, as summarized in Table 24.

Table 24: Analysis of Change in HbA1c from Baseline to Week 12 - DIA2001, LOCF

	PBO (N=65)	50 qd (N=64)	100 qd (N=64)	200 qd (N=65)	300 qd (N=64)	300 bid (N=64)	Sita (N=65)
HbA1c (%)							
Value at Baseline							
N	61	62	62	62	60	62	62
Mean (SD)	7.71 (0.832)	8.01 (1.006)	7.81 (0.967)	7.57 (0.793)	7.70 (1.041)	7.71 (0.883)	7.62 (0.947)
Value at Week 12 LOCF							
N	61	62	62	62	60	62	62
Mean (SD)	7.50 (0.957)	7.22 (0.881)	7.05 (0.853)	6.87 (0.676)	6.78 (0.824)	6.76 (0.723)	6.88 (0.919)
Change from Baseline							
N	61	62	62	62	60	62	62
Mean (SD)	-0.22 (0.702)	-0.79 (0.749)	-0.76 (0.992)	-0.70 (0.720)	-0.92 (0.695)	-0.95 (0.704)	-0.74 (0.615)
P-value(minus PBO)[a]		<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Diff. of L-S Means (SE)		-0.45 (0.116)	-0.51 (0.116)	-0.54 (0.116)	-0.71 (0.117)	-0.73 (0.116)	-0.56 (0.116)
95% CI		(-0.747;-0.148)	(-0.804;-0.207)	(-0.841;-0.244)	(-1.006;-0.405)	(-1.029;-0.432)	(-0.862;-0.265)

KEY: PBO = placebo; qd = once-daily; bid = twice daily; CI = confidence interval; HbA1c=glycosylated hemoglobin; LOCF = last observation carried forward; L-S = least squares; N = total number of subjects per treatment group; SD = standard deviation; SE = standard error; Sita = sitagliptin.

[a] P-values and CIs were based on the pair-wise comparison of least-squares (L-S) means from an ANCOVA model including terms for treatment, baseline value and MMTT strata. For the primary analysis at Week 12 LOCF, p-values and CIs were adjusted using Dunnett's procedure.

Source: CSR DIA2001, Table 8

The applicant proposes that the further incremental reduction in HbA1c observed with 300 mg daily and 300 twice daily compared to 200 mg daily may be due to the local SGLT1 inhibition effect by canagliflozin in the intestine when a higher concentration is achieved with the higher dose of canagliflozin at 300 mg and higher. Similar to glycemic efficacy, incremental weight loss and reductions in systolic and diastolic blood pressure was observed at canagliflozin doses of 300 mg daily and 300 mg twice daily compared to 200 mg daily. Based on this dose-ranging Phase 2 trial, the applicant choose to study both 100 mg and 300 mg, since 100 mg daily provided a lower dose where sufficient efficacy was observed, and 300 mg daily provided incremental glycemic benefit.

In the canagliflozin program, two doses were studied in all Phase 3 trials except for DIA3015 (only 300 mg). The applicant recommend both 100 mg and 300 mg daily, and recommend starting dose of 100 mg daily in patients who may be at a higher risk for volume depletion events such as those on loop diuretics, patients with moderate renal impairment, or ≥75 years of age. After starting on 100 mg dose, these patients may titrate to 300 mg dose for additional glycemic

control if needed. See section 7.3.6 with regard to discussion of volume depletion events. However, in the Phase 3 trials, no titration of canagliflozin dose (either 100 to 300 mg or 300 to 100 mg) was done. Therefore, no data exists to provide clinical recommendation for this dose titration, since we do not know whether starting subjects with lower dose would minimize or lower the risk for volume depletion.

As described above, in all Phase 3 trials, there was a trend for a modest dose response in HbA1c reduction, with incremental HbA1c reduction ranging 0.09 to 0.26% with higher dose of 300 mg. The additional mean HbA1c reduction with higher dose was minimal (0.1%) in special population trials and its substudies (DIA3004 [Moderate Renal Impairment], DIA3010 [Older Adults], and DIA3008 Insulin and Sulfonylurea substudies). The subjects in these trials represent older population, with longer duration of diabetes with comorbidities and renal dysfunction (see section 6.1.2 for demographics).

In the subgroup analyses, subjects who were ≥75 years of age did not obtain additional glycemic benefit with the higher dose of canagliflozin (see section 6.1.7).

Due to its mechanism of action, canagliflozin has not been studied and is not expected to provide any benefit in patients with severe renal insufficiency (<30 mL/min/1.73m^2). Please also refer to section 6.1.10 for a discussion of the dosing recommendations as they pertain to moderate renally impaired subjects.

6.1.9 Discussion of Persistence of Efficacy and/or Tolerance Effects

The applicant evaluated the persistence of efficacy by comparing the change in HbA1c from baseline to Week 52 in DIA3009 and DIA3015. Following endpoints were analyzed at Week 52 for the mITT analysis sets for DIA3009 and DIA3015:

- In those subjects with HbA1c reduction of ≥0.4% through Week 26, the time to develop an increase in HbA1c of ≥0.3% from Week 26 to Week 52;
- Proportion of subjects who achieved HbA1c <7% by Week 26 and also maintained it at Week 52;
- The coefficient of durability, defined as the rise in HbA1c from Week 26 to Week 52.

In DIA3009, among subjects who had HbA1c reduction of ≥0.4% through Week 26, the median time to develop an increase in HbA1c of ≥0.3% from Week 26 through Week 52 was 181 days with canagliflozin 300 mg, 121 days with 100 mg, and 123 days with glimepiride. The hazard ratio with 95% CI between each canagliflozin dose and glimepiride was 0.75 (0.06,0.89) with 100 mg and 0.96 (0.82,1.13) with 300 mg. The proportion of subjects who reached HbA1c <7% by Week 26 and maintained this at Week 52 was similar between three treatment groups: 48.5% with canagliflozin 300 mg, 44.9% with 100 mg, and 46.1% with glimepiride. The coefficient of durability was positive in glimepiride group (0.0057) and negative in canagliflozin groups (-0.0004 with 100 mg and -0.0009 with 300 mg).

In DIA3015, among subjects who had HbA1c reduction of ≥0.4% through Week 26, the median time to develop an increase in HbA1c of ≥0.3% from Week 26 through Week 52 was 112 days with canagliflozin 300 mg and 62 days with sitagliptin. The hazard ratio with 95% CI between canagliflozin and sitagliptin was 0.87 (0.73,1.04). The proportion of subjects who reached HbA1c <7% by Week 26 and maintained this at Week 52 was similar between treatment groups: 52.9% with canagliflozin 300 mg and 56% with sitagliptin. The coefficient of durability was positive in both treatment group, although larger in the sitagliptin group: 0.0069 with canagliflozin 300 mg and 0.0159 with sitagliptin group.

Reviewer's comment: These are exploratory analyses and not conclusive.

6.1.10 Additional Efficacy Issues/Analyses

The impact of renal function on the glycemic efficacy of canagliflozin is discussed in this section. Attenuation of glycemic efficacy with canagliflozin in patients with renal impairment is expected since urinary glucose excretion by canagliflozin depends on the renal threshold for glucose, plasma glucose level, and renal function. With diminished renal function, canagliflozin's effect on urinary glucose excretion would be expected to be reduced. As shown in Table 13, the glycemic efficacy was modest in DIA3004 compared to other Phase 3 trials of canagliflozin. DIA3004 enrolled subjects with moderate renal impairment, compared to other Phase 3 trials which mainly enrolled subjects with normal to mild renal function. In addition, subgroup analyses showed that baseline eGFR has significant interaction with treatment efficacy (section 6.1.7).

In order to further evaluate the efficacy of canagliflozin in subjects with moderate renal impairment, the glycemic efficacy was further evaluated in a pooled analyses of data from subjects with moderate renal impairment, which was defined as baseline eGFR of ≥30 to <60 mL/min/1.73m^2. The Phase 3 trials that allowed enrollment of subjects within this eGFR were DIA3004, DIA3005, DIA3008, and DIA3010, and the subjects from each trial contributing to this pooled dataset are detailed in Table 25. A total of 1085 subjects comprised this moderate renal impairment pooled population, and DIA3008 contributed the largest number of subjects.

Table 25: Subjects in the Pooled Dataset for Moderate Renal Function (mITT)

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

Key: AHA = antihyperglycemic agent, CANA = canagliflozin.
Source: ISE, Table 70

In this pooled moderate renal impairment population, more subjects in the canagliflozin group (86-87%) compared to placebo (62%) completed the double-blind period through the primary assessment timepoint (Table 26). The overall mean duration of subject exposure (before rescue) was similar for two canagliflozin groups (19.6 weeks for 100 mg and 19.4 weeks for 300 mg) and slightly less for placebo (18.4 weeks). The baseline demographics were generally similar between treatment groups. The median age was 67-68 years; about 17% of total subjects were ≥ 75 years of age). The mean baseline eGFR was 48.2 mL/min/1.73m^2, and about a third of subjects (34%) had a baseline eGFR of <45 mL/min/1.73m^2. The mean baseline BMI was 32.5 kg/m^2 and the mean duration of diabetes was 15 years in this pool.

Table 26: Subject Disposition in the Pooled Dataset for Moderate Renal Function (All Randomized)

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

Source: ISS, Table 71, DSUB03E_RF

Table 27 presents the results of HbA1c change from baseline in this pooled dataset of subjects with moderate renal function. The placebo-subtracted LS mean reduction in HbA1c was slightly higher than what was observed in DIA3004 at 0.38 and 0.47% with canagliflozin 100 mg and 300 mg. This is most likely due to the fact that the average renal function, as measured by eGFR, was better in this pooled population compared to DIA3004; the mean eGFR was 40 mL/min/1.73m^2 in DIA3004 compared to 48 mL/min/1.73m^2 in this pooled dataset of subjects with moderate renal impairment. Similar to DIA3004, the incremental HbA1c reduction with the higher dose, when compared to the lower dose of canagliflozin, was minimal at 0.09% in this pool of subjects with moderate renal function.

A subgroup analysis of change in HbA1c by baseline eGFR in this pool of moderate renally impaired population, as shown in Table 27, demonstrate that the magnitude of the placebo-

subtracted LS mean reduction in HbA1c was smaller in subjects with lower baseline eGFR (e.g., <45 mL/min/1.73m^2) compared to those with higher baseline eGFR (≥45 mL/min/1.73m^2). The smallest LS mean decrease in HbA1c compared to placebo was seen with canagliflozin 100 mg dose (-0.23%) in the subgroup with a baseline eGFR of <45 mL/min/1.73m^2, where it barely reached statistical significance with 95% CI (-0.45,-0.01).

Table 27: LS Mean Change in HbA1c (%) from Baseline to Primary Assessment Timepoint in Pooled Subjects with Moderate Renal Function (LOCF; mITT)

	Placebo	Cana 100 mg	Cana 300 mg
N	382	338	365
LS mean (SE) change from baseline	-0.14 (0.06)	-0.52 (0.06)	-0.62 (0.06)
Difference of LS mean (SE) (95% CI)		-0.38 (0.06) (-0.50;-0.26)	-0.47 (0.06) (-0.60;-0.35)
Subgroup by baseline eGFR			
Baseline eGFR <45 mL/min/1.73m^2, N	108	118	122
LS mean (SE) change from baseline	0.05 (0.19)	-0.18 (0.19)	-0.34 (0.19)
Difference of LS mean (SE) (95% CI)		-0.23 (0.11) (-0.45;-0.01)	-0.39 (0.11) (-0.61;-0.17)
Baseline eGFR ≥45 mL/min/1.73m^2, N	248	208	232
LS mean (SE) change from baseline	-0.10 (0.07)	-0.57 (0.07)	-0.62 (-0.07)
Difference of LS mean (SE) (95% CI)		-0.47 (0.08) (-0.61;-0.32)	-0.52 (0.07) (-0.67;-0.38)

Source: ISE, Table 75, 76

Reviewer's comment: This analysis further show that the glycemic efficacy is attenuated in those with renal impairment, and that there is a significant difference in the glycemic efficacy even within a renal category of moderate renal impairment. Subjects with the lower baseline eGFR (i.e., <45 mL/min/1.73m^2) only comprised about a third of total moderate renal impairment pool across the canagliflozin program, and represents a small proportion of subjects in the overall canagliflozin program (~5%). Although this is a post-hoc analysis, this attenuated glycemic efficacy in those with moderate renal impairment must be carefully weighed against increased safety risks in this specific patient population (section 7.3.7).

7 Review of Safety

Safety Summary

The safety data consist of all randomized subjects who received at least one dose of study drug. In addition to individual Phase 3 trial results, four pooled datasets were used to evaluate the safety of canagliflozin, with the primary pooled population for safety in the 26-week Placebo-controlled Studies Dataset (DS1) since it included four placebo-controlled trials with similar

design over a common duration of treatment. A larger pooled dataset (DS3 and DS4 [which has the largest and longest exposure data]) was used to assess safety issues for events with low incidence. A Moderate Renal Impairment Dataset (DS2) was used to assess safety in subjects with moderate renal function. See section 7.1.3 for description of studies that were pooled in each dataset.

A death due to hemorrhagic pancreatitis was notable after treatment with canagliflozin 100 mg. In addition to this death due to pancreatitis, an increased incidence of serious adverse events (SAEs) related to pancreatitis was observed with canagliflozin, with 5 SAEs of pancreatitis [4 with 100 mg dose] and acute pancreatitis in the combined canagliflozin group compared to none with placebo in DS4. In the overall safety database, although the overall incidence was low, a higher incidence of pancreatitis was seen with canagliflozin 100 mg (0.4%) compared to 300 mg or placebo (0.1% in both).

There was an increased incidence in serious adverse skin reactions and in discontinuations/dropouts due to skin events (rash, pruritus, urticaria) indicative of hypersensitivity reactions with canagliflozin compared to placebo. This included a case of angioedema of upper lip with canagliflozin after 22 days of canagliflozin treatment, which required treatment. Although the overall incidence was low, there was an increased incidence of skin and hypersensitivity reactions with canagliflozin (0.4%) compared to non-canagliflozin group (0.2%), and the review of cases that led to discontinuation of treatment showed positive temporal relationship suggesting drug causality; in one case, there was a positive dechallenge and rechallenge.

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

Because canagliflozin leads to volume depletion, there is a concern for potential adverse renal effects. In clinical trials, canagliflozin has been associated with dose-dependent decrease in eGFR. However, the pattern of eGFR decline appear to be different in subjects with different baseline renal function. In the Placebo-controlled Studies Dataset (DS1), which included subjects with normal to mild renal function (median eGFR of 86 mL/min/1.73m^2), the nadir in eGFR occurred at the first ascertained timepoint and appear to recover towards baseline over

time. However, in DIA3008, which enrolled subjects with moderate renal function (median eGFR of 76 mL/min/1.73m^2), the early drop in eGFR appear to persist over time. In addition, evaluation of marked changes in eGFR showed that the incidence of marked decline in eGFR was similarly greater with both doses of canagliflozin compared to placebo in subjects with moderate renal function (DS2; eGFR 30 to 60 mL/min/1.73m^2). In addition to the observed glomerular filtration changes, canagliflozin was associated with changes in electrolyte handling. Use of canagliflozin was associated with dose-dependent increases in mean potassium levels and magnesium levels which were largest at the earliest time point checked. In individuals with normal renal function these changes were small and unlikely to be significant. Larger and potentially clinically significant changes were seen in patients with impaired renal function, especially with potassium. Subgroup analyses suggest that renally-compromised patients on medications that block the renin-angiotensin-aldosterone axis are particularly susceptible to these acute changes. Over the course of the trial changes tended to return toward baseline. Modifications to concomitant antihypertensive therapy occurred more frquently in subjects in the canagliflozin treatment groups compared to the non-canagliflozin groups during volume-depletion events, and this changes may have contributed to normalization.

Related to volume depletion is the potential for thrombosis, since canagliflozin had a osmotic diuretic effect which may lead to hemoconcentration. A small mean percent increases from baseline was seen in hematocrit and hemoglobin levels, but these changes were not associated with an increase in potentially related events such as thromboembolic events.

In nonclinical studies, canagliflozin led to an increase in trabecular bone volume (hyperostosis). In DIA3010, canagliflozin showed placebo-corrected increase in serum CTx (bone resorption marker) which was statistically significant and increase in P1NP (bone formation marker) which did not reach statistical significance. In addition, bone mineral density (BMD) was measure by DXA, and the changes were not consistent or clinically significant at Week 52. However, longer data is required to assess the chronic effect of canagliflozin on BMD. The controlled extension period of DIA3010 will have Week 104 data. In addition to these bone-related findings, fractures were adjudicated throughout clinical development of canagliflozin, and there was an imbalance in the total fractures and upper extremity fractures not favoring canagliflozin which was not statistically significant. However, as Dr. Voss of DRUP pointed out in his consult, the available data may not have enough power to rule out a modest increase in these infrequent events. Also, changes to bone turnover may not inform imbalance in fracture risk with canagliflozin which was observed early. The timing and location of the fractures (i.e., upper extremity) along with the knowledge that canagliflozin causes symptomatic volume depletion suggest that these fractures may have resulted from falls. The search for fall events using the MedDRA preferred term ‘fall’ did not show an imbalance. We found an imbalance not favoring canagliflozin in fall related events when the adverse event database was searched for verbatim terms containing the words ‘fall, fell and collapse’. This imbalance appeared early and was dose dependent.

Because canagliflozin increases urinary glucose excretion, it can potentially increase fungal growth in perineum and increase bacterial growth in urinary tract, treatment with canagliflozin

was associated with an increased incidence of urinary tract infection and genital mycotic infections compared to placebo in Phase 3 trials. This increased incidence was not dose-dependent. The incidence of urinary tract infection leading to serious outcome and discontinuation was slightly higher with canagliflozin compared to placebo. All genital mycotic infections that were serious or led to discontinuation only occurred with canagliflozin.

Canagliflozin increases LDL-C levels; in a pooled dataset of four 26-week controlled trials (DS1), the placebo-adjusted LS mean percent change was 5.7% with canagliflozin 100 mg and 9.3% with 300 mg. Since LDL-C is a well-established biomarker and changes in this marker appear linearly related to cardiovascular (CV) risk, it is possible that canagliflozin may lead to CV harm despite favorable changes in other CV risk factors such as HDL-C, blood pressure, and body weight. In the CV meta-analysis of Phase 2 and 3 trials, the pre-specified interim analyses of MACE or MACE-plus did not appear to show an increased incidence of composite CV endpoints, and showed non-significant increase in stroke. There is a concern of high MACE events during the first 30 days post-dose with canagliflozin which was observed in DIA3008, and it is unclear whether this is a spurious finding or a true increased risk of early CV events with canagliflozin in patients at high risk for CV event.

There is a higher incidence of hypoglycemia with canagliflozin in subjects on a background of insulin or insulin secretagogues. In DIA3002 where canagliflozin was studied as an add-on to metformin and SU, the incidence of hypoglycemia was 30.1% with 300 mg, 27.4% with 100 mg, and 15.4% with placebo.

In the clinical program for another SGLT2 inhibitor (dapagliflozin), significant elevations in liver aminotransferases were not observed with the product when compared to placebo; however, a case that met Hy's Law criteria was identified and raised concern with regard to its hepatotoxicity. As reviewed herein (see section 7.3.15), there was an imbalance in marked shifts in transaminases not favoring canagliflozin, but review of cases that met the Biochemical criteria of Hy's law (AST or ALT ≥3x ULN and total bilirubin ≥2x ULN), in consultation with hepatic expert in the Office of Surveillance and Epidemiology, did not identify any true Hy's law cases. Thus, despite an imbalance of significant elevations in ALT and/or AST not favoring canagliflozin, absence of a Hy's law case is somewhat reassuring.

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

Canagliflozin absorbs light in the UV range that is a concern for photoirritation. In photosensitivity studies, immediate photosensitivity responses were not seen at the standard

irradiance level (30-fold above natural sunlight), and no delayed photosensitivity response was observed. There was a higher incidence of photosensitivity skin adverse events with canagliflozin compared to non-canagliflozin (0.3% for each canagliflozin group compared to 0.2% for non-canagliflozin group), and two subjects who received canagliflozin discontinued due to an adverse event of photosensitivity.

7.1 Methods

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

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

In addition to a dedicated CV trial DIA3008, a CV meta-analysis evaluated MACE plus hospitalized unstable angina from DIA3008 and other Phase 2 and 3 trials.

7.1.1 Studies/Clinical Trials Used to Evaluate Safety

Pooled datasets, as described in section 7.1.3, were mainly used to evaluate the overall safety related to canagliflozin. Deaths, SAEs, and discontinuations in each individual Phase 3 trials were reviewed. Also, the overall safety data in each individual Phase 3 trials were also reviewed to assess any significant events observed that were not evident in the pooled datasets.

7.1.2 Categorization of Adverse Events

Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 14.1. For adverse events of interest (i.e., volume depletion, renal, etc), grouping of MedDRA terms were used to search for events and assess safety. The MedDRA terms used are described in each specific adverse event sections.

7.1.3 Pooling of Data Across Studies/Clinical Trials to Estimate and Compare Incidence

Four pooled datasets from the Phase 3 trials were used to evaluate the safety related to canagliflozin, as shown in Table 28. Of note, the applicant did not include one active-comparator Phase 3 trial, DIA3015, in any pooled datasets because it had only one of two active canagliflozin treatment group (300 mg) and would imbalance exposure in the pooled datasets when comparing the 100 mg and 300 mg groups of canagliflozin.

Table 28: Pooled Datasets for Phase 3 Trials

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

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

Pooled Dataset of Placebo-Controlled Studies (DS1): This dataset includes all data through Week 26 from four placebo-controlled Phase 3 trials (DIA3002, DIA3005 [Main Study only], DIA3006 [excluding sitagliptin group], and DIA3012). All four trials had similar enrollment criteria and had similar study duration (26 week core placebo-controlled double-blind period followed by a 26 week controlled extension period).

Pooled Dataset of Moderate Renal Impairment Subjects (DS2): This dataset includes subjects with moderate renal impairment (eGFR at baseline 30 to 60 mL/min/1.73m^2) from Phase 3 trials, which included subjects from DIA3004, DIA3005, DIA3008, and DIA3010. In other Phase 3 trials, subjects with eGFR <60 mL/min/1.73 m^2 were excluded from enrollment because of metformin use as background therapy was required. This dataset include data through DIA3008 cut-off date (September 15, 2011) and through Week 26 for other three trials (the primary assessment timepoint).

Pooled Dataset of All Controlled Phase 3 Trials (DS3): This dataset includes all placebo- and active-controlled Phase 3 trials, with the exception of DIA3015 as discussed previously since DIA3015 only had one of two active canagliflozin treatment groups. Also, the High Glycemic Substudy of DIA3005 is not included since it did not have a control group. This dataset includes data through Week 26 for all trials except for DIA3008 where all data up to a data cut-off date of September 15, 2011 is included. DIA3008 contributed the largest subject-years exposure in DS3. Canagliflozin groups (individual and combined dose groups) were compared to non-canagliflozin group which pooled both placebo- and active-comparator treatment groups across the trials.

Pooled Dataset of All Controlled Phase 3 Trials Through End of January 2012 (DS4): This dataset includes the same dataset as DS3, but includes all data collected through January 2012 for all trials. Fractures, photosensitivity skin adverse events, cancers (Leydig cell tumors, pheochromocytomas, renal cancers, breast cancers, and bladder cancers), venous thromboembolic events, and hospitalized congestive heart failure were evaluated in this dataset. This dataset also supported CV meta-analysis.

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

The major difference between DS3 and DS4 is that while DS3 includes data through the protocol-specified primary evaluation time point (at Week 26 or Week 52) for all trials except for DIA3008 (data cutoff date of September 15, 2011), DS4 includes data beyond the primary evaluation time point through the end of January 2012. As a result, DS4 provide 50% additional subject-years exposure compared to DS3 for evaluation of safety. The applicant points out that because many studies are still ongoing, data in DS4 are preliminary and not final. A Moderate Renal Impairment Dataset (DS2) was used to assess the safety in subjects with moderate renal function (baseline eGFR ≥30 to <60 mL/min/1.73m^2).

7.2 Adequacy of Safety Assessments

7.2.1 Overall Exposure at Appropriate Doses/Durations and Demographics of Target Populations

Safety data is from 52 completed or ongoing clinical trials of canagliflozin, which include data from 10,285 subjects from nine Phase 3 trials, 1210 subjects from three Phase 2 trials, and 1300 subjects from 40 Phase 1 trials.

At the time of NDA submission, 6645 subjects have been exposed to canagliflozin in the nine Phase 3 trials. Of these, 5936 subjects had been exposed for at least 24 weeks, and 4723 subjects had been exposed for at least 50 weeks. This exposure data include DIA3015 and High Glycemic substudy in DIA3005, which are not included in any of the pooled datasets. Summary of overall subject exposure to study drug from the nine Phase 3 trials is displayed overall in Table 29 and by each trial in Table 30.

Table 29: Overall Exposure in Canagliflozin Phase 3 Program

	Cana 100 mg	Cana 300 mg	Cana Total	Non-Cana
Total Number of Subjects in Phase 3 Program	3139	3506	6645	3640
6 months Exposure	2844	3092	5936	3162
12-month Exposure	2260	2463	4723	2392
18-month Exposure	604	596	1200	569
24-month Exposure	73	71	144	64

NOTE: The cutoff of DIA3015 is end of study and the cutoff of the rest of Phase 3 trials is January 31, 2012.
Source: SCS, Table 14

Table 30: Overall Exposure in Canagliflozin Phase 3 Program by Trial

	Randomized				Exposure ≥24 weeks				Exposure ≥50 weeks				Exposure ≥76 weeks				Exposure ≥102 weeks			
	Cana 100 mg	Cana 300 mg	Cana Total	Non-Cana	Cana 100 mg	Cana 300 mg	Cana Total	Non-Cana	Cana 100 mg	Cana 300 mg	Cana Total	Non-Cana	Cana 100 mg	Cana 300 mg	Cana Total	Non-Cana	Cana 100 mg	Cana 300 mg	Cana Total	Non-Cana
Total Number of Subjects in Phase 3 Program	3139	3506	6645	3640	2844	3092	5936	3162	2260	2463	4723	2392	604	596	1200	569	73	71	144	64
DIA3002	157	156	313	156	131	131	262	123	102	101	203	86								
DIA3004	90	89	179	90	74	82	156	78	31	31	62	29								
DIA3005	242	241	483	192	213	214	427	164	151	164	315	134								
DIA3006	368	367	735	549	322	328	650	481	170	178	348	247								
DIA3008	1445	1441	2886	1441	1339	1292	2631	1289	1205	1160	2365	1138	407	402	809	374	41	39	80	33
DIA3009	483	485	968	482	435	424	859	423	397	386	783	387	183	178	361	182	32	32	64	31
DIA3010	241	236	477	237	226	208	434	197	137	131	268	108	14	16	30	13				
DIA3012	113	114	227	115	104	100	204	93	67	60	127	53								
DIA3015		377	377	378		313	313	314		252	252	210								

Note: The cutoff of Study DIA3015 is end of the study. The cutoff of the rest of the Phase 3 studies is 31 January 2012
NOTE: The cutoff of DIA3015 is end of study and the cutoff of the rest of Phase 3 trials is January 31, 2012.
Source: SCS, Table 15

Table 31 presents the exposure data for each pooled safety dataset described in section 3.1. The mean duration of exposure to canagliflozin was 24 weeks in the Placebo-Controlled Studies

Dataset (DS1), and 88% of subjects were exposed to canagliflozin for at least 24 weeks. The mean duration of exposure to canagliflozin was substantially longer in the Broad Dataset (DS3) and Longer-term Exposure Broad Dataset (DS4) at 38 and 56 weeks respectively. About 30% and 72% of subjects were exposed to canagliflozin for at least 50 weeks in DS3 and DS4 respectively.

Table 31: Duration of Exposure to Study Drug for Each Pooled Dataset - Regardless of Rescue: Safety Analysis Set

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

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

The exposure data for DIA3008, which contributed the largest exposure data in the canagliflozin development program, are presented in Table 32 below. About 37% of subjects had at least 50 weeks of exposure to canagliflozin.

Table 32: Trial DIA3008 - Duration of Exposure to Study Drug: Safety Analysis Set

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

Source: SCS, Table 18

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

7.2.2 Explorations for Dose Response

In a 2-week, Phase 2 trial in T2DM (NAP1002), canagliflozin doses of 30, 100, 200, 400 mg QD, and 300 mg BID were evaluated. This trial showed that canagliflozin dose of 200 mg and higher maximally or nearly maximally lower renal threshold for glucose excretion (RT_G) over the entire 24-hour dosing period, with maximal increase in urinary glucose excretion (UGE). The 100 mg QD dose nearly maximally reduced RT_G only over the first 13 hours of dosing, which led to an effective but not maximal increase in UGE.

The results from Phase2b dose-ranging trial evaluating 50 mg QD, 100 mg QD, 200 mg QD, 300 mg QD, and 300 mg BID was consistent with NAP1002. In DIA2001, 100 mg and 300 mg QD of canagliflozin resulted in placebo-subtracted LS mean change from baseline of -0.51% and -0.71% in HbA1c respectively ($p<0.001$). The maximal reduction were seen with 300 mg QD dose with no further HbA1c lowering response with 300 mg BID dose.

The results from mixed-meal tolerance tests (MMTT) in a Phase 1 trial (DIA1045) also suggested that canagliflozin doses above 200 mg reduced the incremental glucose excursion relative to lower dose despite similar UGE.

In all Phase 3 trials except for DIA3015, treatment arms included both 100 mg and 300 mg doses of canagliflozin to evaluate dose-response.

7.2.3 Special Animal and/or In Vitro Testing

Please refer to Dr. Fred Alavi's review for full details.

7.2.4 Routine Clinical Testing

Routine laboratory tests, vital signs, and ECGs were evaluated during the course of each trial, as summarized in section 5.3.1.1. Although the timing of these time points are reasonable in a usual clinical trial setting, there are some limitations with canagliflozin. Canagliflozin-mediate effects appear to be immediate after starting therapy (within few days) as discussed in section 7.3, and the first ascertained timepoint for laboratory tests and vital signs were 3 or 6 weeks.

7.2.5 Metabolic, Clearance, and Interaction Workup

See section 4.4 Clinical Pharmacology of this review and also Dr. Jaya Vaidyanathan for full details.

7.2.6 Evaluation for Potential Adverse Events for Similar Drugs in Drug Class

Expected adverse events based on the mechanism of action of canagliflozin were adequately assessed in the clinical program. Dapagliflozin, another SGLT2 inhibitor, was reviewed by the Agency and was not approved, and some of the safety issues raised with dapagliflozin was evaluated in the canagliflozin program.

7.3 Major Safety Results

7.3.1 Deaths

All Phase 2 and 3 Trials other than DIA3008

No deaths were reported in any of the Phase 2 trials and in Phase 3 trials DIA3002, DIA3010, DIA3012 during the core double-blind treatment period. A total of twelve deaths that were treatment emergent (i.e., occurred within 30 days after discontinuation from study) were reported from trials DIA3004, DIA3005, DIA3006, DIA3009, and DIA3015 during the core double-blind treatment period, and are summarized in Table 33. Deaths from trial DIA3008 are separately summarized below.

Table 33: Treatment-Emergent Deaths in Subjects During Core Double-Blind Period in Phase 3 Canagliflozin Trials [excluding DIA3008]

Treatment Group	Trial	Subject ID	Age	Sex	Event onset (days)	Cause of Death
Placebo	DIA3004	400823	67	M	133	Septic shock
Placebo	DIA3005	500726	67	F	137	Intracranial hemorrhage, brain herniation
Placebo	DIA3006	600780	42	M	68	Gastric cancer
Glimepiride	DIA3009	903098	43	F	299	Cervical cancer
Glimepiride	DIA3009	900413	50	M	84	Cardiac arrest
Cana 100 mg	DIA3004	400903	82	M	95	Acute pulmonary edema
Cana 100 mg	DIA3005	500539	48	F	157	Pneumonia, septic shock, acute renal failure, acute ischemic hepatitis
Cana 300 mg	DIA3006	601403	56	M	156	Ischemic stroke, brain edema, coma
Cana 300 mg	DIA3009	900977	53	M	189	Injury
Cana 300 mg	DIA3009	900882	35	F	351	Anemia
Cana 300 mg	DIA3015	150018	62	F	195	Respiratory arrest, cardiac arrest
Cana 300 mg	DIA3015	150162	56	M	75	Cardiac arrest

Of these twelve deaths, seven deaths occurred among the canagliflozin-treated subjects (5 with 300 mg and 2 with 100 mg dose), and are further described:

- Subject 400903: A 82-year-old man with past history of myocardial infarction, ischemic cardiomyopathy, systemic arterial hypertension, and anxiety, received canagliflozin 100 mg daily. On Day 93, he was taken to the clinic due to poor appetite, and was discharged after he was hydrated. He had difficulty eating and walking without chest pain or dyspnea for few weeks. On Day 95, he died due to acute pulmonary edema.

- Subject 500539: A 48-year-old obese (BMI >60 kg/m^2) woman with past history of hypertension, asthma, sleep apnea, and chronic obstructive pulmonary disease received canagliflozin 100 mg daily. On Day 157, she experienced bronchitis, which resolved by Day 163 after treatment with azithromycin. However, ten days later (Day 173), her condition worsened and she presented to the emergency room with shortness of breath, cough, and pyrexia. A chest X-ray showed density at the right lower lobe, and she was hospitalized with pneumonia and received IV antibiotics. The last dose of study drug was Day 173. Two days later (Day 175), a repeat chest X-ray showed a slight worsening with bilateral infiltrates and a CT scan confirmed right lower pneumonia. Vancomycin was added due to persistent fever, and cultures of sputum and blood came back negative. She was transferred to ICU next day (Day 176) due to increasing respiratory distress and was placed on mechanical ventilation due to worsening condition (Day 177). Her condition worsened and she was diagnosed with septic shock with acute renal failure and acute ischemic hepatitis. She became progressively acidotic, with severe respiratory acidosis and profound hypotension, and died on Day 183 due to septic shock.

  Reviewer's comment: She experienced bronchitis while receiving canagliflozin, which worsened to pneumonia and progressed to septic shock, leading to her death.

- Subject 601403: A 56-year-old man with multiple cardiovascular history received canagliflozin 300 mg daily. His history included arterial hypertension, arterial insufficiency of lower extremities, atherosclerosis obliterating, coronary artery disease, diabetic angiopathy of lower extremities, heart failure (Class 1), and myocardial slcerosis. On Day 156, he was hospitalized with vertigo, dysphagia, numbness of the right side of face, and difficulty swallowing. A computerized tomography of the brain showed ischemic stroke of the right side of medulla and cerebellar hemisphere, and he was diagnosed with ischemic stroke and hypertensive crisis. Two days later, he developed brain edema, became comatose, and went into cardiac arrest. He was treated with unspecified therapy, resuscitation was unsuccessful, and he died on the same day (Day 158) due to ischemic stroke, coma, and brain edema.

- Subject 900977: A 53-year-old man with history of hyperlipidemia, hypertension, and obesity (BMI of 31 kg/m^2) received canagliflozin 300 mg daily. He was working on restoration of a roof and fell from 8 meters and died due to injuries sustained from the fall on Day 189.

- Subject 900882: A 35-year-old woman with past medical history of diabetic nephropathy received canagliflozin 300 mg daily. She had slightly low hemoglobin levels at study entry (106 g/L and 112 g/L at screening and baseline respectively [normal 116 to 164 g/L]), with an eGFR of 72 mL/min/1.73 m^2 on Day 1. Her eGFR decreased post-baseline with values of 54, 60, 56, and 50 mL/min/1.73 m^2 on Days 29, 86, 184, and 253 respectively (also shown below). On Day 309, her BUN and serum creatinine levels increased, and eGFR was 39 mL/min/1.73 m^2, and she was diagnosed with chronic renal failure on Day 312. On day 337, BUN and serum creatinine further increased, with decrease in eGFR. Her hemoglobin level also was low on Day 344 at 92 g/L. She received the last dose of study drug on Day 343 and was withdrawn from the study on Day 344 since she met protocol-specified withdrawal criteria due to worsening renal function.

Study Day[a]	Date of Specimen Collection	Lab Name[b]	BUN (mmol/L)	BUN LLN/ULN (mmol/L)	CREAT (umol/L)	CREAT LLN/ULN (umol/L)	eGFR mL/min/1.73m^2	HGB g/L	HGB LLN/ULN g/L	PLT x 10^9/L	PLT LLN/ULN x 10^9/L
-36	(b) (6)	(b) (4)	6.1	(1.4 - 8.6)				106	(116-164)	208	(140 - 400)
-28					74	(31 - 101)					
1			4.5	(1.4 - 8.6)	79	(31 - 101)	72	112	(116-164)	201	(140 - 400)
29			5.4	(1.4 - 8.6)	102	(31 - 101)	54				
86			6	(1.4 - 8.6)	93	(31 - 101)	60				
184			6.7	(1.4 - 8.6)	98	(31 - 101)	56				
253			8.6	(1.4 - 8.6)	107	(31 - 101)	50				
309			10.9	(1.4 - 8.6)	133	(31 - 101)	39				
323					132	(31 - 101)	40				
337			11.2	(1.4 - 8.6)	139	(31 - 101)	37				
344[c]					134	(31 - 101)	39	92	(116-164)	185	(140 - 400)
								51	(120-160)	Low	

Note: [a] Relative to first dose of treatment.
Note: (b) (4)
Note: [c] Subject's last dose of study medication occurred on Day 343. Early termination visit occurred on Day 344. Subject died on Day 375
Note: BUN=Blood Urea Nitrogen; CREAT=Creatinine; eGFR=estimated Glomerular Filtration Rate; HGB=hemoglobin; PLT=platelets

Source: CTR DIA3009, narrative (page 3372)

She was diagnosed with anemia on Day 351 and was treated with ferrous sulfate. On Day 371, she experienced weakness without any other symptoms and was hospitalized. She was receiving glimepiride (since unspecified time period) and had switched treatment with glimepiride to metformin. On Day 374, her hemoglobin level was 51 g/L with low platelets (unspecified level). She developed cardiopulmonary arrest on Day 375 and died. An autopsy was not performed.

Reviewer's comment: The applicant listed the cause of death as anemia, but her anemia appeared to be due to renal failure, which developed during treatment with canagliflozin. Although she died almost 30 days after discontinuing the study drug, renal failure that developed during trial while on study drug may have played a role in her death.

- Subject 150018: A 62-year old obese (42 kg/m^2) woman with history of hypertension and hypercholesterolemia received canagliflozin 300 mg daily. She felt unwell for about a week with nonproductive cough, shortness of breath, and fever, and on Day 195, felt unwell with increasing dyspnea and was driven to the hospital by spouse. She became unresponsive on the way to the hospital and presented to the emergency room in acute respiratory arrest. She was found to be in asystole and resuscitated, transferred to intensive care unit, intubated, and treated. Her WBC was 16.1 (no units provided) and arterial blood gas showed severe acidosis, elevated BUN (32 mg/dL) with normal creatinine (1 mg/dL). Chest X-ray showed persistent diffuse, bilateral infiltrated, she was diagnosed with pneumonia, and received antibiotics. An electroencephalogram on the same day showed severe cerebral cortical dysfunction. Brain computed tomography scan on Day 197 suggested generalized cerebral

and cerebellar edema with possible areas of acute infarction. On Day 198, she was found unresponsive with dilated and fixed pupils, and her condition progressed to another episode of cardiac arrest. Cardiopulmonary resuscitation and advanced cardiac life support was performed, but she died on the same day due to cardiac arrest and respiratory arrest. No autopsy was performed.

Reviewer's comment: The applicant coded adverse event related to death as respiratory arrest and cardiac arrest, but respiratory and cardiac arrest was due to pneumonia, which led to her death. Her cause of death appear to be pneumonia.

- Subject 150162: A 56-year-old man with history of hyperlipidemia, heart murmur, hypertension, stroke, arthritis, anxiety, depression, chronic obstructive pulmonary disease, obstructive sleep apnea, received canagliflozin 300 mg daily. On Day 75, he died due to cardiac arrest. He was found dead in his bed. No autopsy was performed.

In addition, five deaths that were not treatment emergent (i.e., occurred more than 30 days after discontinuation from study) were reported in trials DIA3004, DIA3009, and DIA3015. One death due to myocardial infarction occurred in the sitagliptin treatment group from DIA3015. The other five deaths from DIA3004 and DIA3009 occurred in subjects who received canagliflozin 100 mg, and are further described here:

- Subject 400373 (DIA3004): A 78-year-old man with past history of hypertension, premature systolic ventricular, hyperlipidemia, left ventricular dysfunction, aortic valve replacement, and cholelithiasis received canagliflozin 100 mg daily. At screening, his LFT values were within normal limits. On Day 17, he was hospitalized for "suspicion of transient ischemic attack (TIA)", and a diagnosis of TIA was made. A cranial CT showed no evidence of bleeding or ischemia. On Day 28, he discontinued several concomitant medications (acetylsalicylic acid [ASA], ramipril, HCTZ, pentoxifylline, and sulpiride), and on Day 29, started valsartan 160 mg and dipyridamone/ASA 200 mg twice daily. On Day 29, his ALT and GGT was markedly elevated, AST and ALP were modestly elevated, with normal bilirubin levels. Repeat laboratory tests on Day 31 showed downward trend in AST, ALT, and ALP. On Day 35, retest of LFTs showed increased ALT and AST, marked elevation in GGT, and modest elevation in total bilirubin. Serology was negative for hepatitis A, HBs antigen, HBc antigen, and hepatitis C. On Day 37, he was hospitalized with bile duct stone. Abdominal sonography showed cholecystolithiasis, study drug was discontinued on Day 39 due to bile duct stone, and ERCP with papillectomy was performed. On Day 42, he was discharged and scheduled for elective cholecystectomy. On Day 49, he was withdrawn from the study due to bile duct stone, and on Days 87 to 93, was hospitalized for elective laparoscopic cholecystectomy; LFTs were normal. On Day 180, he was found unconscious in his bed by his spouse, and was diagnosed with myocardial infarction and asystole.

- Subject 900001 (DIA3009): A 67-year-old woman with history of myocardial infarction, coronary artery disease, hypertension, hypercholesterolemia, and mild obesity, received canagliflozin 100 mg daily. On Day 72, during a routine stress test, she had chest pain and

was diagnosed with angina pectoris. Study drug was discontinued on the same day due to this event. She was treated with clopidogrel and acetylsalicylic acid, and underwent catherization and CABG. The event resolved on Day 83, and she was withdrawn from the study on Day 127 due to this event. On day 322, she died due to an event of myocardial infarction.

- Subject 900217 (DIA3009): A 69-year-old woman with history of hypertension, hyperlipidemia, depression, and insomnia received canagliflozin 100 mg daily. On Day 58, she experienced headache followed by balance disorder on Day 59. On Day 116, she felt "buzzing feeling in the head", and on Day 130 had another event of headache. On Day 135, she was fatigued. Headaches resolved by Day 173, and "buzzing feeling in the head" resolved on Day 179. On Day 179, she experienced vertigo, and as a result study drug was discontinued on Day 183 and discontinued from the study on Day 184. The events of balance disorder, fatigue, and vertigo resolved on Day 198. On Day 466, she had tiredness and difficulty breathing throughout the day, was hospitalized, and had a cardiac arrest and died the next day. An autopsy performed on an unspecified day reported the cause of death as acute coronary thrombosis due to occlusive coronary atherosclerosis.

- Subject 903307 (DIA3009): A 35-year-old man with history of cerebral infarction, hypertension, hyperthyroidism, arrhythmia, and atrial fibrillation received canagliflozin 100 mg daily. On an unspecified day, he complained of dyspnea on exertion and was diagnosed with left atrial hypertrophy, bilateral pleural effusion, and emphysema on Day 111. Chest X-ray and transthoracic echocardiography on Day 131 showed pulmonary congestion and mitral valve incompetence. He was hospitalized on Day 181 and underwent open heart valvuloplasty of the mitral valve without replacement the next day; heart failure due to uncontrolled thyrotoxicosis was reported as the cause for mitral valve incompetence, and study drug was withdrawn on Day 181. On Day 183, during hospitalization, he became semicomatose. A magnetic resonance imaging scan of the brain showed left middle cerebral artery infarction and brain CT showed low density in the left middle cerebral artery territory with severe midline shifting to the right of up to 9 mm; he was diagnosed with cerebral infarction, carotid arterial embolus, and a non-serious event of cardiac failure. He was also diagnosed with hypertension on Day 184. On Day 184, craniectomy and craniotomy was done for cerebral edema that resulted from cerebral infarction and carotid artery embolism. He had hypokalemia and hypomagnesemia on Day 185 and 186 respectively. He underwent tracheostomy on Day 194. Due to mitral valve incompetence, he was withdrawn from the study on Day 196 (the last dose of canagliflozin was not specified). Brain CT scan on Day 198 showed decreased extent and increased density of brain edema of left cerebral hemisphere, and he was discharged to a local clinic for physical therapy. He was re-hospitalized on Day 241 and underwent cranioplasty on Day 246. He had a follow up transthoracic echocardiography on Day 316 for the open heart valvuloplasty surgery of the mitral valve. On Day 343, he complained of dyspnea, and had worsening cardiac failure. A transthoracic echocardiography showed ejection fraction of 9% with severe global decrease in both right and left ventricular motion, moderate mitral and triscuspid regurgitation. On Day 357, a brain MRI showed acute infarction of the right with poor visualization of the right

intracranial ICA, MCA and distal branches. He was semicomatose and was diagnosed with right cerebral infarction on Day 357 and died on Day 358. An autopsy was not performed.

DIA3008

A total of 10 subjects in each canagliflozin treatment groups and 13 subjects in placebo had deaths that were treatment emergent in DIA3008, and are summarized in Table 34. Of these, 7 subjects in canagliflozin 100 mg, 7 subjects in canagliflozin 300 mg, and 11 subjects in placebo group died due to cardiovascular and/or cerebrovascular-related events (including sudden death).

Three deaths related to malignancies were reported with canagliflozin, two with lung neoplasm and one with hepatic neoplasm. Of two cases of lung neoplasm after receiving canagliflozin 300 mg, one case occurred in an ex-smoker with history of emphysema (b) (4). One subject died from malignant hepatic neoplasm after receiving canagliflozin 100 mg ((b) (4)

In addition, one subject (b) (4) died due to hemorrhagic pancreatitis, altered mental state, respiratory failure, pulmonary edema, and neurogenic shock. One subject died due to bronchopneumonia (b) (4)); another subject (b) (4) was diagnosed with amyotrophic lateral sclerosis and died due to respiratory failure, and pneumonia may have played a role in precipitating respiratory failure.

Table 34: Treatment-Emergent Deaths in Subjects from DIA3008 [up to September 15, 2011 at the time of Interim Analysis]

Treatment Group	Subject ID	Age	Sex	Days to AE onset	Cause of Death
Placebo	(b) (4)	64	M	62	Sudden death
Placebo		77	M	259	Pancreatic carcinoma
Placebo		59	M	173	Cardiac failure chronic
Placebo		64	M	97	Sudden death
Placebo		55	M	153	Sudden cardiac death
Placebo		79	M	119	Cardiopulmonary arrest
Placebo		55	M	99	Sudden death
Placebo		54	M	231	Myocardial infarction
Placebo		65	F	201	Sudden death
Placebo		52	M	68	Death
Placebo		75	F	160	Pulmonary embolism
Placebo		61	M	64	Hemorrhagic stroke
Placebo		76	F	63	Sudden death
Cana 100		71	M	72	Cardiac arrest
Cana 100		62	M	304	Ventricular fibrillation
Cana 100		67	M	446	Sudden death
Cana 100		66	M	57	Hepatic neoplasm malignant
Cana 100		81	M	300	Cardiac failure
Cana 100		63	M	223	Pancreatitis hemorrhagic, mental status changes, respiratory failure, pulmonary edema, neurogenic shock
Cana 100		66	M	318	Sudden death
Cana 100		73	F	162	Acute cardiac failure
Cana 100		74	F	194	Bronchopneumonia
Cana 100		69	M	69	Cerebrovascular accident, aspiration pneumonia
Cana 300		69	M	114	Lung neoplasm
Cana 300		57	M	439	Respiratory failure
Cana 300		68	F	438	Acute myocardial infarction
Cana 300		63	M	370	Sudden death
Cana 300		59	F	109	Cardiac arrest
Cana 300		55	F	54	Sudden cardiac death
Cana 300		74	M	161	Cerebrovascular accident
Cana 300		72	F	191	Sudden death
Cana 300		70	M	120	Cerebrovascular accident

All twenty cases of treatment-emergent deaths reported with canagliflozin treatment are briefly described here:

- Subject (b) (4): A 71-year-old man received canagliflozin 100 mg daily. His past medical history was significant for hypertension, aortic stenosis, heart murmur, MI, diabetic retinopathy, renal artery stent replacement, vascular stent, and hyperlipidemia. At baseline, his eGFR was 50 mL/min/1.73m^2, and on Day 44, his eGFR decreased to 42.8 mL/min/1.73m^2 and he was diagnosed with decreased kidney function. On Day 67, he was

hospitalized for multivessel coronary artery disease, severe aortic stenosis, and acute congestive heart failure, and the study drug was discontinued. On Day 72, he underwent coronary artery bypass graft sugery and aortic valve replacement. During surgery, he arrested and was resuscitated, but had severe cardiac dysfunction that could not be corrected due to underlying cardiac disease and died in the intensive care unit.

- Subject (b) (4): A 62-year-old man received canagliflozin 100 mg daily. He had significant past medical history which included MI, acute anteroseptal infarct, cardiac decompensation, coronary artery bypass, heart failure (Class 2), and angina pectoris. He experienced flu on Day 272, which resolved. On Day 304, he developed ventricular fibrillation and suddenly fell off the chair while at sauna. He received multiple shocks, and after an hour of resuscitation, died due to ventricular fibrillation. An autopsy was not done.

- Subject (b) (4): A 67-year-old man received canagliflozin 100 mg daily. He had significant past medical history which included HTN, heart failure (Class 3), non-Q-wave MI, coronary artery disease, quadruple bypass, five artery bypass, angioplasty to mid LAD, ischemic heart disease, mild left atrial enlargement, chronic obstructive pulmonary disease, and obesity (BMI of 36 kg/m^2). On Day 446, he died suddenly at home. An autopsy was not performed.

- Subject (b) (4): A 66 year-old-man received canagliflozin 100 mg daily. His past medical history was significant for diabetic neuropathy, retinopathy, neuropathy, hypertension, MI, angioplasty, hyperlipidemia, and smoking. At baseline, he had normal ALT (31 U/L), AST (24 U/L), bilirubin (6 umol/L), ALP levels (125 U/L), and high GGT level at 113 U/L (normal 10-50 U/L). On Day 33, he had epigastric discomfort. On Day 43, ALP and GGT levels were elevated (129 U/L [normal 35-125 U/L] and 145 U/L respectively), with normal ALT, AST, and bilirubin. On Day 57, the epigastric discomfort resolved without any further action, and he was diagnosed with malignant hepatic neoplasm. On day 85, ALT (80 U/L), AST (69 U/L), serum bilirubin (282+ umol/L), ALP (400 U/L) and GGT levels (142 U/L) were elevated. Study drug was discontinued on Day 61, and subject was withdrawn from the study on Day 85. On Day 198, he died due to hepatic cancer.

- Subject (b) (4) A 81-year-old man received canagliflozin 100 mg daily. His past medical history included HTN, left heart ventricle aneurysm, MI, cardiac decompensation, arrhythmia or conduction disturbance, right sided trigeminal neuralgia, coronary artery arteriosclerosis, left bundle branch block, cerebral infarction, and carotid sclerosis. On Day 265, he was diagnosed with peripheral ischemia (reported term was pre-gangrene of II-III digit of left foot) and peripheral arterial occlusive disease. On Day 300, he was hospitalized due to cardiac failure, and he died on Day 327 due to cardiac failure. An autopsy was not done, and the direct cause of death was considered to be left ventricular failure. At the time of death, the event of peripheral ischemia was reported as resolving and the event of peripheral arterial occlusive disease was reported as not resolved.

- Subject (b) (4) A 63-year-old man received canagliflozin 100 mg. His past medical history included diabetic neuropathy, hyperlipidemia, HTN, arrhythmia, DVT, MI, CABG, RBBB,

hypothyroidism, and fracture. On Day 20, he was hospitalized with sepsis with altered mental status. Blood culture was positive for group B streptococcus, and chest X-ray showed some degree of redistribution with no acute changes. On Day 19, WBC count ($14.9x10^3$; normal $4.3\text{-}11.0x10^3$) and neutrophil count ($13.7x10^9$/L; normal $2.6\text{-}7.7x10^9$) were elevated. He was treated with antibiotics and study drug was interrupted. Sepsis was reported as resolved on Day 22 and he was discharged on Day 23; study drug was restarted on Day 24. On Day 223, he was hospitalized and diagnosed with mental status changes, respiratory failure, and hemorrhagic pancreatitis. He had pulmonary edema on Day 225 and neurogenic shock on Day 228. He was treated for hemorrhagic pancreatitis, but died on Day 235 due to hemorrhagic pancreatitis, altered mental status, respiratory failure, pulmonary edema, and neurogenic shock.

Reviewer's comment: Some antidiabetic agents, mainly DPP-4 inhibitor and GLP-1 agonists, have been associated with pancreatitis and is a concern for antidiabetic agents. Along with this case of death due to hemorrhagic pancreatitis, SAEs related to pancreatitis with canagliflozin were also reported (section 7.3.2). An overall evaluation of pancreatitis is summarized in section 7.3.2 below.

- Subject (b) (4): A 66-year-old man with past medical history of HTN, MI, and coronary artery disease received canagliflozin 100 mg daily. He had a family altercation on Day 318, where he was pushed over and fell on the ground and died. No autopsy was done.

- Subject (b) (4) A 73-year-old woman received canagliflozin 100 mg daily. Her past medical history included acute coronary syndrome, angina pectoris, arrhythmia, atrial fibrillation, ventricular extrasystoles, coronary artery disease, heart failure (Class 2), and HTN. On Day 162, she died due to acute cardiac failure. No autopsy was done.

- Subject (b) (4) A 74 year-old obese (BMI 44 kg/m^2), postmenopausal woman with past medical history significant for arrhythmia, heart failure (Class 2), hyperlipidemia, hypertension, ischemic heart disease, and diabetic retinopathy received canagliflozin 100 mg daily. She was diagnosed with viral pneumonia on Day 150, which was confirmed by X-ray of the lungs, and was treated with antibiotics. On Day 194, X-ray showed right-sided pneumonia and fluid in thorax, and she was hospitalized the next day due to cough, audible wheezing, and breathing difficulties. Her WBC count was 20.1/nL (normal 3.8 to 10/nL), and serology tests were positive for chlamydia and mycoplasma pneumonia. On Day 202, a CT scan of lungs showed signs of inflammation in both lungs with slight increase in the lymph nodes size; chest X-ray showed pneumonia. She was also diagnosed with ventricular extrasystoles during hospitalization, which resolved on Day 205 and she was discharged. On Day 206, she had weakness, difficulty breathing, and chest pain, and was diagnosed with bronchopneumonia. She was hospitalized on Day 208 due to worsening respiratory insufficiency, and was transferred to ICU for intubation the next day. Her respiratory worsening over the next few days and she died on Day 215 due to bronchopneumonia.

- Subject (b) (4) A 69-year-old man with history of HTN and other diabetic neuropathy received canagliflozin 100 mg daily. He was hospitalized on Day 69 with vomiting, generalized tiredness, and reduced alertness. On examination, he was found to have no power in the left upper and lower limbs, absence of deep tendon reflexes, hyperreflexia of plantar reflexes, and signs of left hemiplegia. He appeared drowsy with pulse rate of 90/minute, blood pressure of 190/96 mmHg, and ECGs were within normal limts. He was diagnosed with cerebrovascular accident and aspiration pneumonia. He died on Day 72 due to cerebrovascular accident and aspiration pneumonia.

- Subject (b) (4) A 69-year-old man received canagliflozin 300 mg daily. His past medical history included diabetic neuropathy and retinopathy, hyperlipidemia, HTN, hypogonadism, hypothyroidism, gastric reflect, emphysema, and he was nonsmoker. On Day 85, he complained of cough and fever, and on Day 95, he was diagnosed with pneumonia. On Day 114, he was diagnosed with lung neoplasm malignant. Study drug was discontinued on Day 131 due to lung neoplasm. Biopsy of left apex mass on Day 139 was suggestive of poorly-differentiated non-small cell carcinoma, and biopsy of large mediastinal masses on Day 153 showed poorly differentiated metastatic carcinoma. Pneumonia was resolved on Day 165. He died on Day 264 due to metastatic, malignant lung neoplasm.

- Subject (b) (4): A 57-year old man received canagliflozin 300 mg daily. His medical history was significant for multiple cardiovascular disorder, sarcoidosis, degenerative disc disease, seasonal allergies and asthma. A month before randomization, he experienced progressive bilateral upper extremity weakness, and neck pain started about 4 months after randomization with increasing upper extremity weakness. He had fleeting paresthesia in the tips of right fingers, intermittent numbness in the lateral region of right thigh, and cervical, thoracic, bilateral upper extremity muscle atrophy with fasciculation noted in the thoracic and bilateral upper extremities. On Day 73, he had neck pain and underwent cervical spine MRI which showed some degenerative disc disease. He was diagnosed with amyotrophic lateral sclerosis (ALS) confirmed by electromyogram nerve conduction study. On Day 439, he had difficulty breathing and was hospitalized for acute respiratory failure (unclear whether this was due to neuromuscular disease). Chest X-ray and chest CT done an unspecified day showed bibasilar consolidation which was consistent with pneumonia. He was diagnosed with asthma, pneumonia, and respiratory failure on Day 439. Asthma and respiratory failure resolved on Day 445, and he was discharged with antibiotics and home ventilator. Study drug was discontinued on Day 458 due to progression of ALS. On Day 469, he presented to ER unresponsive, diaphoretic, rhonchi in lungs, high blood pressure (200/101 mm Hg) and tachycardic (heart rate 114 beats/min). Chest X-ray showed new increased opacity right perihilar and right lower lung which was consistent with possible pneumonia, and arterial blood gases suggested respiratory failure. He refused ventilator support and died on Day 469 due to respiratory failure.

  Reviewer's comment: The applicant determined the cause of death for this case as respiratory failure for this case; however, pneumonia may have played a role in causing respiratory failure.

- Subject (b) (4) A 68-year-old postmenopausal woman received canagliflozin 300 mg daily. Her past medical history included angina pectoris, atherosclerosis vascular low extremity, HTN, ischemic heart disease, encephalopathy, and smoker. On Day 438, she had chest pain. She was transferred to hospital, was diagnosed with MI, and died the same day. The autopsy confirmed the primary cause of death as acute MI.

- Subject (b) (4) A 63-year-old obese (BMI 30 kg/m_2) man received canagliflozin 300 mg daily. His past medical history included HTN, hyperlipidemia, angina pectoris, carotid atherosclerosis, heart failure (Class 3), peripheral vascular disease, and vascular encephalopathy. On Day 72 and 123, he had worsening cardiac failure and treated with diuretics. On Day 127, he was hospitalized for worsening cardiac failure, which resolved on Day 149. On Day 295, he again had worsening cardiac failure and glucose control, and was treated with diuretics for cardiac failure. He also had concomitant pneumonia and received antibiotics, which the investigator possibly considered to be related to worsening glucose level. These events resolved on Day 316. On Day 342, he again had recurrent worsening of cardiac failure and received furosemide. On Day 370, he died suddenly while with his wife.

- Subject (b) (4) A 59-year-old postmenopausal woman received canagliflozin 300 mg daily. Her past medical history included HTN, systolic ejection murmur, stroke, and cerebrovascular accident. On Day 109, she experienced cardiac arrest and was taken to emergency room. The ECG changes were consistent with acute MI. Resuscitation was unsuccessful, and she died the same day.

- Subject (b) (4) A 55-year-old postmenopausal woman with history of acute coronary syndrome, HTN, and CABG received canagliflozin 300 mg daily. On Day 54, after her meal, she suddenly collapsed at home and died. No autopsy was done.

- Subject (b) (4) A 74-year-old man received canagliflozin 300 mg daily. His past medical history included hyperlipidemia, heat failure, MI, postural hypotension, CABG, acute renal failure, diabetic neuropathy, asthma, subdural hematoma, mild dementia, and hip replacement. On Day 116, he was diagnosed with atrial flutter. On Day 161, he was hospitalized with chest pain and sick feeling, and was diagnosed with angina pectoris and cerebrovascular accident. On Day 163, he became unconscious and died due to cerebrovascular accident.

- Subjec (b) (4) A 72-year-old postmenopausal, smoking woman with past history of arterial thromboembolism, asymptomatic aortic stenosis, hyperlipidemia, and HTN received canagliflozin 300 mg daily. On Day 191, she died suddenly. It was reported that she went to the emergency room on Day 190 due to “presyncope” episode, and an echocardiogram showed aortic stenosis. An autopsy was done and the cause of death was unknown.

- Subject (b) (4) A 70-year-old obese (BMI 32 kg/m^2), non-smoking man with history of arrhythmia, hyperlipidemia, HTN, and atrial fibrillation received canagliflozin 300 mg daily.

On Day 120, he was hospitalized after having dysphagia three months before. On unspecified date, he was diagnosed with malignant lung neoplasm. On Day 145, he had stroke and died. An autopsy was not done.

Reviewer's comment: In this subject, the adverse event causing death was listed as cerebrovascular accident, but lung neoplasm may have played a role in stroke.

- Subject (b) (4) A 54-year-old woman with history of diabetic neuropathy and HTN received canagliflozin 300 mg daily. On Day -1 (before randomization), she experienced headache, giddiness, vomiting, and blurred vision. On Day 2, she was hospitalized for these symptoms, received treatment, and was diagnosed with vertebrobasilar insufficiency and systemic infection. On examination, she was afebrile with pulse of 116/minute, oxygen saturation of 97%, and blood pressure of 150/90 mmHg. On Day 7, despite treatment, she died due to vertebrobasilar insufficiency. She only received the study drug on Day 1.

Deaths in seven subjects (two with placebo, one with canagliflozin 100 mg, and four with canagliflozin 300 mg) were not treatment-emergent (i.e., occurred more than 30 days after discontinuation from study). Five deaths reported with canagliflozin are further described here:

- Subject (b) (4) A 82-year-old man with history of dyslipidemia, stroke, HTN, arrhythmia, hyperbilirubinemia, and goiter received canagliflozin 100 mg daily. On Day 6, he presented to hospital with complains of dizziness and vertigo, and was discharged the same day. On Day 9, he had cerebrovascular accident and was hospitalized, and study drug was discontinued. He received treatment and was discharged on Day 157. On Day 164, he had a head injury due to fall and was hospitalized. A cranial CT showed minimal lesions, and he was discharged on Day 165. On Day 201, he died suddenly; at the time of death, the event of cerebrovascular accident was reported as not resolved.

- Subject (b) (4) A 74-year-old man with past medical history of hypertension, heart failure, MI, and hyperlipidemia received canagliflozin 300 mg daily. Her baseline BUN and serum creatinine was slightly elevated with eGFR of 33 mL/min/1.73m^2. On Day 42, his renal function worsened with eGFR of 27 mL/min/1.73m^2. On Day 104, he had loose defibrillator lead, and was hospitalized about 10 days later for insertion of additional wires into his defibrillator. On Day 113, his eGFR was 31 mL/min/1.73m^2. During hospitalization, his health declined, and he developed nasal congestion on Day 167. Study drug was discontinued on Day 169. On Day 203, he was diagnosed with and died due to pneumonia and renal failure.

- Subject (b) (4): A 73-year-old man received canagliflozin 300 mg daily. His past medical history was significant for hyperlipidemia, HTN, MI, coronary artery disease, diabetic retinopathy and neuropathy, gastric operation (clipping of stomach vessels) and swallowing difficulty. On Day 111, he experienced weakness, fatigue, and fell due to dizziness at home; he had elevated glucose level (450, no unit provided). He was hospitalized next day and was diagnosed with Dieulafoy's vascular malformation, leading to gastrointestinal hemorrhage

and sepsis syndrome. On Day 112, he had a pulseless electrical activity leading to cardiac arrest, and was resuscitated; he was also diagnosed with myelodysplastic syndrome. Laboratory results showed elevated WBC count, low RBC count, low hemoglobin and low hematocrit. Gastrointestinal hemorrhage resolved the next day, and sepsis syndrome resolved on Day 127. On Day 143, he was discharged and admitted to a nursing home, with severe swallowing difficulty and requiring suction. On Day 155, he died due to cardiac failure. No autopsy was done.

- Subject (b) (4) A 62-year-old postmenopausal woman with past medical history of HTN, coronary disease, angina pectoris, chronic pyelonephritis, and diabetic retinopathy and neuropathy received canagliflozin 300 mg daily. Her baseline eGFR was 46 mL/min/1.73m^2. On Day 92, she had dyspnea, edema of lower extremities, urinary retention, and nausea, and was diagnosed with worsening renal failure. Study drug was discontinued on Day 106 due to this event. She was hospitalized on Day 108, received four courses of hemodialysis, and was discharged on Day 159. On Day 172, her eGFR decreased substantially to 7 mL/min/1.73m^2. On Day 288, she was hospitalized due to hepatic cirrhosis, and died on Day 288. Her baseline liver function tests were normal except for elevated ALP and GGT levels (171 U/L [normal 35-123 U/L] and 205 U/L [5-50 U/L] respectively). Not much other information was provided regarding hepatic event. Her renal and liver laboratory changes are shown here:

Subject Identifier for the Study (b) (4)

Study Day <a>	Date of Specimen Collection	Lab Name <b>	BUN (mmol/L)	BUN LLN/ULN (mmol/L)	CREAT (umol/L)	CREAT LLN/ULN (umol/L)	eGFR (mL/min/1.73m2)
-21	(b) (4)	(b) (4)	8.4	(1.4 - 8.6)	116	(31 - 101)	41
-14					10.39	(-)	
1					106	(31 - 101)	
1			7.5	(1.4 - 8.6)	13.19	(-)	46
51			12.9	(1.4 - 8.6)	121	(31 - 101)	39
172			14.3	(1.4 - 8.6)	549	(31 - 101)	7

Note: <a>: Relative to first dose of treatment.
Note: <b>: (b) (4) L=LOCAL
Note: BUN=Blood Urea Nitrogen; CREAT=Creatinine; eGFR=Estimated Glomerular Filtration Rate
(b) (4) rtf generated by r9mr61c06.sas, 04NOV2011 22:11

Subject Identifier for the Study: (b) (4)

Study Day <a>	Date of Specimen Collection	Lab Name <b>	ALT (U/L)	ALT LLN/ULN (U/L)	AST (U/L)	AST LLN/ULN (U/L)	BILI (umol/L)	BILI LLN/ULN (umol/L)	ALP (U/L)	ALP LLN/ULN (U/L)	GGT (U/L)	GGT LLN/ULN (U/L)
-21	(b) (4)	(b) (4)	27	(6 - 34)	40	(9 - 34)	11	(3 - 21)	170	(35 - 123)	169	(5 - 50)
1			48	(6 - 34)	61	(9 - 34)	12	(3 - 21)	171	(35 - 123)	205	(5 - 50)
51			27	(6 - 34)	42	(9 - 34)	9	(3 - 21)	136	(35 - 123)	89	(5 - 50)
172			17	(6 - 34)	29	(9 - 34)	10	(3 - 21)	171	(35 - 123)	65	(5 - 50)

Note: <a>: Relative to first dose of treatment.
Note: <b>: (b) (4) L=LOCAL
Note: BILI = BILIRUBIN; ALP = ALKALINE PHOSPHATASE; GGT=GAMMA GLUTAMYL TRANSFERASE.
Note: * ALT>3XULN;
Note: + BILI>2XULN.

Other deaths from ADAE dataset

Table 35 lists adverse events with an outcome of death from ADAE dataset which were reported after Clinical Study Reports (CSR) were completed, which included deaths after the core double-blind period for all trials except DIA3008. For DIA3008, the interim analysis CSR included data up to September 15, 2011, and therefore deaths after September 15, 2011 are listed below. Narratives were not available for these cases since the applicant referred to CSRs for narratives for subjects who died, and these deaths occurred after CSRs were completed. These additional treatment-emergent adverse events with an outcome of death reported with canagliflozin showed similar pattern of events as described above during the core double-blind periods and data up to the interim analysis for DIA3008.

Table 35: Adverse Events with an Outcome of Death from ADAE Dataset - Reported After September 15, 2011 for DIA3008 and After Core Double-Blind Period for Other Phase 3 Trials

Subject ID	Treatment Group	AGE	SEX	Days to Onset	TEAE?	Adverse Event
28431754DIA3004-007012-400309	Cana 100 mg	69	M	83	Y	Intestinal perforation
28431754DIA3005-027003-501279	Placebo	60	F	134	Y	Pulmonary tuberculosis
28431754DIA3006-051011-602651	Sita 100 mg	57	M	75	Y	Acute myocardial infarction
28431754DIA3009-007006-901302	Cana 100 mg	61	F	83	Y	Poisoning
(b) (4)	Cana 100 mg	70	M	600	N	Death
	Cana 100 mg	63	M	495	Y	Haemorrhage intracranial
	Cana 100 mg	62	M	642	Y	Cardiac arrest
	Cana 100 mg	66	F	257	Y	Respiratory distress
	Cana 100 mg	69	M	608	Y	Myocardial infarction
	Cana 300 mg	58	F	563	Y	Cardiac arrest
	Cana 300 mg	83	M	31	N	Sudden death
	Cana 300 mg	68	F	361	Y	Cardiac death
	Cana 300 mg	59	M	305	Y	Cardiogenic shock
	Cana 300 mg	64	M	450	Y	Septic shock
	Cana 300 mg	68	M	124	N	Intestinal ischaemia
	Cana 300 mg	62	F	439	N	Metabolic encephalopathy, Urosepsis
	Placebo	70	M	102	N	Sudden death
	Placebo	70	M	414	Y	Pancreatic carcinoma
	Placebo	70	F	630	Y	Respiratory arrest, Atrial fibrillation, Ischemic stroke, Hemoptysis, Epistaxis
	Placebo	62	M	453	Y	Cardiac arrest
	Placebo	64	F	328	Y	Appendicitis perforated, Septic shock
	Placebo	66	M	370	Y	Death
	Placebo	63	F	430	Y	Brain stem hemorrhage

TEAE=Treatment Emergent Adverse Event, where event occurred within 30 days of study discontinuation; Y=yes; N=no; M=male; F=female

4-Month Safety Update

At 4-Month Safety Update (4MSU), there were additional 8 deaths with canagliflozin 100 mg, 7 with canagliflozin 300 mg, and 24 with placebo that were treatment-emergent, and these deaths are listed in Table 36. Narratives for deaths at 4MSU were not provided. Most of these deaths were reported from trial DIA3008, and appear to be related to cardiovascular and/or cerebrovascular disorder.

There were three additional cases of malignancy-related deaths with canagliflozin, one case of pancreatic carcinoma, esophageal adenocarcinoma, and small cell carcinoma of lung.

Adverse event for subject (b) (4) from Table 35 who received canagliflozin 300 mg daily was also updated from "cardiac death" to "pulmonary embolism" at 4MSU.

Table 36: Listing of New Treatment Emergent Deaths from 4-Month Safety Update

Tx Group	Study	Subject ID	Age	Sex	Days of onset	Adverse Event
Cana 100	DIA3004	400718	80	M	113	Small cell carcinoma of lung, metastatic
Cana 100	DIA3004	400511	84	F	391	Acute myocardial infarction
Cana 100	DIA3008	(b) (4)	67	M	482	Myocardial infarction
Cana 100	DIA3008		62	M	382	Hemorrhagic stroke
Cana 100	DIA3008		68	M	446	Death
Cana 100	DIA3008		66	F	607	Sepsis
Cana 100	DIA3008		66	M	384	Pancreatic carcinoma
Cana 100	DIA3009		49	M	545	Acute renal failure, pulmonary embolism
Cana 300	DIA3008		75	M	470	Esophageal adenocarcinoma
Cana 300	DIA3008		64	M	872	Basilar artery occlusion
Cana 300	DIA3008		70	M	543	Cardiac death
Cana 300	DIA3008		61	M	429	Sepsis with acute kidney failure, Myocardial ischemia
Cana 300	DIA3008		64	M	460	Sudden death
Cana 300	DIA3008		77	M	466	Cardiac arrest
Cana 300	DIA3008		69	M	114	Sepsis
Placebo	DIA3004	400587	69	M	323	Cor pulmonale, Respiratory failure
Placebo	DIA3008	(b) (4)	55	M	232	Myocardial infarction, Pulseless electrical activity
Placebo	DIA3008		77	M	632	Hodgkin's disease
Placebo	DIA3008		66	M	732	Sepsis, Respiratory failure, Pneumnia, Oliguria, Renal failure acute

Placebo	DIA3008	(b) (4)	80	M	119	Cardio-respiratory arrest
Placebo	DIA3008		50	M	364	Myocardial infarction
Placebo	DIA3008		59	M	173	Cardiac failure chronic
Placebo	DIA3008		55	M	99	Cardiac arrest
Placebo	DIA3008		73	F	411	Acute myocardial infarction
Placebo	DIA3008		75	F	160	Pulmonary embolism
Placebo	DIA3008		74	M	472	Sudden death
Placebo	DIA3008		64	M	646	Bronchial carcinoma, lobar pneumonia, metastases to bone
Placebo	DIA3008		77	M	365	Bronchial carcinoma
Placebo	DIA3008		69	M	480	Lung neoplasm malignant, Lung cancer metastatic, Dyspnea
Placebo	DIA3008		64	M	62	Sudden death
Placebo	DIA3008		61	M	64	Hemorrhagic stroke
Placebo	DIA3008		61	M	770	Cardiac failure congestive
Placebo	DIA3008		66	F	201	Sudden death
Placebo	DIA3008		77	M	259	Pancreatic carcinoma
Placebo	DIA3008		55	M	153	Sudden cardiac death
Placebo	DIA3008		52	M	68	Death
Placebo	DIA3008		76	F	63	Cardio-respiratory arrest
Placebo	DIA3008		64	M	97	Sudden death
Placebo	DIA3008		45	M	629	Cardiac failure

Source: LAE01_04_01JUL12, 4-Month Safety Update

One subject died in Phase 2 trial DIA2003. Subject 230105, a 61-year-old man in the canagliflozin 150 mg twice daily group was diagnosed with colon cancer on Day 42 and died on Day 243 due to advanced cancer and metastasis. The oncology and surgical investigational reports showed moderately-differentiated invasive adenocarcinoma.

7.3.2 Nonfatal Serious Adverse Events

Placebo-Controlled Studies Dataset (DS1)

In the Placebo-Controlled Studies Dataset (DS1), the incidence of nonfatal serious adverse events (SAEs) were low and similar between placebo group (3.4%) and canagliflozin groups (3.4% with 100 mg and 2.6% with 300 mg). No dose-dependent trend in SAE reporting by System Organ Class (SOC) or Preferred Term (PT) was observed.

Most SAEs were reported in one subject in the canagliflozin group except for the following events:

- Compared to none with placebo, two subjects with canagliflozin 100 mg reported atrial fibrillation, coronary artery disease, pneumonia, and urticaria.
- Compared to none with placebo, two subjects with canagliflozin 300 mg reported urinary tract infection and deep vein thrombosis.

Adverse events of urinary tract infections are discussed in section 7.3.11, adverse events of thrombosis are discussed in section 7.3.8, and adverse events of urticaria are discussed in section 7.3.3. The overall cardiovascular risk for canagliflozin was not found to be increased, and this is discussed in further detail in section 7.3.13.

Moderate Renal Impairment Dataset (DS2)

In the Moderate Renal Impairment Dataset, the overall incidence of nonfatal SAEs was slightly higher with placebo (19.6%) compared to canagliflozin groups (13.3% with 100 mg and 14.8% with 300 mg). The incidence of any particular SAE was low, with most reported in one or two subjec. The only AE that occurred in more than 2 subjects in a canagliflozin group was cardiac failure congestive, which occurred in 4 subjects with canagliflozin 300 mg group (compared to one with placebo).

Few serious adverse events related to renal disorder such as renal failure, renal failure acute, or renal impairment occurred with canagliflozin 300 mg group (5 subjects) compared to canagliflozin 100 mg (3 subjects) or placebo (4 subjects). Renal-related adverse events are discussed in section 7.3.7.

Broad Dataset (DS3) and Longer-Term Exposure Broad Dataset (DS4)

In the Broad Dataset (DS3), the overall incidence of nonfatal SAEs was comparable between treatment groups, 7.7% with canagliflozin 100 mg, 8.1% with canagliflozin 300 mg, and 8.3% with non-canagliflozin group. In the Longer-term Exposure Broad Dataset (DS4), the overall incidence of nonfatal SAEs was again not increased with canagliflozin groups (10.6% and 10.7% with canagliflozin 100 mg and 300 mg respectively) compared to non-canagliflozin group (11.6%). Since trends in nonfatal SAEs are similar between DS3 and DS4, and DS3 and DS4 are same datasets with longer follow-up in DS4, data from DS4 are further discussed here.

The overall incidence of any particular SAE was low, with most events having an incidence of less than 0.1%. Table 37 lists nonfatal SAEs with at least 2 events (0.1%) in any canagliflozin group, where the incidence was higher with either canagliflozin group compared to non-canagliflozin group.

As previously mentioned, cardiovascular risk for canagliflozin was evaluated through meta-analysis of MACE-plus events across Phase 2 and 3 trials. An increased incidence of phimosis was observed from trial DIA3008, and are further discussed in male genital mycotic infections (see section 7.3.10). Some other increased incidences seen with canagliflozin that are shown in Table 37, such as pulmonary embolism and thrombosis (see section 7.3.8), malignancies (see section 7.3.16), fractures (see section 7.3.9) and renal impairment and related increased blood creatinine (see section 7.3.7) are safety concerns that are discussed in specific sections.

Table 37: Treatment Emergent Nonfatal SAE in DS4 - At Least 2 Events (0.1%) in Any Canagliflozin and Higher Incidence Compared to Non-Canagliflozin

System Organ Class	Preferred Term	Cana 100		Cana 300		Non-Cana	
		N	%	N	%	N	%
Blood and lymphatic system disorders	Iron deficiency anaemia	2	0.1	0	0.0	0	0.0
Cardiac disorders	Angina unstable	3	0.1	6	0.2	3	0.1
	Atrial fibrillation	8	0.3	8	0.3	5	0.2
	Atrial flutter	2	0.1	0	0.0	0	0.0
	Cardiac arrest	2	0.1	2	0.1	1	0.0
	Cardiac failure congestive	4	0.1	7	0.2	4	0.1
	Ventricular tachycardia	1	0.0	2	0.1	0	0.0
Congenital, familial and genetic disorders	Phimosis	1	0.0	3	0.1	0	0.0
Ear and labyrinth disorders	Vertigo	2	0.1	0	0.0	0	0.0
Eye disorders	Cataract	2	0.1	5	0.2	3	0.1
Gastrointestinal disorders	Gastrointestinal haemorrhage	0	0.0	4	0.1	1	0.0
	Haemorrhoids	3	0.1	0	0.0	0	0.0
	Ileus	2	0.1	0	0.0	0	0.0
	Inguinal hernia	3	0.1	3	0.1	1	0.0
	Pancreatitis	2	0.1	1	0.0	1	0.0
	Pancreatitis acute	2	0.1	0	0.0	0	0.0
	Small intestinal obstruction	1	0.0	2	0.1	0	0.0
General disorders and administration site conditions	Chest discomfort	2	0.1	0	0.0	0	0.0
	Chest pain	11	0.4	9	0.3	8	0.2
	Impaired healing	2	0.1	0	0.0	1	0.0
	Medical device complication	0	0.0	2	0.1	0	0.0
Hepatobiliary disorders	Bile duct stone	2	0.1	1	0.0	1	0.0
	Cholecystitis acute	2	0.1	2	0.1	1	0.0
Infections and infestations	Anal abscess	2	0.1	0	0.0	1	0.0
	Localised infection	0	0.0	2	0.1	1	0.0
	Osteomyelitis	4	0.1	5	0.2	2	0.1
	Staphylococcal infection	3	0.1	0	0.0	0	0.0
	Subcutaneous abscess	1	0.0	2	0.1	0	0.0
Injury, poisoning and procedural complications	Concussion	0	0.0	2	0.1	1	0.0
	Humerus fracture	0	0.0	3	0.1	1	0.0
	Laceration	1	0.0	2	0.1	0	0.0
	Lower limb fracture	2	0.1	0	0.0	1	0.0
	Meniscus lesion	2	0.1	1	0.0	0	0.0
	Rib fracture	1	0.0	2	0.1	0	0.0
	Sternal fracture	2	0.1	0	0.0	0	0.0
	Wound	0	0.0	2	0.1	0	0.0
	Wound complication	0	0.0	3	0.1	0	0.0

Investigations	Arteriogram coronary	2	0.1	1	0.0	0	0.0
	Blood creatinine increased	2	0.1	0	0.0	1	0.0
	Hepatic enzyme increased	0	0.0	2	0.1	0	0.0
Metabolism and nutrition disorders	Diabetic ketoacidosis	3	0.1	1	0.0	1	0.0
	Hyperkalaemia	1	0.0	2	0.1	0	0.0
Musculoskeletal and connective tissue disorders	Arthralgia	4	0.1	1	0.0	1	0.0
	Osteoarthritis	12	0.4	7	0.2	3	0.1
	Spinal osteoarthritis	2	0.1	1	0.0	1	0.0
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Breast cancer	1	0.0	4	0.1	1	0.0
	Colon cancer metastatic	0	0.0	2	0.1	0	0.0
	Meningioma	0	0.0	2	0.1	0	0.0
	Myelodysplastic syndrome	1	0.0	2	0.1	0	0.0
	Uterine cancer	0	0.0	2	0.1	0	0.0
	Uterine leiomyoma	0	0.0	2	0.1	1	0.0
Nervous system disorders	Carotid artery stenosis	0	0.0	5	0.2	2	0.1
	Cerebral infarction	1	0.0	2	0.1	0	0.0
	Presyncope	2	0.1	0	0.0	0	0.0
Renal and urinary disorders	Calculus ureteric	2	0.1	0	0.0	1	0.0
	Haematuria	1	0.0	3	0.1	1	0.0
	Hydronephrosis	2	0.1	1	0.0	0	0.0
	Renal artery stenosis	2	0.1	0	0.0	0	0.0
	Renal impairment	3	0.1	5	0.2	3	0.1
Reproductive system and breast disorders	Benign prostatic hyperplasia	1	0.0	4	0.1	0	0.0
Respiratory, thoracic and mediastinal disorders	Pulmonary embolism	2	0.1	5	0.2	1	0.0
Skin and subcutaneous tissue disorders	Urticaria	4	0.1	0	0.0	0	0.0
Vascular disorders	Intermittent claudication	1	0.0	2	0.1	1	0.0
	Peripheral ischaemia	5	0.2	4	0.1	1	0.0
	Thrombosis	2	0.1	0	0.0	0	0.0

SOURCE: ADAE

Pancreatitis: There was a death related to hemorrhagic pancreatitis with canagliflozin (see section 7.3.1), and an increased incidence of SAEs related to pancreatitis was seen with canagliflozin compared to placebo (5 SAEs of pancreatitis and acute pancreatitis in the combined canagliflozin group compared to one in placebo) in DS4.

A search for events related to pancreatitis was conducted in DS4, using the High Level Term "Acute and Chronis Pancreatitis". This showed that there was an increased incidence of pancreatitis with canagliflozin treatment compared to placebo, as shown in Table 38, with the highest incidence observed with canagliflozin 100 mg.

Table 38: Incidence of Pancreatitis in DS4 - Regardless of Rescue

	Non-Cana	Cana 100	Cana 300
Incidence of pancreatitis	0.1% (3/3262)	0.4% (12/3092)	0.1% (4/3085)
Incidence per 1000 subject-years	0.9	3.5	1.2
Pancreatitis	1	2	3
Pancreatitis acute	0	2	0
Pancreatitis chronic	1	6	1
Pancreatitis hemorrhagic	0	1	0
Pancreatic cyst	1	1	0

Source: ADAE

Urticaria: Four SAEs of urticaria are summarized here:

- Subject 501186 (DIA3005), a 76-year-old woman with history of HTN and hypercholesterolemia received canagliflozin 100 mg. She had no known allergies or any history of previous hypersensitivity. On Day 1, about 8.5 hours after the first dose of study drug, she developed SAE of **urticarial skin rash** associated with itching and oozing, all over the body including groin areas and lower and upper extremities. She did not receive any further study drug, and was treated with clemastine, cholecalciferol, hydrocortisone, prednisone, and loratadine. On Day 9, her skin condition improved and oozing was resolved. The following day, prednisone was stopped, and loratidine was started until Day 24. Urticaria resolved on Day 21. She was withdrawn from the study on Day 101 due to this event.

  Reviewer's comment: This SAE of urticarial skin rash, which was oozing all over the body, is suggestive of immediate hypersensitivity reaction. This subject also discontinued the study due to urticaria. Despite treatment, urticaria resolved after 20 days.

- Subject 501382 (DIA3005), a 41-year-old woman with previous history of urticaria received canagliflozin 100 mg and had a recurrence of urticaria on her chest associated with itching, along with diarrhea. She was treated with loratadine on Day 186 but her symptoms of urticaria worsened, and on Day 194, she was hospitalized for urticaria. She was treated with IV dexamethasone and prednisolone ointment during hospitalization. Urticaria resolved on Day 199. No action was taken with the study drug.

- Subject 900799 (DIA3009), a 70-year-old woman with history of penicillin allergy received canagliflozin 100 mg. She was also treated with tramadol on Days 180 to 193 for sciatica. On Day 193, she developed urticaria all over his body with associated fever and was hospitalized. She did not receive any treatment for urticaria and study drug was interrupted on Day 193; urticaria resolved on Day 201. Study drug was not restarted, and she was withdrawn from the study on Day 231 due to protocol violation.

Reviewer's comment: Tramadol is a likely co-suspect drug since it has been associated with skin problems such as urticaria, and there is a positive temporal relationship between tramadol and the onset of urticaria in this subject.

- Subject (b) (4) (DIA3008), a 67-year-old woman with no medical history of urticaria was diagnosed with urticaria on Day 13 and hospitalized. She had itching mainly on her chest region. Urticaria resolved on Day 16, and the subject was discharged the same day. No action was taken with the study drug.

DIA3015

The overall incidence of nonfatal SAEs in this trial was low and similar between canagliflozin 300 mg and sitagliptin 100 mg group. Only one nonfatal SAE, vaginal hemorrhage, were reported in more than one subject in the canagliflozin group. These two cases of vaginal hemorrhage are briefly described:

- Subject 150664, a 61-year-old postmenopausal woman with history of hypertension and hypertriglyceridemia received canagliflozin 300 mg. On Day 158, she presented with vaginal hemorrhage, and a pelvic ultrasound on Day 163 showed thickened echogenic endometrium (early carcinoma) and subserosal fibroid uterus. On Day 164, she was hospitalized and curettage biopsy was done with normal results. On Day 169, subsequent endometrium and cervix biopsy results showed a grade 2 squamous cell carcinoma of cervix extending into endometrium and she was diagnosed with cervix carcinoma. On Day 179, she underwent a total hysterectomy with bilateral salpingo-oophorectomy. Postoperative histology results showed well differentiated squamous cell carcinoma with infiltration into the endomyometrium and lymphovascular invasion. Study drug was discontinued on Day 191 and subject was withdrawn from the study on Day 238.

- Subject 151507, a 55-year-old postmenopausal woman with history of dyslipidemia, systemic arterial hypertension, hepatic steatosis, overweight, uterine leiomyoma, renal cyst, and tubal ligation received canagliflozin 300 mg daily. She had no history of vaginal hemorrhage. On Day 209, she was diagnosed with vaginal hemorrhage, received ferrous sulfate, and resolved the same day. On Day 228, she again had vaginal hemorrhage for a few hours, was treated with tibolone and concentrated red blood cells, and the event again resolved the same day. On Day 290, she again had vaginal hemorrhage, no treatment was given, and the event resolved on Day 299. She received the last dose of study drug on Day 358 and completed the study on the same day.

  Reviewer's comment: This subject had underlying uterine leiomyoma, which may have been the cause for vaginal hemorrhage.

7.3.3 Dropouts and/or Discontinuations

Placebo-Controlled Studies Dataset (DS1)

In the Placebo-Controlled Studies Dataset, the overall incidence of subjects with adverse events that led to discontinuation of study drug was slightly higher with canagliflozin groups (4.3% with 100 mg and 3.6% with 300 mg) compared to placebo (3.1%). Adverse events that led to discontinuation in more than one subject with either canagliflozin group is listed in Table 39.

Table 39: Adverse Events (N[%)) Leading to Treatment Discontinuation in More Than One Subject with Canagliflozin 100 mg or 300 mg Group - DS1

	Placebo (N=646)	Cana 100 mg (N=833)	Cana 300 (N=834)
Nausea	1 (0.2)	2 (0.2)	0
Pneumonia	0	3 (0.4)	0
Vulvovaginal Mycotic Infection	0	3 (0.4)	0
Blood Creatinine Increased	0	0	2 (0.2)
Blood Potassium Increased	1 (0.2)	0	2 (0.2)
Glomerular Filtration Rate Decreased	1 (0.2)	2 (0.2)	5 (0.6)
Weight Decreased	0	2 (0.2)	1 (0.1)
Pollakiuria	0	1 (0.1)	2 (0.2)

Aside from Infections and Infestations SOC (mostly due to pneumonia, vaginal infections-related events), Investigations SOC (mostly due to changes in renal function or potassium), and Renal and Urinary Disorders SOC, which will be discussed in specific event-related in the following sections, there was an imbalance in AEs leading to discontinuation in Skin and Subcutaneous Tissue Disorders SOC. Five subjects (0.6%) with canagliflozin 100 mg group compared to one subject (0.2%) in placebo discontinued due to skin-related AEs (none with canagliflozin 300 mg). Five subjects with canagliflozin 100 mg each discontinued due to angiodema, contact dermatitis, intertrigo, rash maculo-papular, and urticaria; one subject with placebo discontinued due to urticaria. This is further discussed under DS3 and DS4 below.

Moderate Renal Impairment Dataset (DS2)

In the Moderate Renal Impairment Dataset, the incidence subjects who discontinued due to adverse events was slightly higher with canagliflozin 300 mg (7.7%) compared to 100 mg (5.6%) and placebo (5.8%). Not unexpectedly, an imbalance in the Renal and Urinary Disorders SOC was seen, with higher incidence with canagliflozin 300 mg (1.9%; 7/365) compared to canagliflozin 100 mg (0.6%; 2/338) or placebo (0.8%; 3/382). Renal events are further discussed in section 7.3.7.

Broad Dataset (DS3) and Longer-Term Exposure Broad Dataset (DS4)

The overall incidence of subjects who discontinued due to adverse events was slightly higher with canagliflozin 300 mg (5.6%) and 100 mg (4.2%) compared to non-canagliflozin (3.7%). Similarly, a slight higher incidence of subjects who discontinued due to adverse events was

observed with canagliflozin 300 mg (6.5%) and 100 mg (4.8%) compared to non-canagliflozin group (4.4%).

In both datasets, there was a higher rate of discontinuations with canagliflozin in the General Disorders and Administration Site Conditions SOC related to higher incidence of adverse events of fatigue. Fatigue was reported in 10 subjects with canagliflozin (0.2%) compared to none with non-canagliflozin (both DS3 and DS4). Among these 10 subjects with fatigue with canagliflozin, UTI or genital mycotic infection-related events occurred in 3 subjects, and osmotic diuresis-related adverse events were seen in 2 subjects. In the Broad Dataset (DS3), there was a small imbalance in the overall incidence of fatigue between treatment groups, which was 2.1% and 1.7% in the combined canagliflozin group and non-canagliflozin group respectively. In the Longer-term Exposure Broad Dataset (DS4), the incidence is no longer imbalanced between treatment groups (2.2% with combined canagliflozin group compared to 2.1% with non-canagliflozin group).

Skin and Hypersensitivity: There was an imbalance in subjects with canagliflozin who discontinued due to AEs under Skin and Subcutaneous Tissue Disorders SOC in DS3 and DS4, reporting adverse events (rash, pruritus, urticaria) that are indicative of hypersensitivity reactions. DS4 data are shown in Table 40, and DS3 data are very similar with a couple of fewer events. Three subjects with canagliflozin also reported hypersensitivity reactions which led to discontinuation, classified under Immune System Disorders SOC, compared to none with non-canagliflozin group.

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

Three cases of hypersensitivity with canagliflozin leading to discontinuation, all from DIA3008, are summarized:

- Subject (b) (4) a 52-year-old man without any history of hypersensitivity, urticaria or other allergic reactions received canagliflozin 100 mg. On Day 1, one hour after ingestion of study drug, he developed rash, redness, itching and urticaria on trunk, face, and both of the arms, accompanied by pruritus of type 1 allergic reaction. The allergic reaction did not involve mucosa of lips and mouth, and he did not have fever, arthralgia, or lymphadenopathy. He was diagnosed with **hypersensitivity**. He was treated with cetirizine, study drug was discontinued, and the event of hypersenstivity resolved on Day 2.

- Subject (b) (4), a 50-year-old obese (BMI 41 kg/m^2) man with history of HTN, MI, dyslipidemia, hyperuricemia, and hepatitis steatosis received canagliflozin 300 mg. On Day

1, he developed face flush and was diagnosed with **hypersensitivity**. Study drug was discontinued on Day 3 due to hypersensitivity, which resolved on Day 17.

- Subject (b) (4) a 69-year-old man with history of HTN, MI, and arrhythmias received canagliflozin 100 mg daily. On Day 7, he developed erythematous papulous skin lesions on thighs, penis, buttocks, and groin area. He was diagnosed with **drug hypersensitivity**, and a skin biopsy was done to evaluate erythematous papulous skin lesions on Day 64; results were not available. He was treated with miconazole/hydrocortisone and fluticasone. Study drug was discontinued on Day 77, and drug hypersensitivity was reported as resolved on Day 117.

One case of angioedema with canagliflozin leading to discontinuation is summarized:

- Subject 500284 (DIA3005), a 67-year-old woman with seasonal allergic rhinitis (for 5-6 years) received canagliflozin 100 mg daily. On Day 22, she had an adverse event of **angioedema** (reported term was angioedema upper lip). She was treated with fexofenadine and dexamethasone, and the event resolved on Day 23. Study drug was withdrawn and subject withdrawn from study due to angioedema.

Four cases of rash with canagliflozin leading to discontinuation is summarized:

- Subject 602092 (DIA3006), a 63-year-old postmenopausal woman with no previous history of rash, allergies, or psoriasis received canagliflozin 100 mg daily. On Day 65, she complained of pruritus and developed a **maculo-papular rash** (reported term: itchy skin rash occipital scalp, back and right forefoot, type micropapules and erythematosus). The appearance of maculo-papular rash was noted as marked xerosis and excoriated eczematous plaques, with signs of scratching. She was treated with loratadine and ranitidine, but skin rash persisted on Day 77, and she received hydroxyzine. She received betamethasone on Day 86 because skin rash remained unresolved. Study drug was discontinued on Day 113 due to maculo-papular rash. On Day 115, she received desloratadine and clobetasol. She was discontinued from study on Day 127, and was further treated with betamethasone. The event of maculo-papular rash resolved on Day 231.

- Subject 900184 (DIA3009), a 51-year-old postmenopausal woman received canagliflozin 100 mg daily and developed **rash** (patchy red skin over arms, shoulders, and legs) with itching on Day 1. Study drug was discontinued on Day 8 due to pruritus, and rash resolved on Day 11 and pruritus resolved on Day 12. She was withdrawn from the study due to rash on Day 19.

- Subject 900232 (DIA3009), a 48-year old woman with history of acanthosis nigricans, dry skin, and seasonal allergies received canagliflozin 300 mg daily. On Day 32, she developed diffuse pustular lesions associated with itching, burning, and tingling on arms, legs, face, and trunk, and an event of **rash pustular** (reported term: generalized, pustular skin rash) was reported. She was treated with hydrocortisone and diphenhydramine, study drug was

discontinued on Day 127, and she was withdrawn from the study on Day 162. The rash pustular resolved on Day 213.

- Subject 902397 (DIA3009), a 45-year-old woman received canagliflozin 300 mg. On Day 3, she developed generalized maculopapular rash all over the body and reported event of **rash erythematous**. Study drug was discontinued on Day 3 and she was withdrawn from study on Day 5 due to this event. She was treated with dexamethasone, cetirizine, levocetirizine, deflazacort, and pheniramine, and the event resolved on Day 10.

In addition, one case of rash with canagliflozin leading to discontinuation in DIA3005 substudy is summarized (this substudy was not included in any pooled safety dataset):

- Subject 501572, a 58-year-old man received canagliflozin 300 mg. On Day 25, he presented with facial **urticarial rash**, described as red and raised in patches, associated with itching. He had no fever or chills or any other systemic signs or symptoms. On Day 30, he discontinued study drug due to rash, and started treatment with loratadine. He was withdrawn from study on Day 32 due to rash. On Day 33, rash (described as red papular) expanded to the back of the subject's hands, and resolved on Day 44.

There were two subjects with canagliflozin who discontinued due to urticaria, and one also had SAE of urticarial skin rash and are summarized under SAE (subject 501186, section 7.3.2). The remaining other subject is summarized:

- Subject (b) (4) (DIA3010), a 60-year-old man received canagliflozin 100 mg and developed a fine red rash and itching on the arms, legs, and trunk (**urticaria**) on Day 1. Study drug was temporarily interrupted due to urticaria, and he was treated with diphenhydramine with resolution on Day 7. On Day 13, he re-initiated study drug and a second urticarial event occurred the same day. He was discontinued from the study, was treated with diphenhydramine, cetirizine, and ranitidine with resolution on Day 17.

  Reviewer's comment: Positive dechallenge and rechallenge with urticaria are reported with urticaria in this subject.

An event of pemphigoid with canagliflozin that led to study discontinuation are summarized:

- Subject (b) (4) (DIA3008), a 73-year-old man with received canagliflozin 100 mg and developed bullous eruptions with exudative lesions on legs and chest on Day 117, and was diagnosed with **pemphigoid**. He was treated with hydroxyzine, ketoconazole, and hydrocortisone. Study drug was discontinued on Day 197, and pemphigoid resolved on Day 234.

Based on this increased incidence of skin-related allergic and hypersensitivity reactions, combined with SAEs of urticaria with canagliflozin (section 7.3.2), I further investigated for all skin-related and hypersensitivity reactions in DS4, using the following MedDRA terms:

- Under Skin and Subcutaneous SOC, following HLTs: Angioedemas, Urticarias, Bullous conditions, Dermal and epidermal conditions NEC, Dermatitis and eczema, Erythemas, Exfoliative conditions, Papulosquamous conditions, Pruritus NEC, Rashes, eruptions and exanthems NEC
- Under Immune System Disorders SOC, following HLTs: Allergic conditions NEC, Allergies to food, food additives, drugs and other chemicals, and Anaphylactic responses

The result of this search showed that there was a slight increased incidence of skin and hypersensitivity reactions with canagliflozin compared to non-canagliflozin group: 8.2% (255/3092) with 100 mg, 7.8% (240/3085) with 300 mg, and 6.2% (203/3262) with non-canagliflozin. However, non-canagliflozin group contains active comparator sitagliptin arm, and sitagliptin has been associated with hypersensitivity reaction. However, the incidence of skin and hypersensitivity events in non-canagliflozin group without 17 events with sitagliptin was similar at 6.4% (186/2896).

Reviewer's comment: There was an imbalance in the overall incidence of skin and hypersensitivity reactions between canagliflozin and non-canagliflozin not favoring canagliflozin. Review of case narratives in those with SAEs or who discontinued due to hypersensitivity and skin related events showed potential safety concern as these events showed positive temporal relationship with study drug initiation, and one case reported positive dechallenge and rechallenge. One case of angioedema of lips was also reported. These events should be labeled.

DIA3015

The incidence of adverse events leading to discontinuation was higher with canagliflozin 300 mg (5.3%) compared to sitagliptin 100 mg (2.9%) treatment group. The majority of events were reported in only one subject.

Similar to pooled datasets (DS1, DS3, DS4), an imbalance was observed in the Skin and Subcutaneous Tissue Disorders SOC, where 7 subjects in the canagliflozin group discontinued due to erythema, leukocytoclastic vasculitis, papule, rash pruritic, skin lesion, or pruritus generalized (in 2 subject), compared to none in the sitagliptin treatment group. The onset of these skin events varied between 2 to 113 days after randomization with duration of 5 to over 200 days.

One case of leukocystoclastic vasculitis are summarized here:

- Subject 150666, a 61-year-old man with no prior history of skin or autoimmune disease, had an adverse event of influenza on Day 81, which was treated with aspirin and resolved on Day 97. On Day 113, he had slightly itchy, red to purple maculopapulous exanthema on feet, legs, buttocks, and arms; study drug was discontinued on Day 123. On Day 134, he was referred to dermatologist, and was diagnosed with leukocytoclastic vasculitis (LCV) on examination. He was treated with antihistamine and steroid ointment. On Day 140, he was

hospitalized and treated with intravenous prednisolone. The LCV began to resolve and he was discharged on Day 144. He had two subsequent relapses of vasculitis, which worsened on Day 154 and 178 (31 and 55 days off study drug). Skin biopsy was not done. The event has not resolved as of Day 395.

Reviewer's comment: This is the only reported case of leukocystoclastic vasculitis with canagliflozin.

Discontinuations due to metformin creatinine or eGFR withdrawal criteria

Five Phase 3 trials where canagliflozin was studied as an add-on to metformin (either alone or in combination with other AHA) implemented withdrawal criteria based on serum creatinine or eGFR, since metformin label contains restriction for its use based on renal function. The number of subjects who discontinued in these trials because they met the withdrawal criteria for serum creatinine or eGFR is summarized in Table 41. Except for DIA3006, subject who discontinued because of metformin creatinine or eGFR withdrawal criteria was higher in canagliflozin groups compared to the placebo group, but this was not dose-dependent. The highest rate for discontinuation occurred in DIA3015, where 5.8% of subjects who received canagliflozin 300 mg discontinued due to increase in serum creatinine or decrease in eGFR. The reason for this is unclear, but it is notable that the rate for discontinuation for the active comparator group, sitagliptin, also had a higher rate of discontinuation due to this withdrawal criteria in DIA3015 (3.7%) compared to DIA3006 (0.8%). In DIA3015, 19 of 22 canagliflozin subjects had low baseline eGFR values of between 50 and 70 mL/min/1.73m^2.

Table 41: Number of Subjects (%) Discontinued due to Metformin Creatinine or eGFR Withdrawal Criteria

	Placebo	Cana 100	Cana 300	Sitagliptin	Glimepiride
DIA3006 - add-on to metformin	1 (0.5)	2 (0.5)	2 (0.5)	3 (0.8)	
DIA3009 - add-on to metformin		4 (0.8)	7 (1.4)		1 (0.2)
DIA3002 - add-on to metformin & SU	0	1 (0.6)	1 (0.6)		
DIA3012 - add-on to metformin & pioglitazone	0	3 (2.7)	1 (0.9)		
DIA3015 - add-on to metformin & SU			22 (5.8)	14 (3.7)	

Source: Table 3, Clinical Study Reports for each trial

7.3.5 Significant Adverse Events - Osmotic Diuresis

Because canagliflozin increases urinary glucose excretion, it acts as an osmotic diuretic with an increase in urine output. Phase 1 trials have shown that there is an increase in urine output as soon as Day 1. The applicant used the following PTs to identify and evaluate the clinical importance of diuresis related events with canagliflozin: PTs related to increase in urine output

such as increase in urine frequency [pollakiuria (i.e., abnormally frequent urination), micturition urgency, or micturition disorder], urine output (PTs of polyuria or urine output increased), and night time micturition (PT of nocturia), as well as those related to thirst (PTs of thirst, polydipsia, dry mouth, throat dry, or tongue dry).

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

Placebo-Controlled Studies Dataset (DS1)

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

Table 42: Osmotic Diuresis-Related Adverse Events in DS1 - Regardless of Rescue

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

Source: ISS, Table 113

Reviewer's comment: The incidence of osmotic diuresis-related adverse events is about 7-fold with canagliflozin group compared to placebo group.

Moderate Renal Impairment Dataset (DS2)

The incidence of osmotic diuresis-related adverse event was slightly higher in the canagliflozin 100 mg treatment group (4.1%) compared to canagliflozin 300 mg (3.8%) or placebo (3.7%), as shown in Table 43. The incidence of osmotic diuresis-related events did not increase in DS2 compared to DS1; however, the number of subjects in DS2 are smaller. None of the events were serious or led to discontinuation. Similar to DS1, pollakiuria and thirst were most commonly reported adverse event terms.

Table 43: Osmotic Diuresis-Related Adverse Events in DS2 - Regardless of Rescue

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

Source: ISS, Table 114, 115

Broad Dataset (DS3)

The incidence of osmotic diuresis-related adverse events was higher in the canagliflozin treatment groups (6.8% and 7.1% with 100 mg and 300 mg respectively) compared to placebo (1.9%) without dose-dependency, as shown in Table 44. None of the events were serious, and 16 subjects (0.3%) in the combined canagliflozin group and 1 subject (<0.1%) in the non-canagliflozin group discontinued due osmotic diuresis-related adverse event. Similar to DS1, the most commonly reported terms were pollakiuria, thirst, and polyuria.

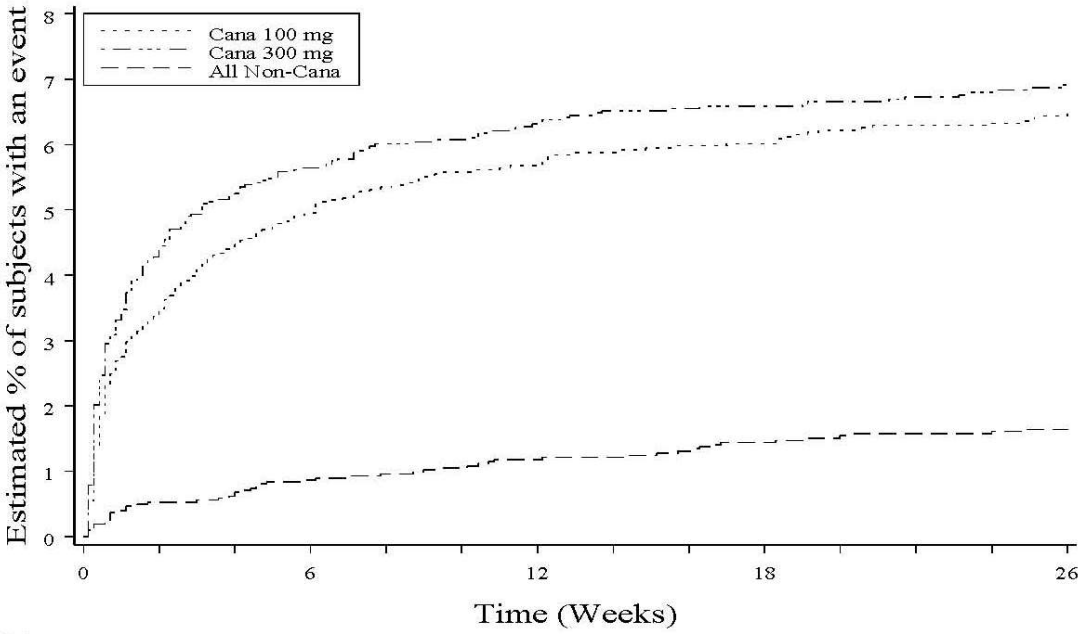
Table 44: Osmotic Diuresis-Related Adverse Events in DS3 - Regardless of Rescue

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

Source: ISS, Table 116, 117

In both canagliflozin groups, the majority of osmotic diuresis related adverse events occurred during the first 6 weeks of study and appear to plateau, as shown in the Kaplan-Meier curve in Figure 14 for DS3. The median duration of these adverse events was similar in the non-canagliflozin group (69 days) and canagliflozin group (73 and 62 days in 100 mg and 300 mg group respectively).

Figure 14: Kaplan-Meier Plot of Time to First Osmotic Diuresis Related Event in DS3



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

Source: ISS, Figure 12

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

7.3.6 Significant Adverse Events - Volume Depletion

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

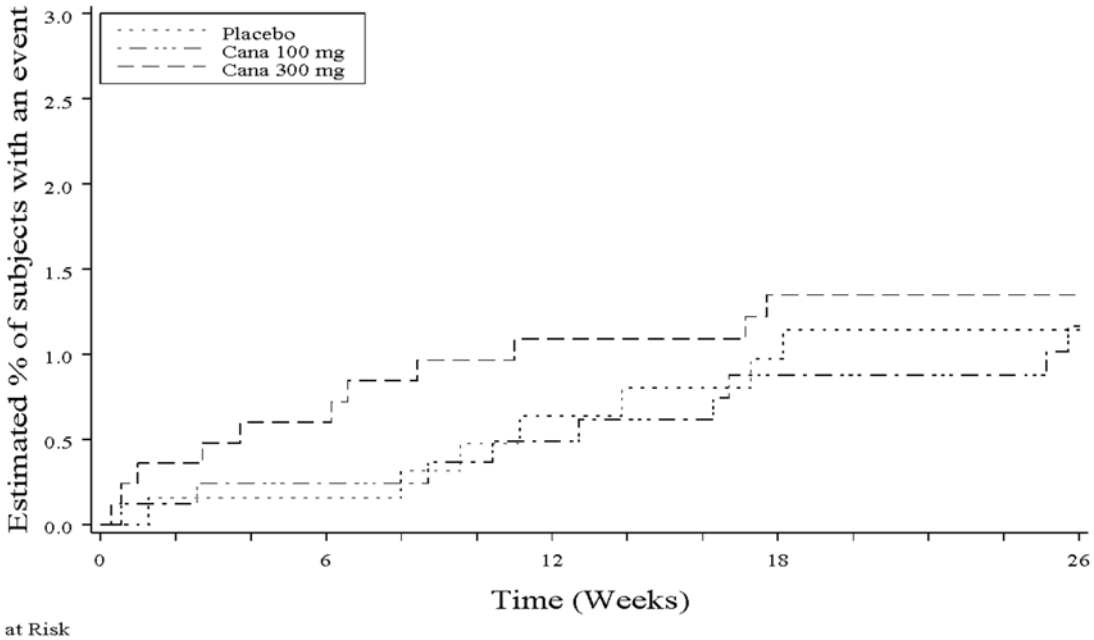
DS1 was the primary dataset for adverse event analysis, and results from DS2, DIA3008, and DS3 are also evaluated in order to provide information regarding volume depletion-related adverse events in older subjects, subjects with diminished renal function, and diabetic complications and co-morbidities,

Placebo-Controlled Studies Dataset (DS1)

The incidence of volume depletion-related adverse events was slightly higher in the canagliflozin treatment groups compared to the placebo group, and occurred in 10 (1.2%), 11 (1.3%), and 7 (1.1%) subjects in canagliflozin 100 mg, 300 mg, and placebo groups respectively. The incidence rate per 100 subject-years of exposure was 2.6, 2.8, and 2.4 for canagliflozin 100 mg, 300 mg, and placebo groups respectively. No subjects in the canagliflozin treatment group had volume depletion adverse events that were serious or led to discontinuation. The most commonly reported PT were hypotension (8 [0.5%] subjects in the combined canagliflozin group and 4 [0.6%] in the placebo group), dizziness postural (7 [0.4%] subjects in the combined canagliflozin group and 2 [0.3%] subjects in the placebo group), and orthostatic hypotension (4 [0.5%] in the canagliflozin 300 mg group and 1 [0.2%] subject in the placebo group). One subject in canagliflozin 100 mg group reported syncope.

The median time to onset of volume depletion adverse event was shorter in canagliflozin 300 mg group (43 days) compared to canagliflozin 100 mg group (102 days) or placebo group (78 days). In addition, more subjects in the canagliflozin treatment groups, particularly 300 mg dose group, had volume depletion-related adverse events within the first 30 days of treatment (5 [0.6%] subjects in canagliflozin 300 mg, 2 [0.2%] subjects in canagliflozin 100 mg, and 1 [0.2%] subject in placebo group). The Kaplan-Meier curve of volume depletion adverse event (Figure 15) showed that the higher incidence in the canagliflozin 300 mg group compared to canagliflozin 100 mg or placebo groups occur for about 18 weeks, after which difference between treatment groups narrowed.

Figure 15: Kaplan-Meier Plot of Time to First Volume Depletion Adverse Event - DS1



No. Subjects at Risk

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

Source: ISS, Figure 13

Moderate Renal Impairment Dataset (DS2)

The overall incidence of volume depletion adverse events was higher in DS2 compared to DS1, and was higher in the canagliflozin groups compared to the placebo group as shown in Table 45, showing dose-relationship. Similar to DS1, the canagliflozin treatment group showed an increase in the specific adverse events of dizziness postural, hypotension, and orthostatic hypotension. More syncope was reported with canagliflozin 300 mg in DS2 (three events) compared to DS1 (none).

Table 45: Volume Depletion Adverse Events in DS2 - Regardless of Rescue

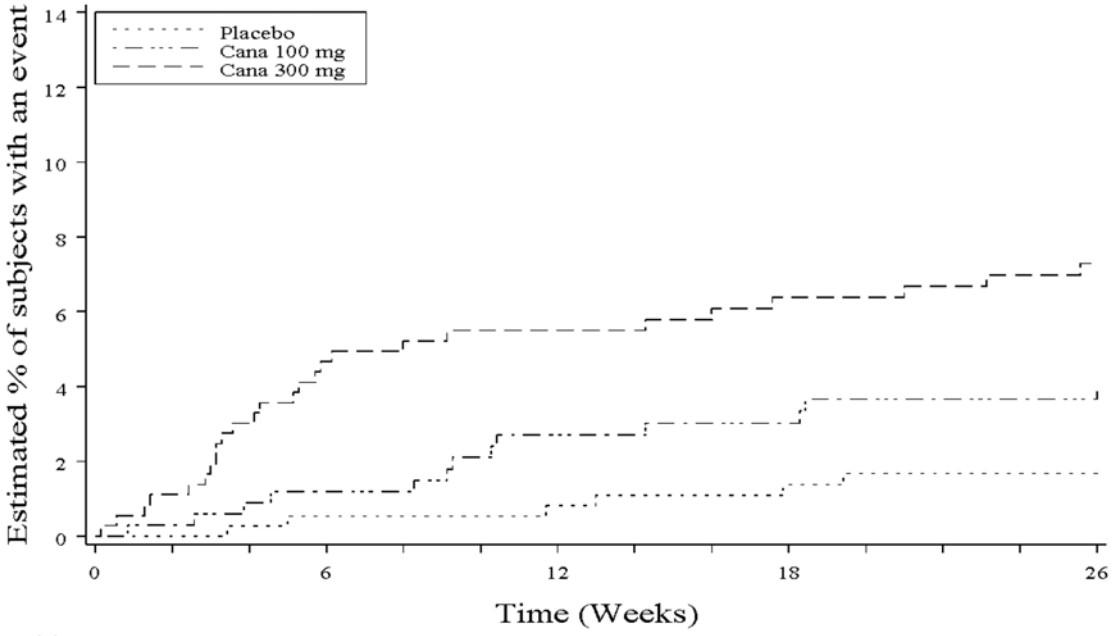
	Placebo (N=382)	Cana 100 (N=338)	Cana 300 (N=365)	Cana Total (N=703)
Any volume depletion AE, n (%)	10 (2.6)	17 (5.0)	31 (8.5)	48 (6.8)
Serious AE of volume depletion, n (%)	5 (1.3)	1 (0.3)	3 (0.8)	4 (0.6)
Volume depletion leading to discontinuation, n (%)	0	1 (0.3)	2 (0.5)	3 (0.4)
Incidence rate per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

Source: ISS, Table 121, 122

Reviewer's comment: The incidence of volume depletion-related events with canagliflozin was dose-dependent and 2-3 fold higher compared to placebo. The greater risk of volume depletion events was seen with both doses of canagliflozin in those with moderate renal impairment (DS2).

Similar to DS1, the median time to onset of volume depletion adverse event was shorter with canagliflozin 300 mg (40 days) compared to canagliflozin 100 mg (73 days) or placebo (131 days). Again, more subjects in the canagliflozin treatment groups, particularly with 300 mg dose, had volume depletion-related adverse events within the first 30 days of treatment (13 [3.6%] subjects in canagliflozin 300 mg, 3 [0.9%] subjects in canagliflozin 100 mg, and 1 [0.3%] subject in placebo group). This trend can be seen in the Kaplan-Meier curve for DS2 (Figure 16). However, unlike the Kaplan-Meier curve for DS1 (Figure 15), the difference between treatment group does not narrow over time.

Figure 16: Kaplan-Meier Plot of Time to First Volume Depletion Adverse Event - DS2



No. Subjects at Risk

Placebo	382	376	356	343	295
Cana 100 mg	338	330	318	305	259
Cana 300 mg	365	348	329	317	266

Source: ISS, Figure 14

Broad Dataset (DS3)

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

In DS3, the incidence of volume depletion adverse events was higher in the canagliflozin groups, and showed dose-relationship similar to DS2, as displayed in Table 46. The volume depletion adverse events that were serious or led to discontinuation were not notably different between treatment groups. Similar to DS1 and DS2, the increase in the incidence of volume depletion-related adverse events were due to dizziness postural, hypotension, and orthostatic hypotension.

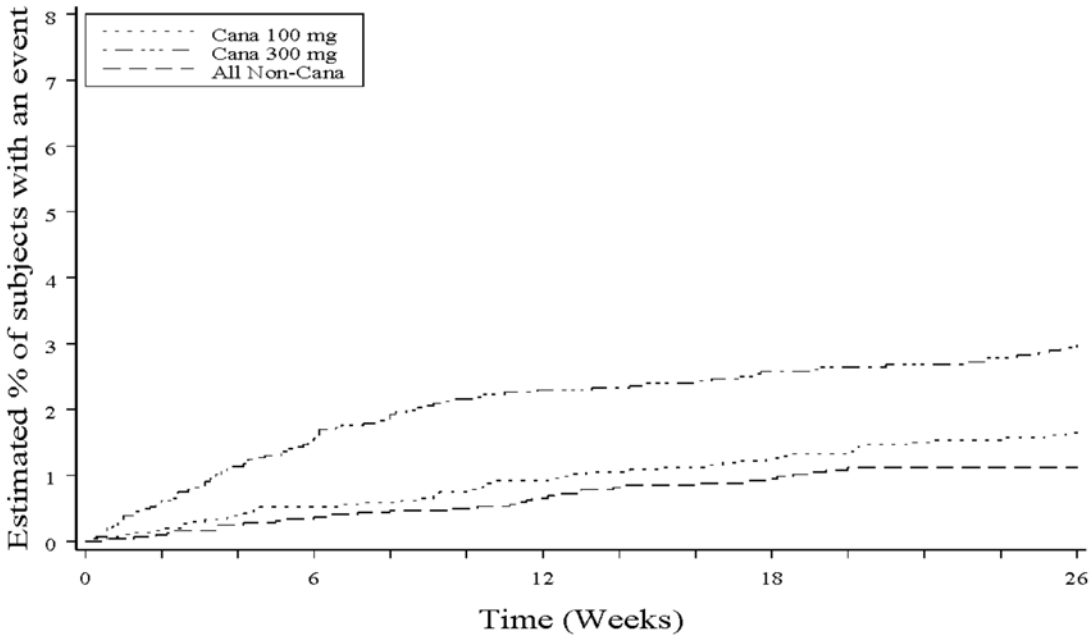
Table 46: Volume Depletion Adverse Events in DS3 - Regardless of Rescue

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

Source: ISS, Table 126, 127

Similar to DS1 and DS2, the median time to onset of volume depletion adverse event was shorter with canagliflozin 300 mg (46 days) compared to canagliflozin 100 mg (117 days) or non-canagliflozin (91 days) in DS3. Again, more subjects in the canagliflozin treatment groups, particularly with 300 mg, had volume depletion-related adverse events within the first 30 days of treatment (38 [1.2%] in canagliflozin 300 mg, 14 [0.5%] in canagliflozin 100 mg, and 9 [0.3%] in non-canagliflozin group). The Kaplan-Meier curve of time to first volume depletion adverse event for DS3 is shown in Figure 17, and the higher incidence with canagliflozin 300 mg compared to canagliflozin 100 mg or placebo persisted over 26 weeks.

Figure 17: Kaplan-Meier Plot of Time to First Volume Depletion Adverse Event - DS3



No. Subjects at Risk

Cana 100 mg	3092	3051	2955	2862	2513
Cana 300 mg	3085	3008	2864	2771	2407
All Non-Cana	3262	3224	3096	2973	2533

Source: ISS, Figure 16

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

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

Table 47: Subjects with Change in Selected Concomitant Medications in DS3

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

Source: ISS, Table 129, 130

Since volume depletion adverse events are related to the diuretic action of canagliflozin, the overlap of osmotic diuresis-related events with volume depletion-related events was evaluated. As shown in Table 48, a higher proportion of subjects in the combined canagliflozin group experienced volume depletion-related adverse events in subjects with osmotic diuresis-related adverse event (6.8%), compared to subjects without osmotic diuresis-related adverse event (2.6%). The overlap of diuresis and volume-depletion events showed dose-relationship, as 3.8% and 9.6% of subjects with canagliflozin 100 mg and 300 mg respectively had both diuresis and volume depletion events.

Table 48: Volume Depletion Adverse Events in Subjects With Diuresis-Related Adverse Events in DS3 - Regardless of Rescue

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

Source: ISS, Table DAE45BC_03, DAE45BCC_03

In order to assess risk factors for volume depletion-related adverse events, subgroup analyses based on baseline characteristics are evaluated, as shown on Table 49. Subjects with low baseline eGFR (<60 mL/min/1.73m^2) had an increased, dose-related risk of volume depletion adverse events. Concomitant use of ACE inhibitors or ARB or diuretics also demonstrated dose-related increase in the incidence of volume depletion adverse events. Higher risk of volume depletion was also seen in elderly (≥65 years of age) compared to younger subjects, and this increase in the incidence of volume depletion events were more prominent in subjects ≥75 years of age compared to <75 years of age.

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

Table 49: Subjects with Volume Depletion Adverse Events by Baseline Characteristics in DS3 - Regardless of Rescue

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

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

Source: ISS, Table 131

Since use of loop diuretics and low eGFR may potentially overlap, the effect of combining these two factors on the incidence of volume depletion events was assessed. As shown in Table 50, an increase in the incidence of volume depletion events in subjects with both factors (e.g., eGFR <60 and use of loop diuretics) compared to those with only one of these factors was only appreciably seen with canagliflozin 300 mg.

Table 50: Subjects with Volume Depletion Adverse Events by eGFR and Use of Loop Diuretics at Baseline in DS3 - Regardless of Rescue

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

[a] Incidence of volume depletion adverse events based upon a prespecified list of preferred terms from a MedDRA query listed in the SAP.
[b] Number of subjects in the Safety Analysis Set with the baseline characteristic.
Source: ISS, Table 132

Based on these subgroup analyses, the applicant propose labeling the starting canagliflozin dose of 100 mg for subjects on loop diuretics, moderate renal impairment, and ≥75 years of age, with titration to 300 mg dose if additional glycemic control is needed.

Reviewer's comment: Although subgroup analyses showed that subjects with these factors are at higher risk for developing volume depletion-related event, whether this dose titration would reduce the risk of volume depletion-related adverse events in these subjects has not been prospectively evaluated.

DIA3008 (CANVAS) Interim Analysis

As discussed previously, subjects enrolled in trial DIA3008 are older, with longer duration of diabetes, declining renal function, and more diabetes complications and co-morbidities compared to subjects enrolled in trials comprising DS1 and are likely to be affected by the volume depletion-related events.

In DIA3008, the overall incidence of volume depletion adverse events was higher in the canagliflozin groups compared to placebo, and showed dose-relationship, as shown in Table 51. Tthree subjects in the canagliflozin group and none in the placebo group discontinued due to

volume depletion-related adverse event. Similar to DS1 and DS2, the increase in the incidence of volume depletion-related adverse events were due to dizziness postural, hypotension, and orthostatic hypotension.

Table 51: Volume Depletion Adverse Events in DIA3008 Interim Analysis - Regardless of Rescue

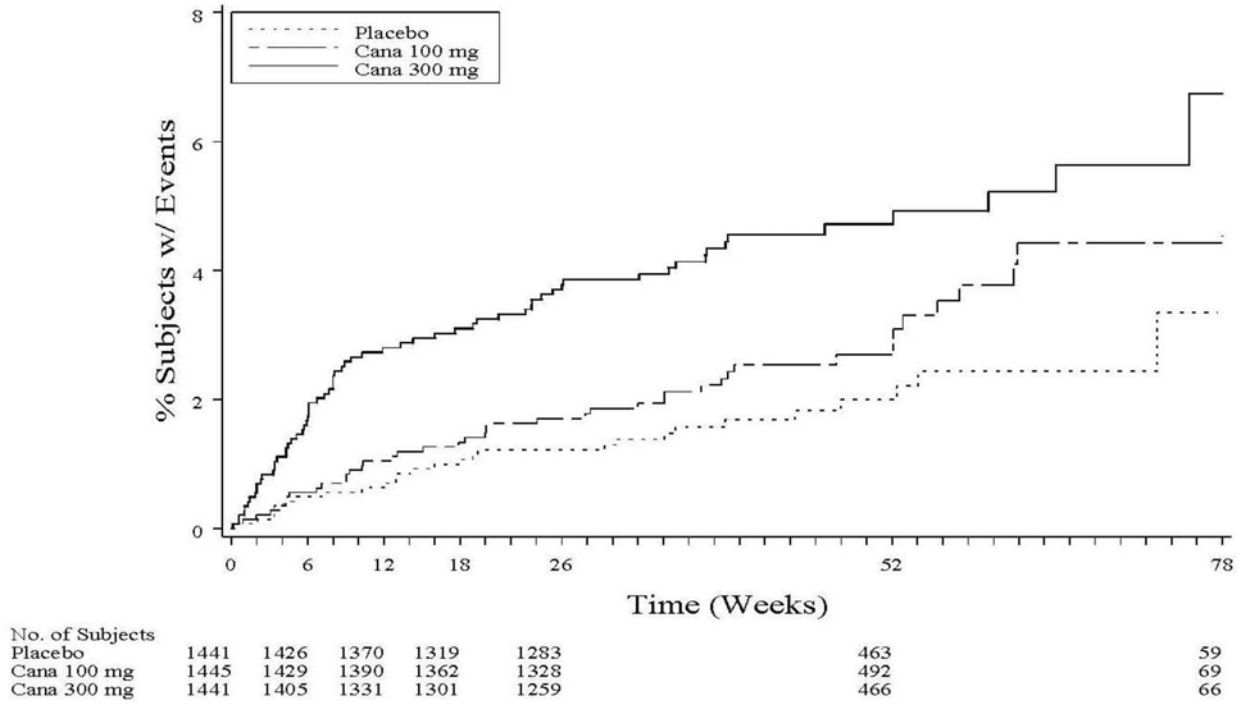
	Placebo (N=1441)	Cana 100 (N=1445)	Cana 300 (N=1441)
Any volume depletion AE, n (%)	27 (1.9)	41 (2.8)	66 (4.6)
Serious AE of volume depletion, n (%)	7 (0.5)	4 (0.3)	4 (0.3)
Volume depletion leading to discontinuation, n (%)	0	1 (0.1)	2 (0.1)
Incidence rate per 1000 person-years exposure	20	30	50
Reported Terms, n (%):			
Blood Pressure Decreased	0	0	1 (0.1)
Dehydration	5 (0.3)	3 (0.2)	7 (0.5)
Dizziness Postural	7 (0.5)	9 (0.6)	13 (0.9)
Hypotension	5 (0.3)	23 (1.6)	35 (2.4)
Orthostatic Hypotension	3 (0.2)	4 (0.3)	12 (0.8)
Orthostatic Intolerance	0	1 (0.1)	0
Presyncope	2 (0.1)	1 (0.1)	2 (0.1)
Syncope	8 (0.6)	4 (0.3)	7 (0.5)

Source: ISS, Table 124, 125

Similar to DS1 and DS2, the median time to onset of volume depletion adverse event was shorter in canagliflozin 300 mg group (57 days) compared to canagliflozin 100 mg group (129 days) or placebo group (106 days). Again, more subjects in the canagliflozin treatment groups, particularly 300 mg dose group, had volume depletion-related adverse events within the first 30 days of treatment (1.2% in canagliflozin 300 mg, 0.5% in canagliflozin 100 mg, and 0.4% in placebo group). This trend can be seen in the Kaplan-Meier curve for DIA3008 in Figure 18, and the difference does not appear to converge over time up to 52 weeks; since this is an interim analysis, caution should be used in assessing the curve past this time point due to low number of subjects.

Based on the Kaplan-Meier analysis of time to first volume depletion event, the hazard ratio of time to first volume depletion for canagliflozin 300 mg group was 2.5 (95% CI of 1.58, 3.86), with canagliflozin 100 mg hazard ratio of 1.5 (95% CI:0.91,2.40) and combined canagliflozin hazard ratio of 1.97 (95% CI: 1.29, 3.0).

Figure 18: Kaplan-Meier Plot of Time to First Volume Depletion Adverse Event - DIA3008 Interim Analysis



Source: ISS, Figure 15

An analysis of volume depletion events by concomitant diuretic and ACE/ARB taken within 7 days before the event, regardless of rescue, show that there was more than 2-fold increase of volume depletion events with concomitant diuretic and ACE/ARB agent. This is consistent with what was observed with subgroup analysis of DS3 (Table 49)

Table 52: Volume Depletion Events by Concomitant Diuretics or ACE/ARB agent Within 7 Days before Event - DIA3008, Regardless of Rescue

	Placebo (N=1441)	Cana 100 (N=1441)	Cana 300 (N=1441)
Total subjects with AE, n (%)	27 (1.9%)	41 (2.8%)	66 (4.6%)
Using ACE/ARB			
Yes	21 (1.5%)	34 (2.4%)	59 (4.1%)
No	6 (0.4%)	7 (0.5%)	7 (0.5%)
Using diuretics			
Loop	10 (0.7%)	9 (0.5%)	14 (1.0%)
Non-loop only	7 (0.5%)	15 (1.0%)	23 (1.6%)
None	10 (0.7%)	17 (1.2%)	29 (2.0%)

Source: CSR-DIA3008-int, page 1599

7.3.7 Significant Adverse Events - Changes in Renal Function

As discussed, canagliflozin increases urinary glucose excretion, which leads to an osmotic diuresis. In Phase 1 trials, the increase in urine volume occurred and peaked on Day 1 post-dosing, and attenuated over time. Changes in renal function including increases in serum creatinine and blood urea nitrogen (BUN) were observed in Phase 1 trials with canagliflozin, along with increases in hemoglobin and reductions in systolic and diastolic blood pressure.

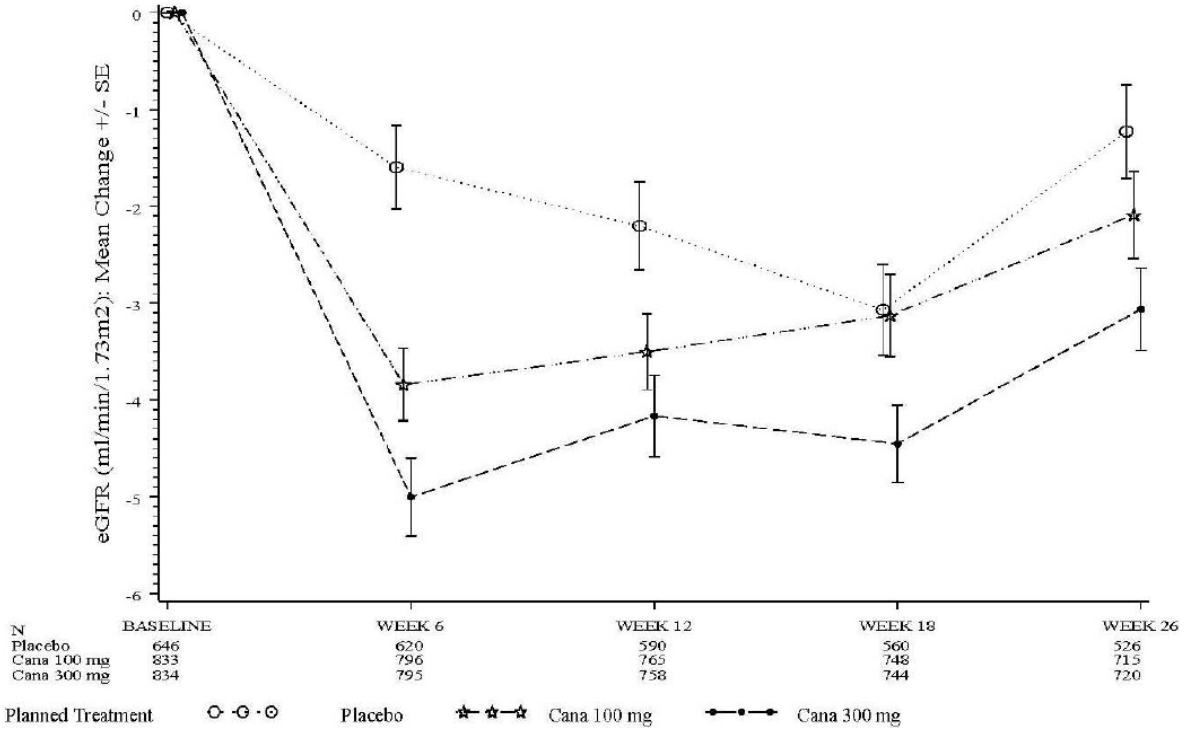
In order to evaluate renal changes induced by canagliflozin, subjects were regularly monitored for their renal function (serum creatinine and BUN) at scheduled study visits throughout Phase 3 trials. Pre-specified renal-related adverse events were prospectively defined, collected, and adjudicated by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

Changes in Renal Laboratory Values

Data from 26-week results from DS1, DIA3004, and 52 week results from DIA3008 and DIA3009. DS2 and DS3 were not provided since study visit schedule for DS2 and DS3 were different, limiting assessment of mean changes over time.

In the Placebo-Controlled Trials Dataset (DS1), there was a larger initial mean decrease from baseline in eGFR with canagliflozin treatment groups compared to placebo, with nadir at Week 6 and subsequent increases, as shown in Figure 19 below. At Week 26, the mean percent change from baseline was -1.8% and -3.0% in the canagliflozin 100 mg and 300 mg groups respectively, compared to -0.5% in the placebo group.

Figure 19: Mean Change (+/-SE) in eGFR (mL/min/1.73m^2) from Baseline Over Time (DS1 Dataset: Safety Analysis Set)



Source: ISS, Figure 18

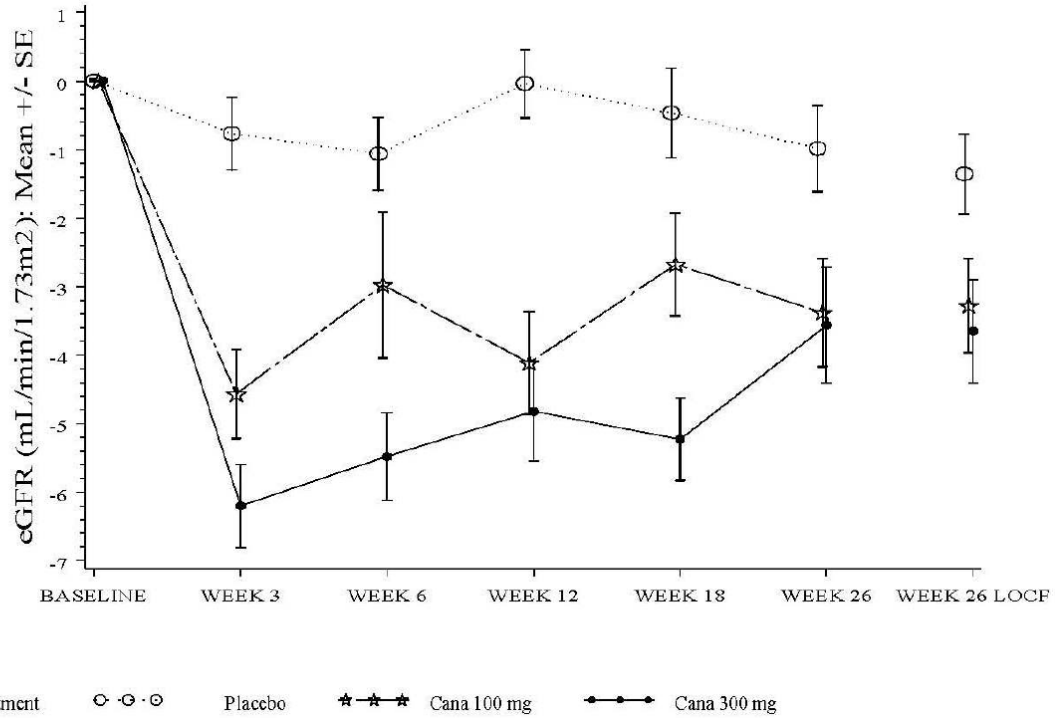
Increases from baseline in BUN were observed in the canagliflozin treatment groups by Week 6 and continued to increase over time, whereas the slight increase in BUN observed in the placebo group returned to almost baseline level by Week 26, as shown in **Error! Reference source not found.** below. The mean change in BUN from baseline at Week 26 was 17% with canagliflozin 100 mg and 18% with 300 mg compared to 2.7% with placebo.

A slight increase in serum creatinine was observed with canagliflozin compared to placebo, with peak at Week 6; the increase in creatinine from baseline at Week 26 were 0.02 mg/dL, 0.03 mg/dL, and 0.01 mg/dL in the canagliflozin 100 mg, 300 mg, and placebo groups respectively.

Reviewer's comment: Changes in renal function appear to be dose-related.

Similar to DS1, the nadir in dGFR with canagliflozin occurs at the earliest ascertained timepoint (Week 3) in the Moderate Renal Impairment Trial (DIA3004). But unlike those in DS1 who had normal to mild renal function, the decline in eGFR in subjects with moderate renal function appear to persist over time, as reflected in Figure 20. In addition, although there is an initial dose-dependent decrease in eGFR at Week 3, by the end of Week 26, the overall decline in eGFR between the two doses of canagliflozin was similar and more significant compared to placebo.

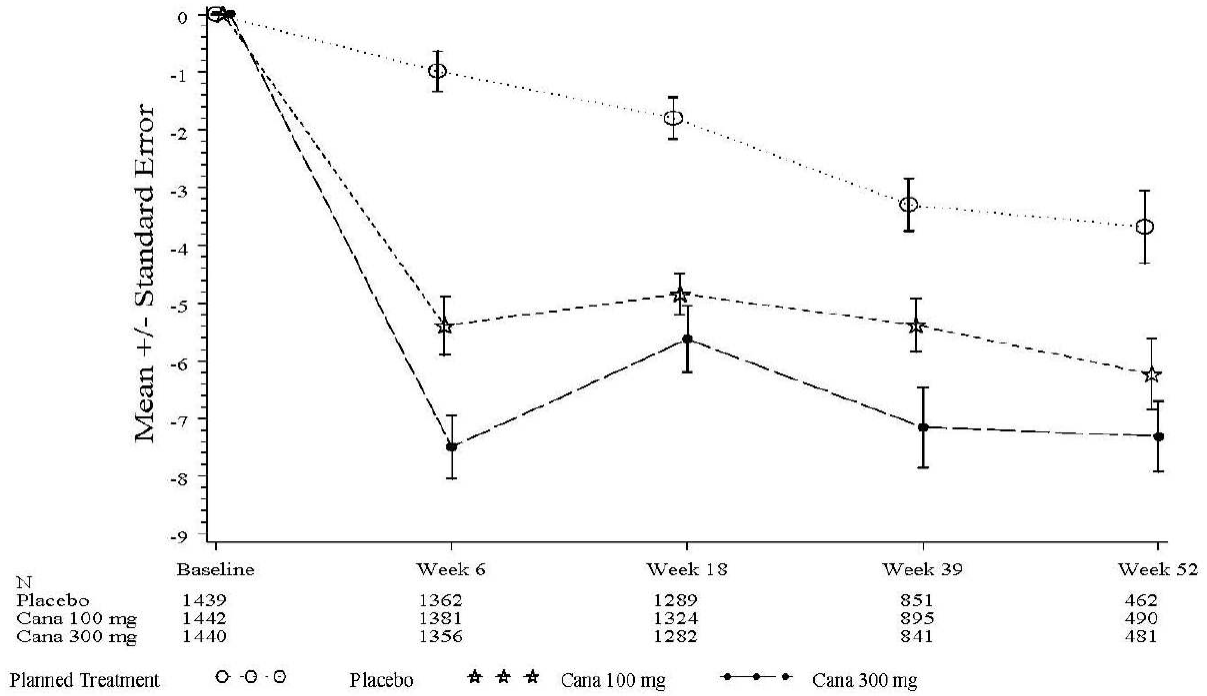
Figure 20: Mean Change (+/-SE) in eGFR (mL/min/1.73m^2) from Baseline Over Time (DIA3004: Modified Intent-to-Treat Analysis Set)



Source: ISS, Figure 19

In DIA3008, subjects at high cardiovascular risk, the largest decline in eGFR occur at the earliest ascertained timepoint similar to DS1 and DIA3004. Similar to DIA3004, the decline in eGFR is dose-dependent and does not appear to reverse over time. It should be noted that this is based on an interim analysis of DIA3008, where all subjects reached Week 18 visit, but a smaller proportion of subjects have reached Week 39 or 52 visits.

Figure 21: Mean Change (+/-SE) in eGFR (mL/min/1.73m^2) from Baseline Over Time (DIA3008 Interim Safety Analysis: Safety Analysis Set)



Source: CSR DIA3008, Figure 5

Reviewer's comment: Review of these figures showing the mean change in eGFR over time in DS1, DIA3004, and DIA3008 show that the magnitude and pattern of change in eGFR is different in different patient population.

Predefined Limits of Change Criteria (PDLC) for eGFR

The proportion of subjects with potentially clinically important changes in renal function as measured by eGFR were assessed using two PDLC criteria: 1) <80 mL/min/1.73m^2 and >30% reduction from baseline, and 2) >50% reduction from baseline. This criteria was assessed for "any" post-baseline value and also based on the "last" on-treatment value (defined as a value within two days of last study drug dose). The incidences of subjects with PDLC of eGFR for DS1, DS2, and DS3 are summarized in Table 53.

In the Placebo-controlled Studies Dataset (DS1) and Broad Dataset (DS3), the incidence of marked changes in eGFR was increased only with canagliflozin 300 mg group with similar incidence between 100 mg and placebo groups. However, in Moderate Renal Impairment Dataset (DS2), the incidence of marked changes in eGFR was greater with both doses of canagliflozin compared to placebo. In DIA3004, this incidence of marked changes in eGFR was even greater than DS2, and this is most likely reflective of slightly worse renal function in subjects from DIA3004 (mean baseline eGFR of 40 mL/min/m^2) compared to DS2 (mean

baseline eGFR of 48 mL/min/m^2), and thereby at a higher risk for having marked changes in eGFR.

Table 53: Number of Subjects with eGFR Values Outside Pre-Defined Limits - Regardless of Rescue (DS1, DS2, DIA3004, DS3: Safety Analysis Set)

PDLC Criteria	Placebo N (%)	Cana 100 N (%)	Cana 300 N (%)
Placebo-Controlled Studies Dataset (DS1)	624	809	805
ANY POST-BASELINE VALUE			
eGFR <80 mL/min/1.73m^2 & decrease >30% from baseline	13 (2.1)	16 (2.0)	33 (4.1)
eGFR decrease >50% from baseline	1 (0.2)	0	1 (0.1)
LAST POST-BASELINE VALUE			
eGFR <80 mL/min/1.73m^2 & decrease >30% from baseline	3 (0.5)	6 (0.7)	11 (1.4)
eGFR decrease >50% from baseline	0	0	0
Moderate Renal Impairment Dataset (DS2)	367	332	352
ANY POST-BASELINE VALUE			
eGFR <80 mL/min/1.73m^2 & decrease >30% from baseline	18 (4.9)	31 (9.3)	43 (12.2)
eGFR decrease >50% from baseline	0	5 (1.5)	3 (0.9)
LAST POST-BASELINE VALUE			
eGFR <80 mL/min/1.73m^2 & decrease >30% from baseline	12 (3.3)	10 (3.0)	14 (4.0)
eGFR decrease >50% from baseline	0	1 (0.3)	0
Moderate Renal Impairment Trial (DIA3004)	90	90	89
ANY POST-BASELINE VALUE	87	89	89
eGFR <80 mL/min/1.73m^2 & decrease >30% from baseline	6 (6.9)	16 (18.0)	20 (22.5)
eGFR decrease >50% from baseline	0	2 (2.2)	3 (3.4)
LAST POST-BASELINE VALUE	87	89	89
eGFR <80 mL/min/1.73m^2 & decrease >30% from baseline	4 (4.6)	3 (3.4)	3 (3.4)
eGFR decrease >50% from baseline	0	1 (1.1)	0
Broad Dataset (DS3)*	3160*	3017	2970
ANY POST-BASELINE VALUE			
eGFR <80 mL/min/1.73m^2 & decrease >30% from baseline	124 (3.9)	126 (4.2)	188 (6.3)
eGFR decrease >50% from baseline	8 (0.3)	13 (0.4)	17 (0.6)
LAST POST-BASELINE VALUE			
eGFR <80 mL/min/1.73m^2 & decrease >30% from baseline	61 (1.9)	52 (1.7)	77 (2.6)
eGFR decrease >50% from baseline	2 (0.1)	3 (0.1)	5 (0.2)

*For DS3, placebo column is all non-cana group since the dataset included active-controlled trials.
Source: SCS, Table 92, 93, 94, and 95

Renal Adverse Events

To assess renal-related adverse events (AEs), the Standardized MedDRA Query for acute renal failure adverse events were used, and this included the following PTs: acute phosphate nephropathy, acute prerenal failure, anuria, azotemia, continuous hemodiafiltration, dialysis, hemodialysis, neonatal anuria, nephropathy toxic, oliguria, peritoneal dialysis, renal failure, renal failure acute, renal failure neonatal, renal impairment, and renal impairment neonatal. In

addition, the applicant defined renal-related adverse events which included acute renal failure SMQ plus the PT of blood creatinine increased and glomerular filtration rate decreased under Investigations SOC. Renal AEs were evaluated in DS1, DS2, and DS3, and are presented in Table 54.

In the Placebo-controlled Studies Dataset (DS1), the overall incidence of renal-related adverse event was low and >2-fold higher with canagliflozin 300 mg compared to canagliflozin 100 mg and placebo groups. However, in the Moderate Renal Impairment Dataset (DS2), the incidence of renal-related events was >2-fold higher with both doses of canagliflozin compared to placebo. In the Broad Dataset (DS3), although the proportion of subjects with renal-related events were slightly increased with canagliflozin (2.6% with 100 mg and 2.3% with 300 mg) compared to placebo (2.0%), the incidence rate adjusted for subject-exposure show >2-fold increased incidence with canagliflozin 300 mg (63.5/1000 subject-years) compared to placebo (26.8/1000 subject-years).

Table 54: Overall Summary of Renal-related Adverse Event - DS1, DS2, DS3, Regardless of Rescue

	Placebo	Cana 100	Cana 300
Placebo-controlled Studies Dataset (DS1), N	646	833	834
Any selected renal-related adverse event	4 (0.6)	5 (0.6)	14 (1.7)
Incidence rate per 1000 subject-years	**13.6**	**12.9**	**36.1**
Any selected renal-related adverse event leading to discontinuation	1 (0.2)	3 (0.4)	7 (0.8)
Any selected renal-related serious adverse event	0	1 (0.1)	0
Moderate Renal Impairment Dataset (DS2), N	382	338	365
Any selected renal-related adverse event	14 (3.7)	30 (8.9)	34 (9.3)
Incidence rate per 1000 subject-years	**53.8**	**123.8**	**130.2**
Any selected renal-related adverse event leading to discontinuation	4 (1.0)	4 (1.2)	6 (1.6)
Any selected renal-related serious adverse event	5 (1.3)	4 (1.2)	5 (1.4)
Broad Dataset (DS3), N	3262*	3092	3085
Any selected renal-related adverse event	42 (1.3)	61 (2.0)	79 (2.6)
Incidence rate per 1000 subject-years	**18.5**	**27.0**	**35.8**
Any selected renal-related adverse event leading to discontinuation	12 (0.4)	11 (0.4)	23 (0.7)
Any selected renal-related serious adverse event	6 (0.2)	11 (0.4)	10 (0.3)

*Non-Canagliflozin in DS3
Source: ISS, Table 141, 145, 149

In DS3, the mean baseline eGFR in subjects who experienced renal-related events were 56, 60, and 63 mL/ mL/min/1.73 m^2 with canagliflozin 100 mg, 300 mg, and non-canagliflozin respectively. The renal-related events occurred earlier with 300 mg dose of canagliflozin compared to 100 mg or non-canagliflozin; the median time to onset of renal-related events was 83 days with canagliflozin 300 mg compared to 125 days and 128 days with canagliflozin 100 mg and non-canagliflozin respectively.

In order to assess risk factors for renal-related adverse events, I conducted subgroup analyses based on baseline characteristics in DS3, as shown on Table 55. An increased risk for renal-

related events with canagliflozin was seen in subjects with lower eGFR (<60 mL/min/1.73 m^2), and this increased risk was similarly seen with both canagliflozin doses compared to non-canagliflozin group. A higher risk for renal-related events with canagliflozin was also seen in elderly (≥65 years of age) compared to younger subjects, and although the total number of subjects who were ≥75 years of age was relatively small, this increased risk with both doses of canagliflozin was more prominent in subjects ≥75 years of age compared to <75 years of age.

A higher, dose-related increased risk for renal-related events with canagliflozin was also seen with diuretics, and in particular loop diuretics, as well as concomitant use of ACE/ARB agents.

Table 55: Subjects with Renal-related Adverse Events by Baseline Characteristics in DS3-Regardless of Rescue

	Cana 100			Cana 300			Non-Cana		
	n	N	%	n	N	%	n	N	%
eGFR (mL/min/1.73m^2)									
< 60	35	382	**9.2%**	39	405	**9.6%**	21	436	**4.8%**
60 - < 90	26	1686	**1.5%**	32	1680	**1.9%**	20	1788	**1.1%**
>= 90	1	1021	**0.1%**	8	999	**0.8%**	4	1035	**0.4%**
Age (years)									
< 65	32	2100	**1.5%**	41	2114	**1.9%**	29	2285	**1.3%**
>= 65	30	982	**3.1%**	38	971	**3.9%**	16	977	**1.6%**
Age (years)									
<75	52	2929	**1.8%**	72	2913	**2.5%**	43	3107	**1.4%**
>=75	10	163	**6.1%**	7	172	**4.1%**	2	155	**1.3%**
Use of ACE/ARB									
No	8	970	**0.8%**	11	969	**1.1%**	7	1022	**0.7%**
Yes	54	2122	**2.5%**	68	2166	**3.1%**	38	2240	**1.7%**
Use of Diuretics									
No	22	2016	**1.1%**	31	2009	**1.5%**	15	2093	**0.7%**
Yes	40	1076	**3.7%**	48	1076	**4.5%**	30	1169	**2.6%**
Use of Loop Diuretics									
No	50	2876	**1.7%**	62	2835	**2.2%**	33	3006	**1.1%**
Yes	12	216	**5.6%**	17	250	**6.8%**	12	256	**4.7%**
Duration of Diabetes (years)									
< 10	25	1536	**1.6%**	22	1502	**1.5%**	20	1667	**1.2%**
≥ 10	37	1536	**2.4%**	57	1583	**3.6%**	25	1595	**1.6%**
Systolic Blood Pressure (mmHg)									
<= 110	3	178	**1.7%**	5	184	**2.7%**	1	213	**0.5%**
> 110	59	2914	**2.0%**	74	2901	**2.6%**	44	3049	**1.4%**

Source: ADAE, ADSL

Reviewer's comments: The risk factors that predispose subjects to renal-related events with canagliflozin were similar to the risk factors for volume depletion-related adverse events (see Table 49).

Adjudicated Renal Events

The applicant also adjudicated renal events in a blinded fashion, with the following adjudication criteria:

- Sustained doubling of serum creatinine from baseline value (or ≥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 ≥50% decrease in baseline eGFR) at last recorded laboratory value.
- End stage renal disease (ESRD, new or worsening) or renal replacement (dialysis or transplant).

At 4MSU, as of January 31, 2012, 43 subjects (12 in the canagliflozin 100 mg group, 16 in the 300 mg group, and 15 in the non-canagliflozin group) were identified meeting the adjudication criteria. Table 56 summarizes the adjudication criteria that these 43 subjects met by treatment arm. Table 57 summarizes the adjudicated results of causality for these 43 cases by treatment arm. The number of events per treatment arm was small and there was no clear imbalances among treatment arms.

Table 56: Summary of Cases in Phase 3 Trials Sent for Renal Clinical Event Committee Adjudication - 4-Month Safety Update

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

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

Note: "Number of Cases" is the number of cases meeting the CEC criteria classification.

Note: Renal Clinical Events Committee (CEC) consisted of 3 nephrologists who served on the committee to adjudicate causality for each case.

[a] Any refers to any of the following 5 CEC criteria (number of new [ie, since ISS] subjects = 6. 4, 4, and 8 in all Non-Cana, Cana 100, Cana 300, and All Cana, respectively):
- A. Sustained elevation in serum creatinine (new subjects = 0 in all treatment groups)
- B. Sustained decrease in eGFR (new subjects = 2, 0, 0, and 0, respectively)
- C. Last value elevation in serum creatinine (new subjects = 0. 1. 1. and 2, respectively)
- D. Last value decrease in eGFR (new subjects = 4, 1, 3, and 4, respectively)
- E. ESRD or renal replacement (dialysis or transplant) (new subjects = 0, 2, 0, and 2, respectively)

[b] Sustained increase (decrease) was determined based on the clinical review of the searched results from the database

[c] Based on a clinical and safety database search of selected AE preferred terms; ESRD = end stage renal disease

Source: 4MSU, Table 27

Table 57: Summary of Renal Clinical Event Committee Causality for Cases in Phase 3 Trials Sent for Adjudication - 4-Month Safety Update

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

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

Note: "Number of Cases" is the number of cases meeting the CEC criteria classification.

Note: Renal Clinical Events Committee (CEC) consisted of 3 nephrologists who served on the committee to adjudicate causality for each case.

[a] Any refers to any of the following 5 CEC criteria:
A. Sustained elevation in serum creatinine
B. Sustained decrease in eGFR
C. Last value elevation in serum creatinine
D. Last value decrease in eGFR
E. ESRD or renal replacement (dialysis or transplant)

[b] Number of new (ie, since ISS) subjects meeting any criteria = 6. 4, 4, and 8 in all Non-Cana, Cana 100, Cana 300, and All Cana, respectively, with the number of new subjects in each category as follows:
Probable (new subjects = 0. 0. 1, and 1, respectively)
Possible (new subjects = 3. 0. 1, and 1, respectively)
Doubtful (new subjects = 2. 1. 1, and 2, respectively)
Not Related (new subjects = 1. 3. 1, and 4, respectively)

Source: 4MSU, Table 28

The clinical consequence of declining renal function resulting in dialysis or transplant is serious and not reversible. There were 6 subjects who were adjudicated due to ESRD or replacement (dialysis or transplant), all of whom met the criteria based on initiation of hemodialysis. Of these 6 cases, 5 cases were considered "not related" to study drug by Renal Clinical Event Committee; I reviewed narratives of these five cases (400823, 500539, (b) (4)) and agree with this assessment since all of these five cases had other precipitating events (e.g., sepsis, cardiac) that resulted in worsening renal function requiring hemodialysis. However, one case (subject (b) (4) with canagliflozin 300 mg was adjudicated with a causality of "possibly" related to study drug. This subject was summarized under section 7.3.1 Deaths; she died due to non-treatment emergent event after discontinuation of study drug. However, she was discontinued due to worsening renal function necessitating hemodialysis after receiving canagliflozin; her eGFR declined to 7 mL/min/1.73m^2 on Day 172 from baseline of 46 mL/min/1.73m^2.

We also consulted Division of Cardiovascular and Renal Products for their assessment of renal safety with canagliflozin, and they concluded that the data as a whole suggested that the observed changes in renal function with canagliflozin are secondary to volume depletion. Dr. Aliza Thomspon, Medical Officer who completed the consult, stated that "the applicant has not

provided data that speak to the long-term renal consequences of extended exposure to the drug in the proposed population", "the long term renal consequences of canagliflozin's effect on eGFR are unknown", and that "the volume depletion and corresponding reduction in eGFR caused by canagliflozin places patients at increased risk for clinically significant episodes of acute kidney injury (AKI) and that larger treatment effects on eGFR will translate into greater risk".

She also stated the following with regard to safety of canagliflozin in patients with moderate renal impairment:

The amount of safety data in subjects with diabetes and moderate renal impairment is limited (particularly in subjects with an eGFR< 45 mL/min/1.73m$_2$) and what data exist suggest a high absolute risk of potentially clinically meaningful episodes of AKI at both doses and, in particular, at the high dose. This risk may be related to the presence of underlying renal disease, age, concomitant therapies commonly used in this population (such as diuretics), or a combination of these and possibly other factors. In addition, this risk may be magnified in the postmarketing setting when canagliflozin is used outside the carefully monitored setting of a clinical trial and in a less selected population. Given these issues, we think considerable uncertainty remains regarding renal safety in patients with diabetes and moderate renal impairment.

Please see Dr. Aliza Thomspon's review, dated December 2, 2012, for complete details of her assessment.

7.3.8 Significant Adverse Events - Hemoconcentration and Thromboembolic Events

Hematology

Small mean percent increases in hemoglobin concentration and hematocrit occurred at the initial assessment timepoint (Week 6) and persisted through Week 26 in DS1, as summarized in Table 58. The mean percent increases in hemoglobin were 3.5% and 3.8% in canagliflozin 100 mg and 300 mg group respectively, compared to a slight decrease in the placebo group (-1.1%). Similar increases in hematocrit were also observed. No significant changes in platelet count were observed.

Table 58: Selected Hematology Laboratory Values in DS1 - Regardless of Rescue

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

Source: ISS, DLAB01C_01

Thromboembolic Events

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

Throughout Phase 3 trials, VTE events were independently adjudicated by an EAC. VTE events were identified using a Standard MedDRA Query (SMQ) of 'embolic and thrombotic events, venous'. A total of 21 potential VTE events were identified at the time of NDA submission throughout all Phase 3 trials, including three fatal events that were adjudicated as CV deaths. Of 21 VTE events, one was not treatment-emergent since it occurred more than 30 days off study drug. Two subjects were not confirmed to be VTE events (subjects 400873 and (b) (4). The remaining 18 events confirmed by EAC as VTE events are summarized in Table 59 and listed in Table 60. Of these 18 VTE events, 16 were serious, and one event led to study drug discontinuation.

Table 59: Summary of Venous Thromboembolic Events, Regardless of Rescue - DS4

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

Source: ISS, Tables 187, 188

Table 60: Listing of Adjudicated VTE Events

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

Source: ISS, Narratives

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

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

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

7.3.9 Significant Adverse Events - Bone Safety

In nonclinical studies of rats, an increase in trabecular bone volume (hyperostosis) was observed. Please refer to Dr. Alavi's review for details regarding nonclinical bone safety findings. Also,

because of its mechanism of action, canagliflozin may potentially affect bone safety since it may change renal tubule reabsorption of calcium and phosphorus, potentially alter vitamin D metabolism, and cause weight loss. Fractures as well as markers of bone metabolism were monitored and collected throughout clinical development program of canagliflozin. Fractures were adjudicated by an independent blinded Fracture Adjudication Committee.

Calcium and Phosphate and Hormones Regulating Calcium Metabolism:

The following were notable changes in three 12-week Phase 2 studies (OBE2001, DIA2001, and MTPC study TA-7284-04) where serum and urine calcium and phosphorus and hormones regulating calcium were assessed:

- In DIA2001 trial of subjects with T2DM, a small, non-dose dependent increase in PTH was seen at Week 3 in the treatment arm compared to control that returned to baseline at Week 6 through Week 12. This is in contrast to rat studies where reduction in PTH was observed.
- In OBE2001 trial of non-diabetic obese subjects, a slight (5-11%) increase in urinary phosphate to creatinine ratio was seen.
- In 12-week MTPC trial TA-7284 in Japanese T2DM subjects, a small, dose-dependent increase (up to 10%) in serum phosphate occurred with canagliflozin treatment compared to placebo. A slight, transient decrease in 1,25-dihydroxy-vitamin D levels with canagliflozin treatment returned to baseline at the end of double-blind treatment period in all groups except 100 mg group.

A summary of serum calcium and phosphate levels in the Placebo-controlled Studied Dataset (DS1) is presented in Table 61. In DS1, there was a small, dose-dependent increase in the mean serum calcium levels with canagliflozin (0.8 and 1.1% with 100 mg and 300 mg respectively) compared to placebo (0.2%). There was a larger, dose-dependent increase in the mean serum phosphate at Week 26 with canagliflozin; 3.6% and 5.1% with canagliflozin 100 mg and 300 mg groups respectively compared to 1.5% with placebo.

Table 61: Summary of Change from Baseline in Serum Calcium and Phosphate - DS1, Regardless of Rescue

	Placebo	Cana 100	Cana 300
Serum Calcium, mg/dL	N=526	N=715	N=720
Baseline	9.72	9.68	9.68
Mean change from baseline	0.01	0.06	0.10
Mean % change from baseline	0.2	0.8	1.1
Serum Phosphate, mg/dL	N=526	N=715	N=718
Baseline	3.64	3.64	3.62
Mean change from baseline	0.02	0.09	0.15
Mean % change from baseline	1.5	3.6	5.1

Source: ISS, DLAB01C_01, Table 212

Since alterations in calcium metabolism are seen in subjects with renal impairment, the change in calcium and phosphate in DIA3004 (subjects with moderate renal impairment) are relevant. In DIA3004, as shown in Table 62, there was a moderate increase in 25-dihydroxy vitamin D with canagliflozin compared to placebo, with a slight decrease in 1,25-dihydroxy vitamin D with canagliflozin. The mean serum parathyroid hormone decreased with canagliflozin compared to placebo. Similar to DS1, there was a slight increase in serum calcium and phosphate levels with canagliflozin.

Table 62: Change from Baseline in Calcium Regulatory Axis Analytes in DIA3004 - Regardless of Rescue

	Placebo	Cana 100 mg	Cana 300 mg
Serum 25-dihydroxy vitamin D (nmol/L)	N=76	N=68	N=79
Mean Baseline	57.50	56.02	56.89
Mean change from baseline	0.61	5.76	3.85
Mean % change from baseline	1.1	10.3	6.8
Serum 1,25-dihydroxy vitamin D (pmol/L)	N=63	N=62	N=67
Mean Baseline	69.41	67.03	76.65
Mean change from baseline	-2.13	-0.29	-6.19
Mean % change from baseline	-3.1	-0.4	-8.1
Serum Parathyroid Hormone, Intact (pmol/L)	N=68	N=66	N=66
Mean Baseline	7.96	8.88	11.57
Mean change from baseline	0.54	0.74	-1.21
Mean % change from baseline	6.8	8.3	-10.5
Phosphate (mmol/L)	N=75	N=72	N=79
Mean Baseline	1.17	1.16	1.16
Mean change from baseline	0	0.04	0.09
Mean % change from baseline	0	3.4	7.8
Calcium (mmol/L)	N=75	N=72	N=80
Mean Baseline	2.41	2.40	2.39
Mean change from baseline	-0.01	0.03	0.03
Mean % change from baseline	-0.4	1.3	1.3

Source: CSR3004, percentage calculated from Table 39 [note that the % calculation is different from the applicant's calculation]

Bone Turnover Markers and Bone Density Measurements:

In DIA2001 and OBE2001 trials, there was an increase in serum beta-type 1 collagen cross-linked C-telopeptide (beta-CTx) from baseline to Week 12 in subjects treated with canagliflozin compared to placebo.

In DIA3010, in addition to evaluating the efficacy and safety of canagliflozin in older subjects (55 to 80 years inclusive), bone safety in particular was evaluated by obtaining levels of bone turnover markers, and bone density was measured by DXA at Weeks 26, 52, and 104. At the

time of NDA submission, only results from the 26-week assessment were available, as the controlled extension period was still ongoing. On November 30, 2012, the applicant submitted 52-week interim data for bone turnover markers and bone density measures by DXA and QCT.

The placebo-adjusted percent change in bone turnover markers from DIA3010 are summarized in Table 63. Except for serum beta-CTx and P1NP at 26 weeks, the other values were assayed from archived serum samples. In DIA3010, consistent with Phase 2 trials, there was a mean increase in bone resorption marker, beta CTx, with canagliflozin compared to placebo, which was statistically significant with both doses at 26 and 52 weeks. There was a smaller, non-significant decrease in one of the bone formation marker, P1NP, with canagliflozin compared to placebo. An increase in another bone formation marker, osteocalcin, with both doses of canagliflozin reached statistical significance at 52 weeks. The serum estradiol levels dose-dependently decreased during the course of study with canagliflozin. In contrast to DIA3004, the serum parathyroid hormone levels increased during the study with canagliflozin compared to placebo.

Table 63: Placebo-adjusted LS Mean Percent Change (95% CI) in Bone Turnover Markers From Baseline to Week 26 and 52 - DIA3010, Regardless of Rescue

	26 Weeks		52 Weeks	
	Cana 100	Cana 300	Cana 100	Cana 300
Serum collagen type 1 beta-carboxy-telopeptide (beta CTx)	17.1 (7.3, 26.9)	24.9 (15.0, 34.8)	10.3 (2.1, 18.6)	22.0 (13.6, 30.4)
Serum propeptide amino-term type 1 procollagen (P1NP)	-5.7 (-13.1, 1.7)	-6.9 (-14.3, 0.6)		
Serum osteocalcin	3.2 (-2.0, 8.4)	4.3 (-1.0, 9.6)	9.4 (3.6, 15.2)	10.1 (4.3, 16.0)
Serum estradiol	-4.4 (-17.5, 8.8)	-13.7 (-27.2, -0.2)	-14.2 (-28.7, 0.3)	-21.0 (-36.2, -5.8)
Serum parathyroid hormone	7.0 (1.4, 12.6)	2.0 (-3.6, 7.6)	6.2 (-0.2, 12.6)	1.5 (-5.0, 8.0)

Source: ISS, Table 155, 156; NDA 204042, November 30, 2012 submission, Table 11-17

The bone density was measured at four sites in DIA3010, with the primary interest of lumbar spine, and secondary sites examined wrist, femoral neck, and total hip. The lumbar spine is a trabecular bone site, wrist is a cortical bone site, and femoral neck and total hip are mixed cortical and trabecular bone. The placebo-adjusted LS mean percent change in bone mineral density (BMD) by DXA are summarized in Table 64. The BMD measure by DXA decreased at lumbar spine and total hip with both doses of canagliflozin, which achieved statistical significance with the higher dose of canagliflozin with 95% CI excluding zero.

Table 64: Placebo-Adjusted LS Mean Percent Change (95% CI) in Bone Density Measurements by DXA From Baseline to Week 52 - DIA3010, Regardless of Rescue

Corrected BMD measurement	Cana 100 mg (N=241)	Cana 300 mg (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)

Source: NDA 204042, November 30, 2012 submission, Table 6

As a secondary endpoint, BMD was also measured using Quantitative CT of the spine and hip at 52 weeks in a subset of subjects. Similar to DXA results, a dose-dependent decrease in BMD was seen in the lumbar spine and total hip, and achieved statistical significance with the higher dose of canagliflozin with 95% CI excluding zero, as summarized in Table 65.

Table 65: Placebo-Adjusted LS Mean Percent Change (95% CI) in Bone Mineral Density by Quantitative CT From Baseline to Week 52 - DIA3010, Regardless of Rescue

Integral volumetric BMD	Cana 100 mg (N=38)	Cana 300 mg (N=38)
Lumbar spine	-0.8 (-2.7, 1.1)	-1.9 (-3.8, -0.0)
Femoral neck	0.8 (-1.7, 3.3)	-1.9 (-4.4, 0.6)
Total hip	-0.5 (-1.0, 1.1)	-1.6 (-3.1, -0.0)

Source: NDA 204042, November 30, 2012 submission, Table 7

Fractures:

All clinical fractures were adjudicated in Phase 3 program to determine the type of fracture (low trauma, high trauma, pathologic), and the primary analysis was based on low trauma fractures. Since fractures occur with a low incidence and longer duration of exposure is particularly important in assessing fractures, they were analyzed using the Longer-term Exposure Broad Dataset (DS4), including all reported fractures post-randomization (including >30 days after the last dose of study drug). All fracture adverse events were adjudicated by an independent, blinded committee to confirm the events, and to determine the type and location of fracture.

The Fracture Adjudication Committee defined the type of fracture as:

- High Trauma Fracture: resulting from severe trauma such as motor vehicle crashes, being struck by a vehicle or other fast-moving projectile, or to fall from greater than standing height (e.g., off a ladder, chair, porch, table, not including stairs);
- Low Trauma Fracture: falls from standing height or less; falls on stairs, steps, or curbs; moderate trauma other than a fall (collision with objects during normal activities); and minimal trauma other than a fall (turning over in bed);

- Pathological Fracture: fractures in an area that is weakened by another disease process such as tumor, metastatic cancer of the bone, infection, and inherited bone disorder, etc;
- Stress Fracture: identifiable fractures caused by repetitive stress;
- Other Fracture: fractures that cannot be attributed to above definitions.

The incidence of fractures in DS4 is summarized in Table 66. The overall incidence of unadjudicated fractures in DS4 was higher in the canagliflozin treatment groups (1.9% and 1.8% in 100 mg and 300 mg group respectively) compared to the placebo (1.4%). This slight increase in fractures in the canagliflozin treatment group compared to placebo was also seen in low trauma fractures. When the fractures were categorized by region (lower limb, pelvis, skull of facial bone, spine, thoracic cage, and upper limb), there was an imbalance in the upper limb fractures not favoring canagliflozin, and this imbalance persisted in low trauma upper limb fractures, as shown in Table 66. A higher incidence of upper limb fractures occurred in females in the combined canagliflozin treatment group (1.2% [31/2608]) compared to placebo (0.4% [5/1338]).

Table 66: Fracture Adverse Events in DS4 - Regardless of Rescue

	All Non-Cana	Cana 100 mg	Cana 300 mg	All Cana
DS4	N=326	N=3092	N=3085	N=6177
Subjects with Fracture AEs, n (%)	47 (1.4)	58 (1.9)	54 (1.8)	112 (1.8)
Incidence rate of fracture per 1000 PY	13.9	17.2	16.3	16.8
Subjects with Adjudicated Fractures	44 (1.3)	55 (1.8)	49 (1.6)	104 (1.7)
Adjudicated Low Trauma Fracture, n (%)	31 (1.0)	41 (1.3)	39 (1.3)	80 (1.3)
Incidence rate of Low Trauma Fracture, n (%)	9.2	12.1	11.8	12.0
Upper Limb Adjudicated Fracture	12 (0.4)	23 (0.7)	26 (0.8)	49 (0.8)
Upper Limb Adjudicated Fracture in Females	5 (0.4)	17 (1.3)	14 (1.1)	31 (1.2)
Upper Limb Low Trauma Fracture	7 (0.2)	20 (0.6)	22 (0.7)	42 (0.7)
Subset of DS4: eGFR 30 to <60	N=382	N=338	N=365	N=703
Subjects with Fracture AEs, n (%)	5 (1.3)	9 (2.7)	4 (1.1)	13 (1.8)
Incidence rate per 1000 PY	13.3	25.6	10.6	17.8
Upper Limb Adjudicated Fracture, n (%)	1 (0.3)	3 (0.9)	2 (0.5)	5 (0.7)

Source: ISS, Table 158, 159, 160

The applicant updated fracture data at 4MSU, and the overall incidence of reported unadjudicated fractures was higher in the combined canagliflozin group (2.4%) compared to non-canagliflozin group (1.7%), which approached statistical significance, as shown in Table 67. When the incidence was adjusted by patient exposure, the treatment group difference did not reach statistical significance, but the imbalance in fractures not favoring canagliflozin remains, with exposure-adjusted incidence rates of 18.11 compared to 14.16 fractures per 1000 person-years for combined canagliflozin and non-canagliflozin group respectively.

Table 67: Post Randomization Fracture Adverse Events by Type of Fracture - 4MSU

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

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

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

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

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

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

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

Source: 4MSU, Table 29

As shown on Table 68 and Table 69, the imbalance in the upper limb, in both overall fractures and in low trauma fractures, was still observed with the updated safety data; the incidence of adjudicated low trauma fractures was 1.6% for each canagliflozin group compared to 1.2% with non-canagliflozin group. Although the overall number is small, an imbalance in low trauma spine fractures is also noted; 6 subjects in the combined canagliflozin group compared to none with placebo had low trauma spine fractures (Table 69).

Table 68: Post Randomization Fracture Adverse Events by Anatomical Region - 4MSU

Anatomical Region	Cana 100 mg (N=3092) n (%)	Cana 300 mg (N=3085) n (%)	All Cana (N=6177) n (%)	All Non-Cana (N=3262) n (%)
Total no. subjects with adverse events[a]	76 (2.5)	70 (2.3)	146 (2.4)	57 (1.7)
Incidence rate per 1,000 person-years exposure[a,b]	18.65	17.56	18.11	14.16
Total no. subjects with adjudicated fracture region[c]	68 (2.2)	61 (2.0)	129 (2.1)	53 (1.6)
Lower limb	25 (0.8)	25 (0.8)	50 (0.8)	29 (0.9)
Pelvis	2 (0.1)	0	2 (<0.1)	1 (<0.1)
Skull or facial bone	0	1 (<0.1)	1 (<0.1)	1 (<0.1)
Spine	7 (0.2)	2 (0.1)	9 (0.1)	2 (0.1)
Thoracic cage	9 (0.3)	9 (0.3)	18 (0.3)	7 (0.2)
Upper limb	28 (0.9)	27 (0.9)	55 (0.9)	17 (0.5)

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. Percentages calculated with the number of subjects in each group as denominator.
[a] Fracture adverse events based upon a prespecified subset of preferred terms from a MedDRA query listed in the SAP.
[b] Exposure adjusted incidence rates are per 1,000 person-years and calculated as 1,000*(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).
[c] Adjudicated fracture region for confirmed fractures by the FAC (note that events not confirmed as a fracture or without information available to the FAC are excluded).
Source: 4MSU, Table 30

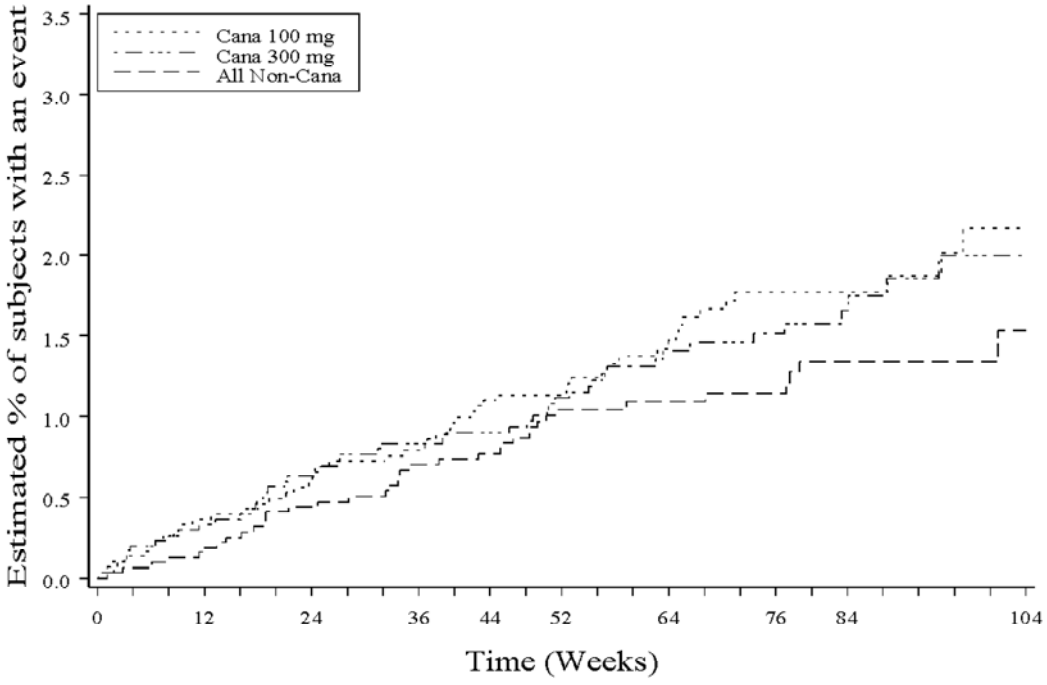
Table 69: Post Randomization Low Trauma Fractures by Anatomical Region - 4MSU

Anatomical Region	Cana 100 mg (N=3092) n (%)	Cana 300 mg (N=3085) n (%)	All Cana (N=6177) n (%)	All Non-Cana (N=3262) n (%)
Total no. subjects with Adjudicated Fracture Region[a]	51 (1.6)	48 (1.6)	99 (1.6)	38 (1.2)
Incidence rate per 1,000 person-years exposure	12.51	12.04	12.28	9.44
Lower limb	20 (0.6)	18 (0.6)	38 (0.6)	22 (0.7)
Pelvis	1 (<0.1)	0	1 (<0.1)	1 (<0.1)
Spine	5 (0.2)	1 (<0.1)	6 (0.1)	0
Thoracic cage	5 (0.2)	7 (0.2)	12 (0.2)	5 (0.2)
Upper limb	22 (0.7)	22 (0.7)	44 (0.7)	11 (0.3)

Note: Percentages Calculated With The Number of Subjects In Each Group As Denominator.
Note: Exposure adjusted incidence rates are per 1,000 person-years and calculated as 1,000*(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).
Note: The table summarizes subjects with fracture events for which the adjudicated type and location of fracture is available.
[a] Adjudicated fracture region for confirmed fractures by the FAC (note that events not confirmed as a fracture or without information available to the FAC are excluded).
Source: 4MSU, Table 31

Figure 22 is the Kaplan-Meier curve of low trauma fractures in 4MSU, which shows that more fractures occurred in the canagliflozin treatment groups during the first 12 weeks after study drug initiation compared to the placebo.

Figure 22: Kaplan-Meier Plot of Time to First Low Trauma Fractures in 4MSU



No. Subjects at Risk

Cana 100 mg	3092	3042	2983	2931	2882	2840	2021	1621	1166	421
Cana 300 mg	3085	3020	2940	2870	2844	2801	1983	1601	1125	413
All Non-Cana	3262	3192	3095	3011	2964	2877	1932	1537	1113	413

Source: 4MSU, Figure 2

We also consulted the Metabolic Bone Disease Team in the Division of Reproductive and Urology Products (DRUP) for review of bone-related findings submitted with the NDA, which included assessment on calcium, phosphate and hormones regulating calcium metabolism, bone turnover markers, bone density measurement for the first 26-weeks of DIA3010, as well as incidences of fractures. Dr. Voss concluded that the increase in fracture with canagliflozin is apparent within 12-26 weeks of treatment, during which time there is no apparent decline in bone density that would be sufficient to provide plausible mechanism. In addition, the excess in fractures in upper extremity would be highly unusual for bone fragility issue and suggested that falls may be a factor. He suggested that further data on BMD and fractures in the future would be helpful to further determine safety signal related to fractures. Please refer to Dr. Stephen Voss's review, dated December 5, 2012, for his findings.

Because the increased incidence of fractures with canagliflozin appears to occur early, it is feasible that these fractures, especially the upper limb fractures, were possibly related to falls due to volume depletion-related events such as hypotension. In order to assess this, I looked to see whether there was an increase in the incidence of volume depletion events in those subjects with fractures. Among those with fractures in DS4, the reported number of volume depletion events were few and no significant imbalance was seen between treatment groups: 3 subjects in each

canagliflozin 100 mg and 300 mg group, compared to 2 subjects with placebo reported volume depletion-related events such as hypotension.

In addition, we evaluated whether there was an increased incidence of falls with canagliflozin by searching Broad Dataset (DS3) using the Preferred Term of "fall". This search result did not show an increased incidence with canagliflozin: 0.34% (21/6177) of combined canagliflozin group compared to 0.43% (14/3262) with non-canagliflozin group reported fall. However, it was noted that the investigator reported adverse event terms (i.e., verbatim terms) suggestive of falls were not coded to Preferred Term of "fall" (i.e., painful left wrist from fall was coded to arthralgia PT, facial bruising after fall was coded to contusion PT). A broad search strategy to identify adverse event with verbatim terms containing the word "fall, fell, or collapse" was done in DS3. The result of this broad search showed slightly higher incidence of falls with canagliflozin group: 0.97% (60/6177) in the combined canagliflozin group compared to 0.74% (24/3262) in the non-canagliflozin group.

7.3.10 Significant Adverse Events - Genital Mycotic Infections

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

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

Female Genital Mycotic Infections

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

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

Vulvovaginal disorder, Vulvovaginal dryness, Vulvovaginal erythema, Vulvovaginal pain, Vulvovaginal pruritis, Vulvovaginal ulceration.

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

The incidence of female genital mycotic infections in DS1, DIA3010, and DIA3008 are summarized in Table 70. In the Placebo-Controlled Studies Dataset (DS1), the incidence of female genital mycotic infections were higher in both canagliflozin treatment groups (12.9% and 14.9% in 100 mg and 300 mg group respectively) compared to placebo (3.2%) without dose-dependency. The incidence using the 'specific' list show similar trend as the 'broad' list. The most commonly reported adverse event terms were vulvovaginal mycotic infection and vulvovaginal candidiasis.

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

DIA3010 included older subjects with T2DM with a median age of 63 years (57 years in DS1) and greater median duration of diabetes (10 years compared to 6 years in DS1). The proportion of women who were post-menopausal was also higher in DIA3010 (97%) compared to DS1 (73%). The incidence of female genital mycotic infections was higher in both canagliflozin groups compared to placebo in DIA3010, and higher in the canagliflozin 100 mg group (15.4%) compared to 300 mg group (11.2%) as shown in Table 70.

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

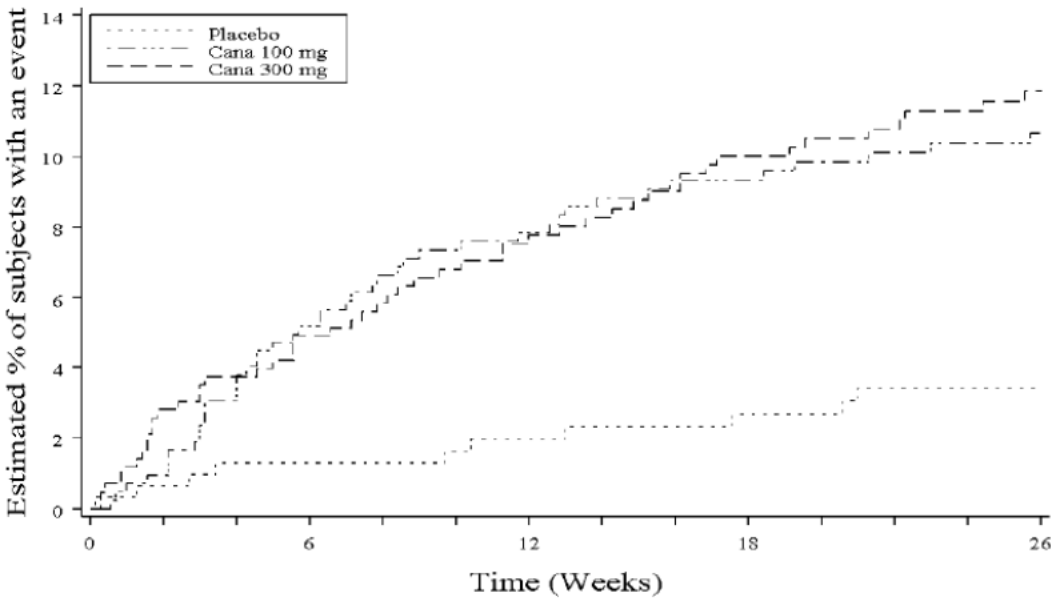
Table 70: Summary of Female Genital Mycotic Infections - Regardless of Rescue

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

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

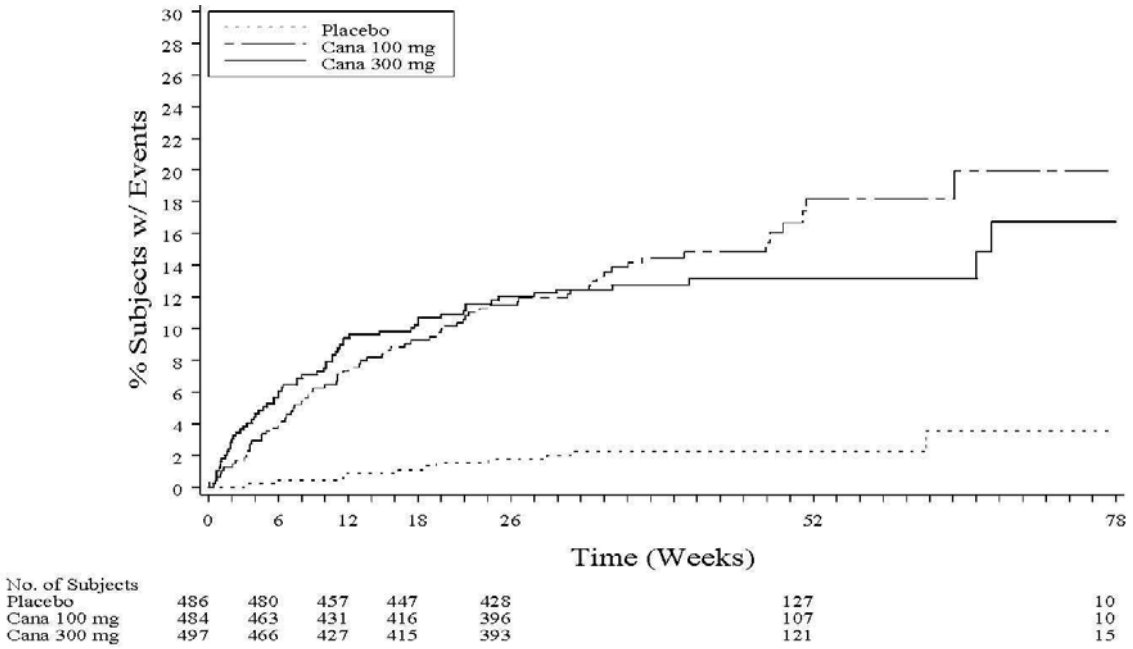
The Kaplan-Meier curve for female genital mycotic infections in DS1, as shown in Figure 23, showed a linear increase in the incidence of female genital mycotic infections in both canagliflozin groups without a plateau at the end of Week 26. However, in the Kaplan-Meier curve for DIA3008 (Figure 24), which contained longer duration of follow-up compared to DS1, the curve appear to plateau after 26 weeks.

Figure 23: Kaplan-Meier Plot of Time to First Mycotic Vulvovaginitis (Specific) in DS1



Source: ISS, Figure 1

Figure 24: Kaplan-Meier Plot of Time to Female Mycotic Infections (Specific) in DIA3008



In DS1, the mean duration of genital mycotic infections in women was not significantly different between treatment groups (19 days and 20 days for combined canagliflozin and placebo groups respectively). The mean duration of symptoms was slightly longer in the combined canagliflozin treatment group (11 days) compared to placebo (9 days). In DIA3010, the mean duration of vaginal symptoms was dose-dependently longer: 26 days, 15 days, and 4 days with canagliflozin 300 mg, 100 mg, and placebo respectively. Among women with genital mycotic infection, more women in the combined canagliflozin group had more than one event (23% [20/93]) compared to placebo (10% [1/10]).

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

Male Genital Mycotic Infections

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

The incidence of male genital mycotic infections in DS1, DIA3010, and DIA3008 are summarized in Table 71. In DS1, the overall incidence of male genital mycotic infections was higher in both canagliflozin groups (4.2% and 3.7% with 100 mg and 300 mg respectively) compared to placebo (0.6%) without dose-dependency.

Table 71: Summary of Male Genital Mycotic Infections - Regardless of Rescue

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

Source: ISS, Table 93, 96, 97

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

- Male genital mycotic infections were more commonly reported in men who were uncircumcised; among 31 men with known circumcision status in the combined canagliflozin treatment group, myotic infections occurred in 0.7% (2/291) of circumcised men compared to 5.7% (29/506) uncircumcised men;
- A larger number of men had a prior history of balanitis/balanoposthitis in men who had genital mycotic infections (25%) compared to men who did not have genital mycotic infections (2%) in the combined canagliflozin group;
- The mean duration of diabetes was slightly longer in men with mycotic infections (9.3 years) compared to those without mycotic infections (7.2 years);
- Male genital mycotic infections occurred more in Europe compared to North America (44% and 25% respectively), but this may be partly be due to the lower prevalence of circumcision in Europe compared to North America (62% and 4% of men respectively).

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

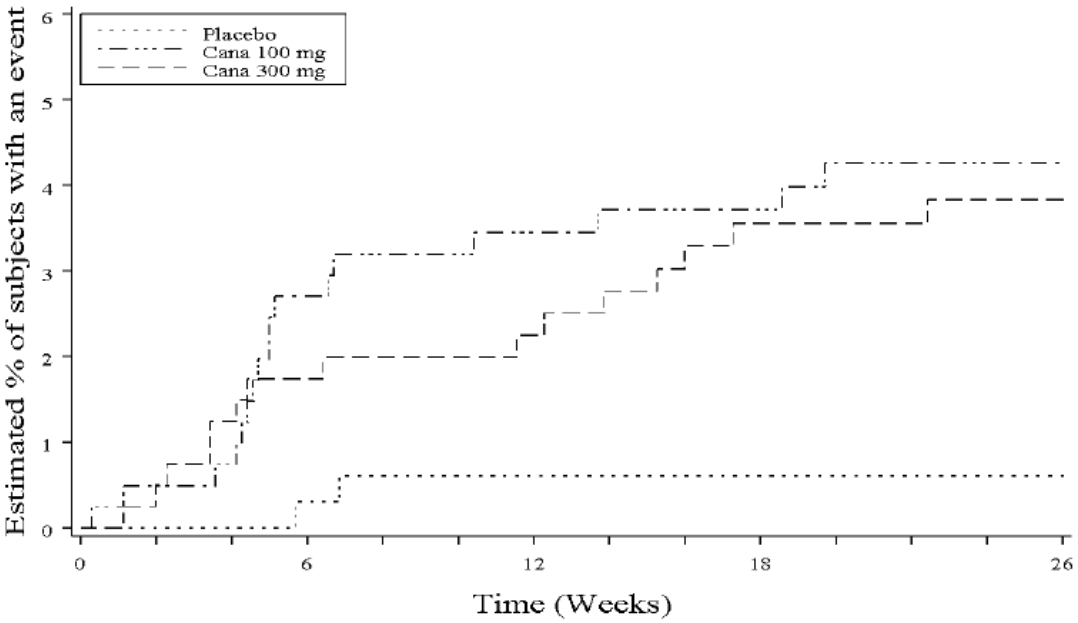
The incidence of male genital infections was higher in DIA3008 compared to DS1 or DIA3010, with a higher incidence with canagliflozin 300 mg (10.2%) compared to 100 mg (6.8%) showing dose-dependency. The higher incidence of male genital infections in DIA3008 compared to DS1 may be related to the fact that more male subjects in DIA3008 were uncircumcised (72% versus

62%) and had a history of balanitis or balanoposthitis (5% versus 3%) compared to DS1. As previously noted, subjects in DIA3008 were also older, had a longer duration of diabetes, with a lower eGFR at baseline, and the mean duration of exposure to study drug in DIA3008 at interim analysis was almost twice as long as DS1.

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

As shown in Figure 25, the increase in the incidence of male genital infections with canagliflozin was apparent early in DS1, and most events occurred by Week 18. In DIA3008, as shown in Figure 26, the proportion of male subjects with genital mycotic infections appear to increase linearly without plateau, at least until Week 52; since this is an interim analysis, not much data is available past Week 52.

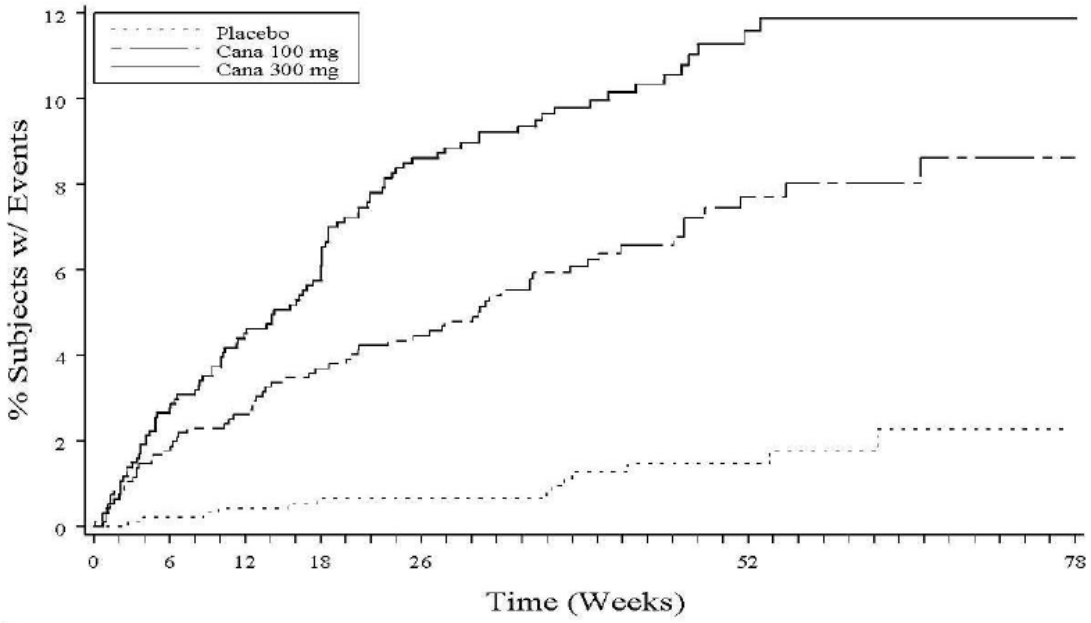
Figure 25: Kaplan-Meier Plot of Time to the First Male Genital Infections - DS1



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

Source: ISS, Figure 4

Figure 26: Kaplan-Meier Plot of Time to First Male Genital Infections - DIA3008 Interim Analysis



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

Source: ISS, Figure 5

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

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

7.3.11 Significant Adverse Events - Urinary Tract Infections

Increases in urinary glucose excretion caused by canagliflozin could also potentially increase bacterial growth in the genito-urinary tract and lead to increased incidence of urinary tract

infections (UTI). The results of UTI included all events regardless of glycemic rescue therapy since glycemic rescue therapy have not been associated with UTIs.

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

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

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

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

The incidences of UTI for DS1, DS2, DIA3010, and DIA3008 are presented in Table 72. In DS1, the incidence of UTI was slightly higher in the canagliflozin 100 mg group (5.9%) compare to canagliflozin 300 mg (4.3%) or placebo group (4.0%).

Table 72: Summary of Urinary Tract Infections - Regardless of Rescue

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

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

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

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

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

The incidence of UTI in subjects in **the Moderate Renal Impairment Dataset (DS2)** was higher with canagliflozin 300 mg (7.4%) compared to canagliflozin 100 mg (6.2%) or placebo (6.0%). Three subjects in placebo and one subject in canagliflozin 100 mg reported serious UTI events. Two subjects in placebo and one subject in canagliflozin 100 mg discontinued due to UTI. No UTIs in canagliflozin 300 mg group were serious or led to discontinuation. One subject in each treatment groups had upper UTI based on the search of MedDRA terms indicative of upper UTIs; only one adverse event of urosepsis in placebo group was serious.

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

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

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

7.3.12 Significant Adverse Events - Increase in Low-Density Lipoprotein-Cholesterol (LDL-C)

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

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

Fasting Lipid Changes By Phase 3 Trial

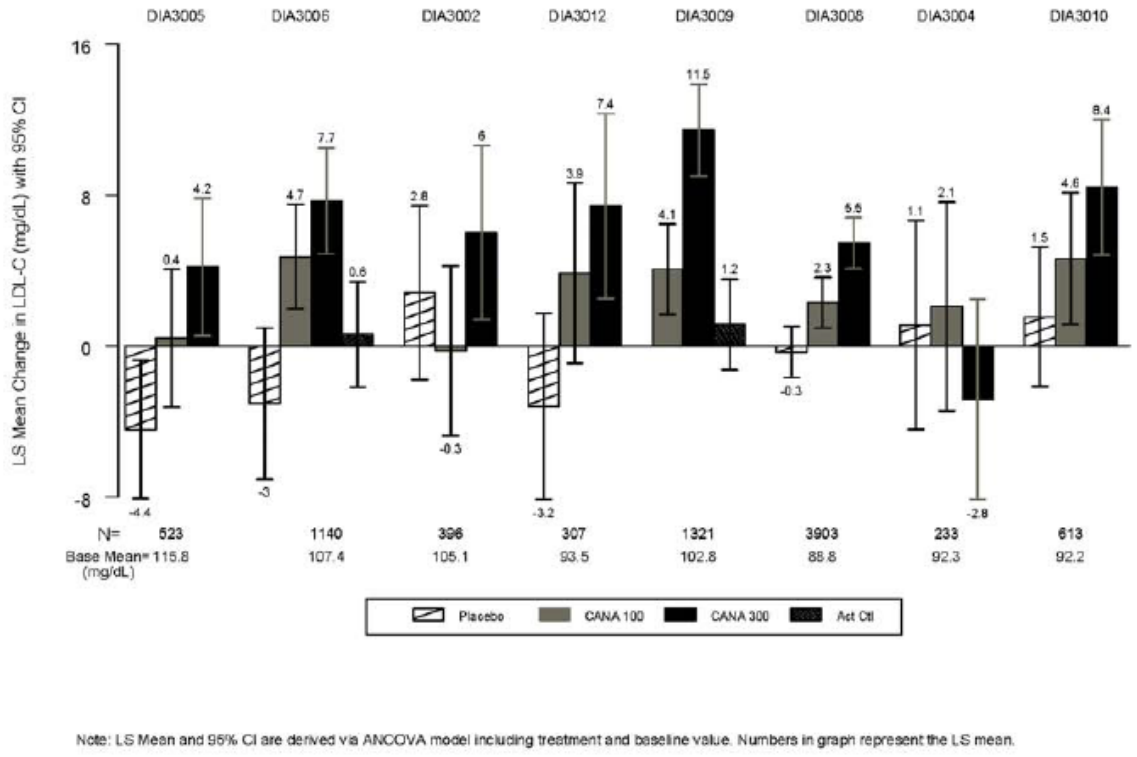
The change in the least squares (LS) mean in LDL-C from baseline to the end of core period for eight Phase 3 trials are summarized in Table 73. The LS mean absolute changes in LDL-C from baseline are shown by treatment group for each Phase 3 trial in Figure 27, and the placebo- or active-control subtracted LS mean absolute change in LDL-C are shown in Figure 28. Unlike other trials which showed a dose-dependent increase in LDL-C levels with canagliflozin, there was a decrease in the LS mean absolute change in LDL-C from baseline with canagliflozin 300 mg in DIA3004 (-3.9 mg/dL); DIA3004 was a smaller trial in subjects with moderate renal impairment. The canagliflozin 100 mg group in DIA3002 also showed a decrease in LS mean absolute change in LDL-C from baseline (-3.1 mg/dL). The largest placebo-subtracted increase in LS mean absolute change in LDL-C from baseline with canagliflozin occurred in DIA3006 and DIA3012.

Table 73: Summary of LS Mean Absolute Change in LDL-C (mg/dL) from Baseline at the End of Core Period By Phase 3 Trial - LOCF, Regardless of Rescue

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

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

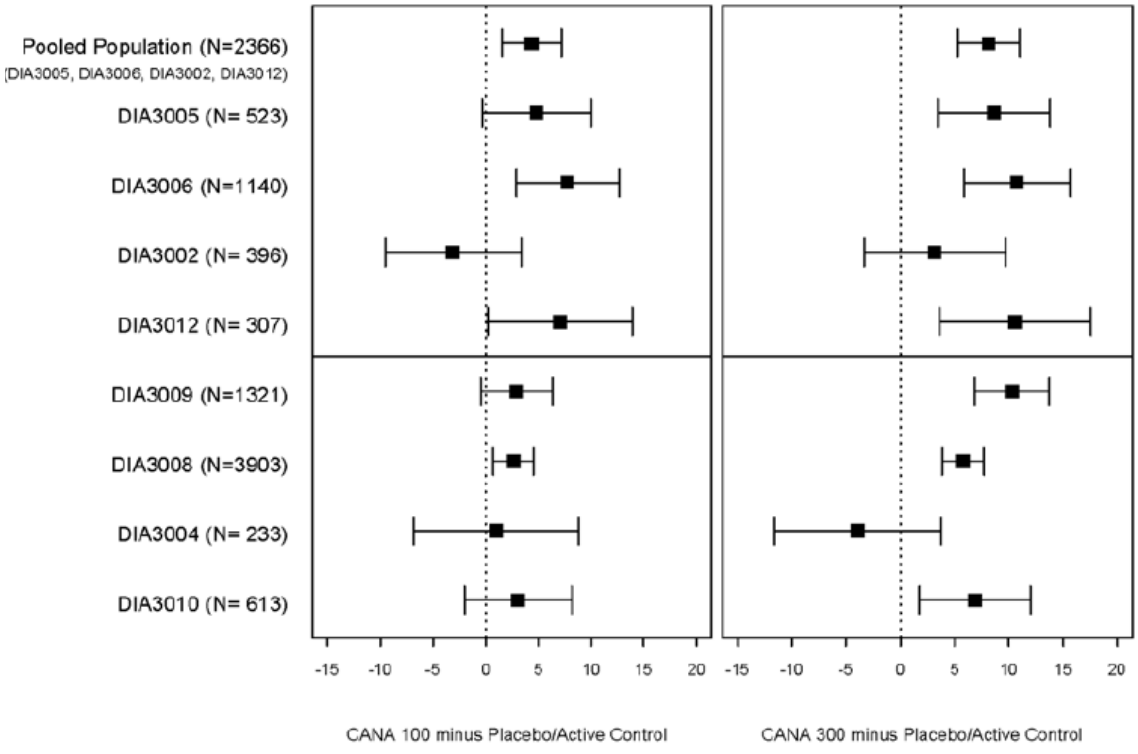
Figure 27: LS Mean Absolute Change in LCL-C (mg/dL) from Baseline at the End of Core Period By Phase 3 Trial - LOCF, Regardless of Rescue



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

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

Figure 28: Placebo- or Active-Control Subtracted LS Mean Absolute Change in LDL-C (mg/dL) from Baseline at the End of Core Period By Phase 3 Trial

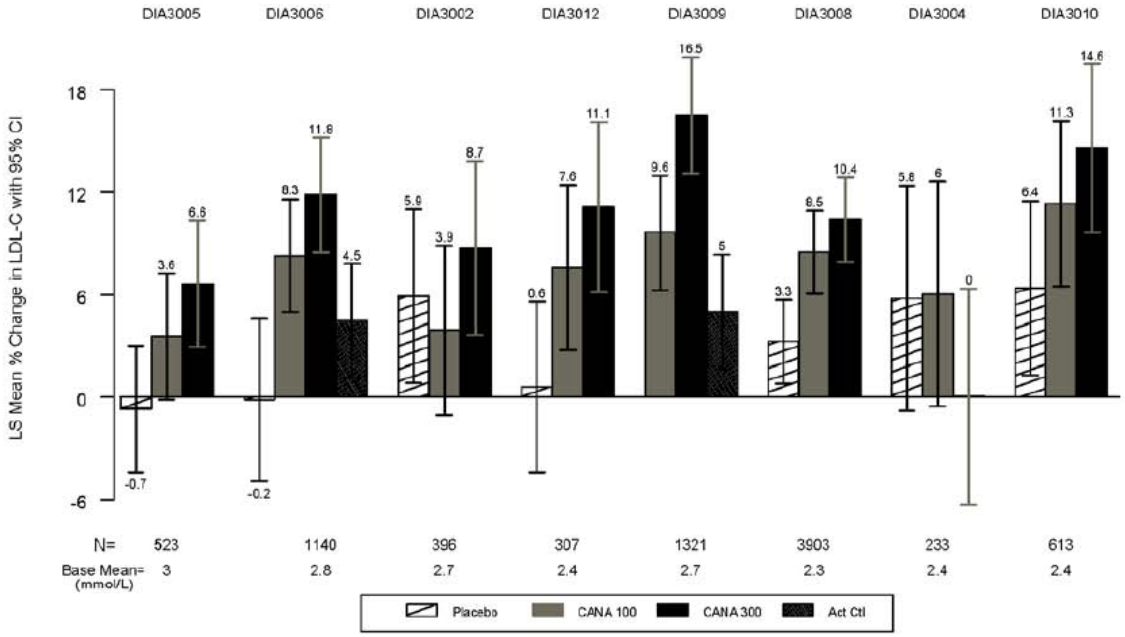


Note: LS Mean diff and 95% CI is between Cana and Glimepiride for DIA3009, is between Cana and Placebo for the rest studies.
Pooled Population includes Study DIA3005, DIA3006, DIA3002, DIA3012.

Source: ISS, Figure 33

The LS mean percent changes in LDL-C from baseline at the end of core period for each Phase 3 trial are shown in Figure 29, and placebo- or active-control subtracted LS mean percent changes are shown in Figure 30. The placebo- or active-control subtracted LS mean percent change in LDL-C from baseline ranged from -2% (DIA3002) to 8.5% (DIA3006) for canagliflozin 100 mg and 2.8% (DIA3002) to 12% (DIA3006) for canagliflozin 300 mg.

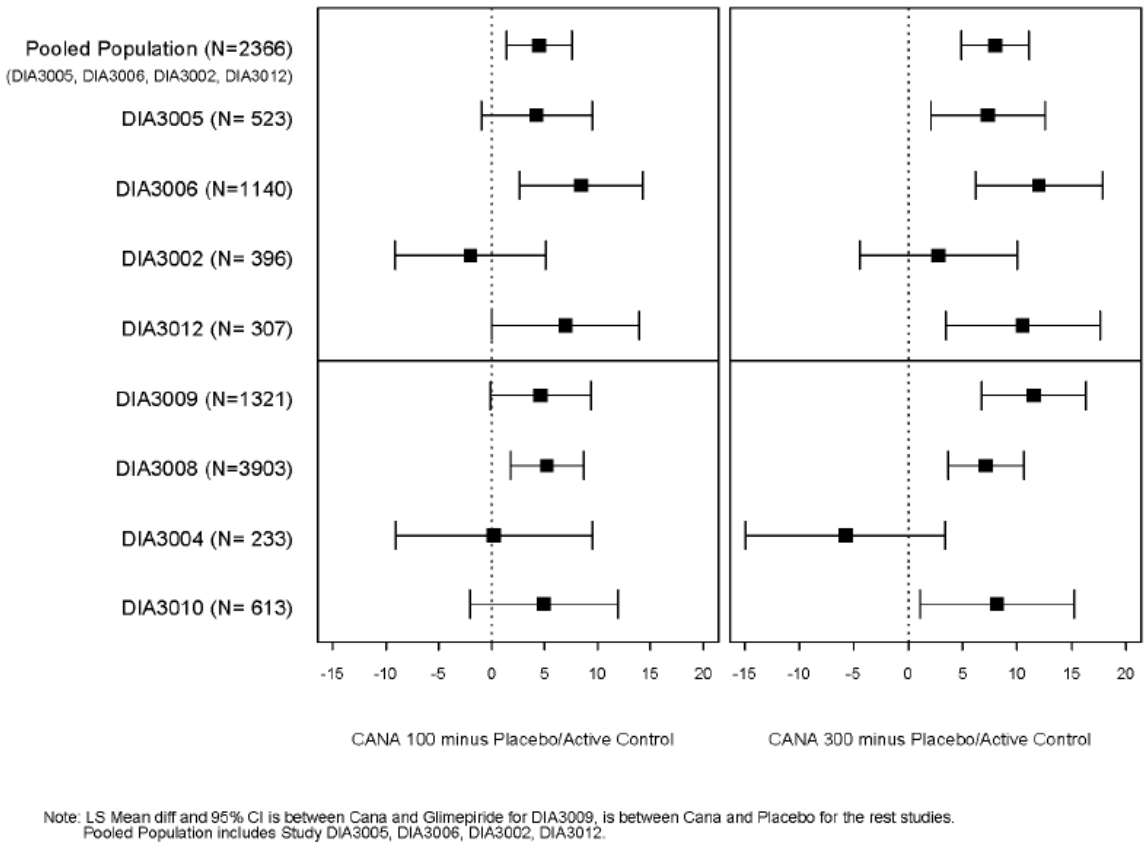
Figure 29: LS Mean % Changes in LDL-C from Baseline at the End of Core Period By Phase 3 Trial



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

Source: ISS, Figure 34

Figure 30: Placebo- or Active-Control Subtracted LS Mean % Change in LDL-C from Baseline at the End of Core Period By Phase 3 Trial



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

Source: ISS, Figure 35

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

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

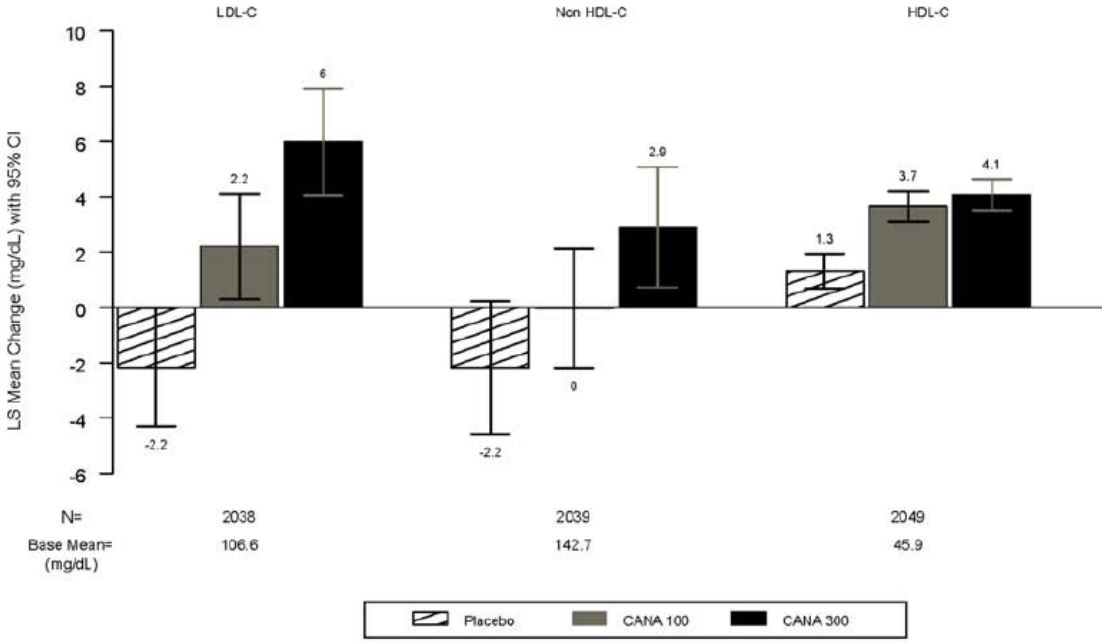
Lipid Changes in the Placebo-controlled Studies Dataset (DS1)

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

The use of statin drugs would be an important factor that would affect LDL-C levels, and statin use at baseline and during post-baseline was assessed in DS1. About 41% of subjects in each treatment group were receiving statin at baseline in DS1. Slightly lower proportion of subjects on canagliflozin 300 mg started or modified their statin dose during the trial (1.6% [13/834]) compared to canagliflozin 100 mg (2.5% [21/833]) or placebo (2.5% [16/646]). It is unlikely that such a small change in statin use during the study period would significantly alter the effects of canagliflozin on lipid levels.

The LS mean absolute changes for LDL-C, non-HDL-C, and HDL-C from baseline for DS1 are presented in Figure 31. There was a dose-dependent increase in the LS mean change in LDL-C from baseline with canagliflozin 100 mg (2 mg/dL) and 300 mg (6 mg/dL), compared to a decrease in LS mean change from baseline with placebo (-2 mg/dL). The placebo-subtracted LS mean change in LDL-C from baseline to Week 26 was 4.4 mg/dL (95% CI:1.5; 7.2) and 8.2 mg/dL (95% CI:5.3;11.0) in canagliflozin 100 mg and 300 mg group respectively. The placebo-subtracted LS mean change in HDL-C from baseline to Week 26 was 2.3 mg/dL (95% CI:1.5; 3.1) and 2.8 mg/dL (95% CI:1.9; 3.6) in canagliflozin 100 mg and 300 mg group respectively. The placebo-subtracted LS mean change in triglycerides from baseline to Week 26 was -9.23 mg/dL (95% CI:-18.4;-0.0) and -19.1 mg/dL (95% CI:-28.3;-9.8) in canagliflozin 100 mg and 300 mg group respectively.

Figure 31: LS Mean Absolute Changes in Fasting Lipids (mg/dL) from Baseline to Week 26 in DS1

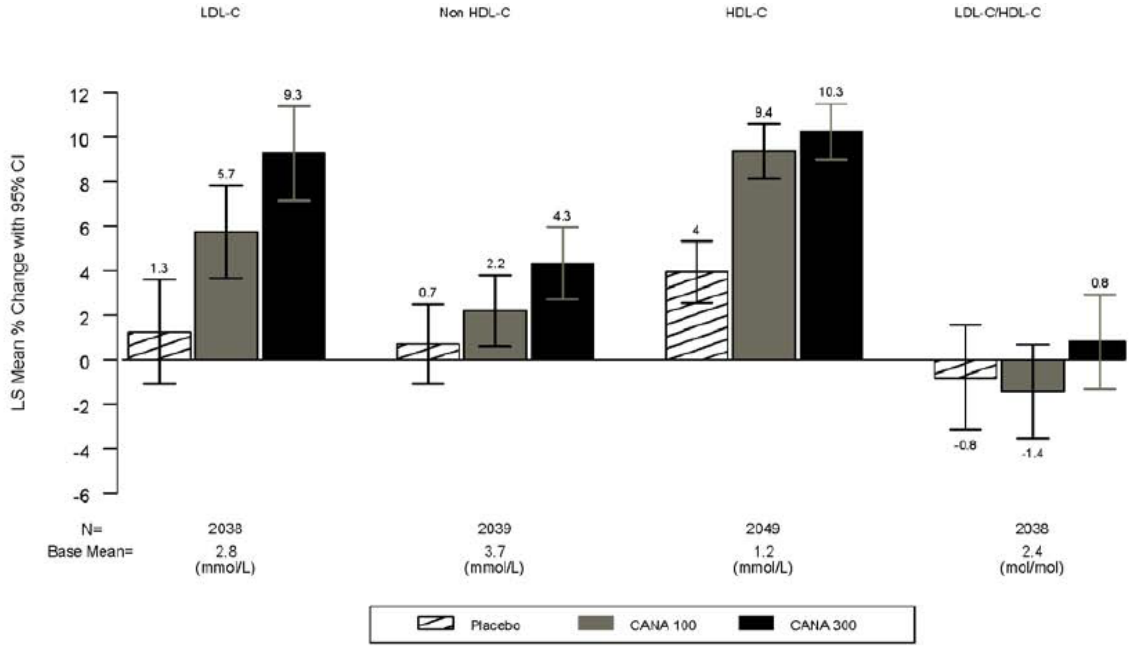


Note: LS Mean and 95% CI are derived via ANCOVA model including treatment, Study ID and baseline value. Numbers in graph represent the LS mean.

Source: ISS, Figure 38

The LS mean percent changes in LDL-C, non-HDL-C, and HDL-C from baseline for DS1 are presented in Figure 32. Corresponding to absolute mean change, there was a dose-dependent increase in the LS mean percent change in LDL-C from baseline at Week 26 with canagliflozin 100 mg (5.7%) and 300 mg (9.3%), compared to placebo (1.3%). The placebo-subtracted LS mean percent change in LDL-C at Week 26 was 4.5% (95% CI:1.4;7.6) and 8.0% (95% CI:4.9;11.1) with canagliflozin 100 mg and 300 mg respectively. The placebo-subtracted LS mean percent change in HDL-C at Week 26 was 5.4% (95% CI:3.6;7.2) and 6.3% (95% CI:4.5;8.2) with canagliflozin 100 mg and 300 mg respectively. The placebo-subtracted LS mean percent change in triglyerides at Week 26 was -5.2% (95% CI:-10.0;-0.3) and -7.6% (95% CI:-12.5;-2.8) with canagliflozin 100 mg and 300 mg respectively.

Figure 32: LS Mean Percent Change from Baseline at Week 26 in DS1

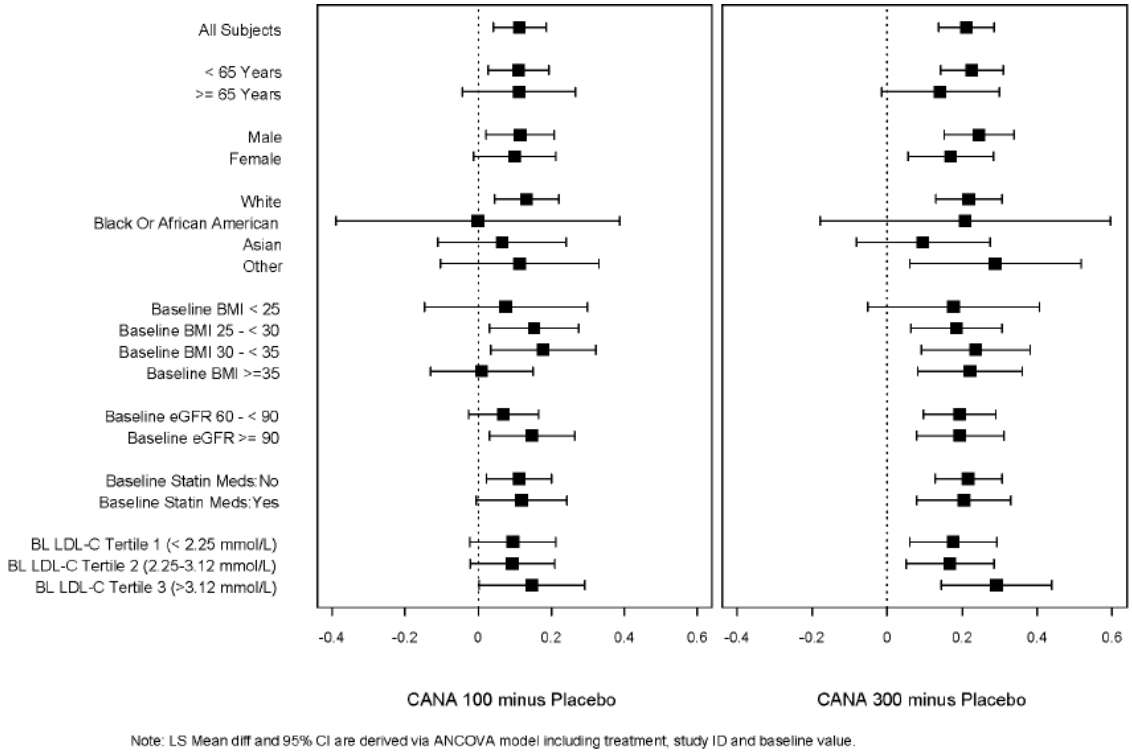


Note: LS Mean and 95% CI are derived via ANCOVA model including treatment, Study ID and baseline value. Numbers in graph represent the LS mean.

Source: ISS, Figure 39

Subgroup analyses were conducted in DS1 in order to assess potential baseline factors that may affect the LDL-C change observed with canagliflozin. The LS mean change in LDL-C in various subgroups based on age, sex, race, BMI, estimated eGFR, baseline statin use, and baseline LDL-C by tertile did not demonstrate any meaningful change in a particular subgroup, as shown in Figure 33. Figure 34 shows the pattern of LS mean percent change in LDL-C in various subgroups in DS1. The nominal p-value for interaction between treatment and each of the subgroup was >0.1.

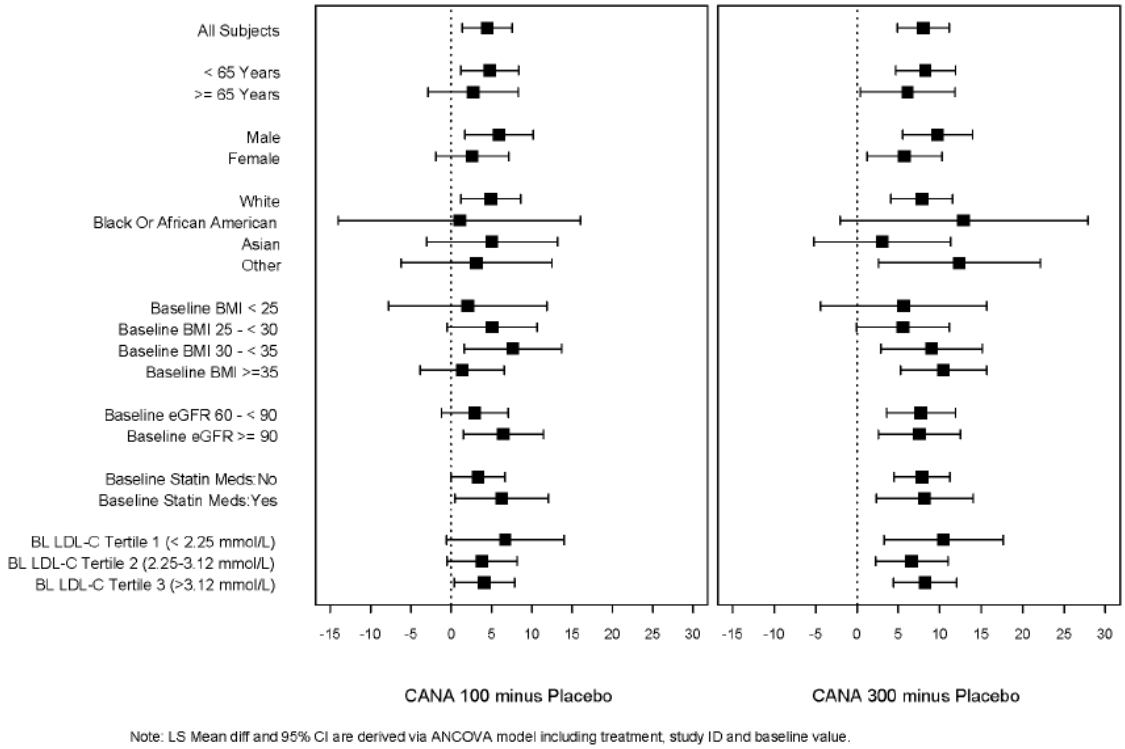
Figure 33: Placebo-Subtracted LS Mean Absolute Change in LDL-C from Baseline in Subgroups - DS1



Note: LS Mean diff and 95% CI are derived via ANCOVA model including treatment, study ID and baseline value.

Source: ISS, Figure 40

Figure 34: Placebo-Subtracted LS Mean % Change in LDL-C from Baseline in Subgroups - DS1



Note: LS Mean diff and 95% CI are derived via ANCOVA model including treatment, study ID and baseline value.

Source: ISS, Figure 41

The applicant conducted additional analysis of Apo B measurement through a specialty core laboratory (b) (4) in archived samples from two trials, DIA3005 and DIA3006. The applicant selected DIA3006 for assessment of Apo B because of relatively large sample size and higher LDL-C increase compared to other trials. DIA3005 was selected by applicant for comparison since the LDL-C changes in this trial was more modest. In addition, LDL-C particle number was obtained using nuclear magnetic resonance (NMR) spectroscopy done by a specialty core lab (b) (4) for DIA3006.

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

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

respectively. In DIA3006, the placebo-subtracted mean percent change in non-HDL-C from baseline to Week 26 was 4.4% and 6.5% in canagliflozin 100 mg and 300 mg respectively.

Table 74 presents the LDL particle assessment by NMR spectroscopy for DIA3006. There was a dose-dependent increase in the total LDL-C particle number with canagliflozin, with placebo-subtracted LS mean percent increase of 3.2% and 5.0% in canagliflozin 100 mg and 300 mg group respectively. These changes in the total LDL-C particle number was smaller than changes for LDL-C; using Friedewald calculation, the placebo-subtracted LS mean percent change was 9.6% and 14.5% in canagliflozin 100 mg and 300 mg respectively. The increase in the total LDL-C particle number was largely driven by an increase in the large LDL-C subfraction in both canagliflozin 100 mg and 300 mg group, with little to small increase in the small LDL-C particle number (Table 74).

Table 74: Placebo-Adjusted LS Mean Percent Change (95% CI) From Baseline to Week 26 - DIA3006, Regardless of Rescue

	Cana 100 (N=368)	Cana 300 (N=367)
Plasma LDL particles	3.2 (-1.4, 7.9)	5.0 (0.3, 9.7)
Plasma Large LDL Particles	41.4 (-2.9, 85.7)	22.2 (-22.4, 66.8)
Plasma Small LDL Particles	-1.4 (-19.7, 16.9)	5.7 (-12.8, 24.1)

Source: ISS, TAble DEFF27IP_ISS

Reviewer's comment: An increase in LDL-C observed with canagliflozin have clinical implication, as data from the Cholesterol Treatment Trialists' Collaboration have shown that for each 1 mmol/L (~38.7 mg/dL) LDL cholesterol reduction, the annual major vascular events are reduced by about a fifth, irrespective of baseline cholesterol level.[5] Given that there is a continuous positive linear relationship between CV risk and LDL cholesterol level, a 8.2 mg/dL (~0.2 mmol/L) mean absolute increase in LDL-C observed with canagliflozin 300 mg in DS1 would translate into ~4% increase in the incidence of major vascular events annually.

The clinical significance of this increased LDL-C observed with canagliflozin should be further studied. Changes in lipids are reported in the proposed labeling.

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

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

7.3.13 Submission Specific Primary Safety Concerns - Cardiovascular Safety

Please refer to Dr. Eugenio Andraca-Carrera's review of cardiovascular meta-analysis for a full discussion on the applicant's meta-analysis.

The cardiovascular meta-analysis was done for the Major Adverse Cardiovascular Events Plus (MACE-plus), which was a composite endpoint consisting of cardiovascular death, myocardial infarction, stroke, and hospitalization for unstable angina. This composite endpoint is consistent with FDA guidance.

The data cutoff date for CV meta-analysis was January 31, 2012. CV meta-analysis was conducted using the mITT analysis set, which included all randomized subjects who took at least one dose of the double-blind study drug. Events were included if it occurred while subject was on drug or within 30 days of study drug discontinuation. An independent EAC composed of external specialists adjudicated the CV events while blinded to treatment assignment. The analysis of MACE-plus events in canagliflozin group (pooling both dose groups) versus comparator was tested at a 2-sided significance level of 0.05 in mITT analysis set, and the 95% CI was derived from a Cox proportional hazards model with treatment (canagliflozin and control) and the explanatory variable and CANVAS versus non-CANVAS as a stratification variable.

The mITT analysis set included 9632 subjects randomized in nine trials, which included a Phase 2 trial (DIA2001) and all Phase 3 trials except DIA3015. DIA2001, a Phase 2 12-week trial, was included even though it did not contribute any events to CV meta-analysis. A total of 6305 subjects were treated with canagliflozin and 3327 were treated with placebo or active comparator (e.g., glimepiride, sitagliptin). Trial DIA3008 contributed a large portion (45%) of total mITT subjects for meta-analysis.

There were no notable differences in baseline demographic, clinical, and anthropometric characteristics between the pooled canagliflozin and control groups. The mean and median age were 60 years, with about 30% of subjects ≥65 years. The majority of subjects were male (58%) and Caucasian (73%). The mean BMI was 32 kg/m2, mean eGFR was 82 mL/min/1.73m^2, and the mean HbA1c and FPG was 8% and 165 mg/dL respectively. The mean LDL-C level was 96 mg/dL, and 58% of subjects were receiving statin therapy at baseline. About 33% of subjects had a prior history of CV disease, and 30% had at least one CV risk factor at baseline. About 50% of subjects had diabetes for 10 years or more.

The pre-specified MACE-plus analysis did not show an increased incidence of cardiovascular events with canagliflozin, with estimated hazard ratio of 0.91 (95% CI: 0.68, 1.22), as shown in Table 75 below. Among individual components for MACE-plus, the point estimate for stroke is greater than 1 at 1.46, although the 95% CI is wide and crosses 1 (0.83, 2.58). Most strokes with canagliflozin were ischemic in nature; 79% (37/47) and 56% (9/16) of strokes with canagliflozin and comparators were ischemic strokes respectively.

Table 75: Number of Cardiovascular Events (Rate per 1000 Patient-Years) and Hazard Ratio - All Trials in the Pre-Specified Meta-Analysis.

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

Source: Dr. Andraca-Carrera

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

As shown in Table 76, although there is slight imbalance in history of previous CV history and CV risk factor between subjects receiving canagliflozin who had early CV events (within 30 days) compared to those receiving canagliflozin who had CV event after 30 days, or compared to subjects who received placebo and had a CV event in DIA3008, the numbers were small and inconclusive.

Table 76: Baseline Characteristics for Canagliflozin Subjects With CV Events, Before and After 30 Days, and Placebo - DIA3008

Baseline Characteristics	**Canagliflozin** Subjects who had early CV events (N=13)	**Canagliflozin** Subjects with CV event after 30 days (N=95)	**Placebo** All subjects with CV event (N=53)
Mean age, yrs	62.4	63.2	64.4
Male, %	77%	73%	64%
Mean HbA1c (%)	8.3	8.2	8.2
Mean eGFR, mL/min/1.73m^2	77.3	75.1	73.5
Mean LDL, mg/dL	101	100	94
Mean BMI, kg/m^2	31	33	33
Previous CV history, %:	69%	79%	85%
HTN	92%	88%	83%
MI	54%	44%	45%
Dyslipidemia	46%	63%	72%
CV risk factor, %			
Current smoker	31%	18%	13%
Diabetes ≥10 years	77%	63%	72%
Low HDL-C (<39 mg/dL)	31%	33%	42%
Micro or macro-albuminuria	54%	36%	34%
SBP >140 mmHg at screening	46%	43%	43%

Source: Response to information request

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

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

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

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

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

Cardiovascular Death

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

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

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

Nonfatal Myocardial Infarction (MI)

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

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

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

Day 186. This subject also experienced muscle pain in both legs on Day 69, and flu on Day 209, both non-serious.

Subject (b) (4) Treatment canagliflozin 300 mg

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

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

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

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

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

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

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

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

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

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

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

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

26, CK and CK-MB decreased to 1049 U/L and 12 ng/mL respectively, whereas troponin I level remained elevated. On Day 24, he underwent PCI of LAD and circumflex artery. LAD was 100% occluded and stent was inserted. Due to persistent arrhythmia, second drug-eluding stent was placed in circumflex artery. Echocardiogram showed anteroapical infarct of moderate degree and left ventricular systolic function with ejection fraction of 45%. He recovered post procedure, was discharged on Day 26, and continued in the study.

Nonfatal Stroke

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

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

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

Subject (b) (4) Treatment canagliflozin 100 mg

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

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

Subject (b) (4) Treatment Canagliflozin 100 mg

Background AHA therapy: Baseline: huminsulin 50/50 40, huminsulin R 26, anti-hyperglycemic agents 2000, continuous insulin 2007,

Concomitant medications: From baseline: clopidogrel, acetylsalicylic acid, atorvastatin, metoprolol, ramipril, mecobalamin, pregabalin, thioctic acid, itopride, pantoprazole
Pertinent medical history: constipation, backache, hypertension 2003, MI 2009, diabetes 2000, diabetic neuropathy 2007.

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

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

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

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

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

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

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

Hospitalized Unstable Angina

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

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

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

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

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

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

One subject in the placebo group who experienced nonfatal myocardial infarction

Subject (b) (4); Treatment Placebo

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

A 67-year old man presented to emergency department on Day 23 with after having episodic chest pain, diaphoresis, and dyspnea lasting 30 minutes during previous night. ECG showed bundle branch block. Echocardiogram showed left ventricular ejection fraction of 40-45%. Cardiac enzymes were "elevated at 0.63" (normal range not provided). Cardiac angiography showed severe two-vessel coronary artery disease. Stents were placed in LAD artery and distal right coronary artery. He recovered and was discharged on Day 25.

7.3.14 Submission Specific Primary Safety Concerns - Hypoglycemia

A dedicated eCRF collected information on hypoglycemic episodes, and the analyses for hypoglycemia used results from this hypoglycemia eCRF and not from the adverse event eCRF. Applicant stated that during data review, any event of hypoglycemia reported as adverse event was cross checked to make sure that the event was also reported on the dedicated eCRF hypoglycemia page. Investigators were counseled to report all episodes of hypoglycemia on the dedicated eCRF for hypoglycemia and also to report episodes of hypoglycemia as adverse events as appropriate. For all analyses, hypoglycemia data was derived from hypoglycemia eCRF.

In Phase 3 trials with canagliflozin, subject with either a biochemically documented hypoglycemic episode or a severe hypoglycemic episode was counted as having a documented hypoglycemia, as defined here (an episode may meet both criteria):

- Biochemically documented hypoglycemic episode: hypoglycemia with a concurrent fingerstick glucose of ≤70 mg/dL, regardless of presence of symptoms.
- Severe hypoglycemic episode: When the answer is yes to any of the following 3 questions on the hypoglycemia eCRF: 1) Did the subject require the assistance of others to treat?, 2) Did the subject lose consciousness during the episode?, or 3) Did the subject have a seizure during the episode?

<u>Hypoglycemia in Studies with Subjects **NOT** on a Background of Insulin or Insulin Secretagogues</u>

Table 77 summarizes treatment-emergent documented hypoglycemia in subjects not on a background of insulin or insulin secretagogues for one pooled dataset and for each individual Phase 3 trial.

A pooled dataset of DIA3005 (monotherapy), DIA3006 (add-on to metformin), and DIA3012 (add-on to metformin and pioglitazone) was used to assess the incidence of hypoglycemia with canagliflozin without background regimen of insulin or insulin secretagogues. In this pool, as shown in Table 77, the incidence of documented hypoglycemic episodes were slightly higher

with canagliflozin compared to placebo: 3.8% with canagliflozin 100 mg, 4.3% with 300 mg, and 2.2% with placebo. The event rate per subject year exposure was also greater with canagliflozin (0.22 and 0.18 with 100 mg and 300 mg respectively) compared to placebo (0.10). The incidence of severe hypoglycemia was low, with one subject in each canagliflozin group reporting severe hypoglycemia; both subjects were from DIA3006.

Table 77: Treatment-Emergent Documented Hypoglycemia in Phase 3 Trials with Subjects (%) Not on a Background of Insulin or Insulin Secretagogues - Before Rescue (Safety Analysis Set)

	Placebo	Cana 100	Cana 300	Comparator
Pooled dataset: DIA3005, DIA3006, DIA3012	490	676	678	
Subjects with any documented hypoglycemia	11 (2.2)	26 (3.8)	29 (4.3)	
Severe hypoglycemia	0	1	1	
Total number of episodes	20	69	57	
Event rate per subject-year exposure	0.10	0.22	0.18	
DIA3005 (monotherapy)	192	195	197	
Subjects with any documented hypoglycemia	5 (2.6)	7 (3.6)	6 (3.0)	
Severe hypoglycemia	0	0	0	
Total number of episodes	14	8	11	
Event rate per subject-year exposure	0.18	0.09	0.12	
DIA3006 (add-on to metformin)	183	368	367	366 (sitagliptin)
Subjects with any documented hypoglycemia	3 (1.6)	16 (4.3)	17 (4.6)	5 (1.4)
Severe hypoglycemia	0	1	1	0
Total number of episodes	3	56	37	9
Event rate per subject-year exposure	0.04	0.33	0.21	0.05
DIA3009 (add-on to metformin)		483	485	482 (glimepiride)
Subjects with any documented hypoglycemia		27 (5.6)	24 (4.9)	165 (34.2)
Severe hypoglycemia		2 (0.4)	3 (0.6)	15 (3.1)
Total number of episodes		67	33	710
Event rate per subject-year exposure		0.16	0.08	1.72
DIA3012 (add-on to metformin/pioglitazone)	115	113	114	
Subjects with any documented hypoglycemia	3 (2.6)	3 (2.7)	6 (5.3)	
Severe hypoglycemia	0	0	0	
Total number of episodes	3	5	9	
Event rate per subject-year exposure	0.06	0.09	0.17	

Note: Documented hypoglycemia includes episodes with concurrent glucose measurement <70 mg/dL (3.9 mmol/L) and/or meeting criteria for severe hypoglcyemia.
Source: ISS, Table 172, 173

Consistent with the pooled dataset as described above, the incidence of documented hypoglycemic episodes was slightly higher with canagliflozin (3.6% with 100 mg and 3.0% with

300 mg) compared to placebo in the monotherapy study, DIA3005. In an add-on to metformin/pioglitazone study DIA3012, the incidence of documented hypoglycemia was higher with canagliflozin 300 mg (5.3%) compared to 100 mg (2.7%) or placebo (2.6%); the event rate per subject-year was similarly increased with 300 mg group (0.17) compared to 100 mg (0.09) or placebo (0.06).

The increased difference in the incidence of documented hypoglycemic episodes with canagliflozin was notable in the add-on to metformin study DIA3006: 4.3% with canagliflozin 100 mg, 4.6% with 300 mg, compared to 1.6% with placebo and 1.4% with sitagliptin. The event rates per subject-year was also significantly greater with canagliflozin (0.33 and 0.21 with 100 mg and 300 mg respectively) compared to comparator (0.04 and 0.05 with placebo and sitagliptin respectively). One subject in each canagliflozin group reported a severe hypoglycemic episode, in subjects without any previous history of severe hypoglycemic episodes.

In the active-comparator add-on to metformin study against glimepiride (DIA3009), the incidence of documented hypoglycemia was not surprisingly significantly higher with glimepiride (34.2%) compared to canagliflozin (5.6% with 100 mg and 4.9% with 300 mg). Although the number of subjects reporting severe hypoglycemia was higher with glimepiride (15 subjects), there were 5 subjects in the combined canagliflozin group reporting severe hypoglycemia. In 4 of 5 subjects in the pooled canagliflozin group reporting severe hypoglycemia, concurrent values were reported with values ranging from 58 to 160 mg/dL. One subject (300 mg) experienced more than one severe hypoglycemia, two subjects had loss of consciousness, and all required assistance; no seizures were reported. None of these 5 subjects had a previous history of severe hypoglycemia.

Reviewer's comment: In DIA3006, the relative incidence of documented hypoglycemia with canagliflozin compared to placebo was more than 2-fold, with 5 to 8 relative increased incidence per subject-year exposure. Among trials included in the pool (DIA3005, DIA3006, and DIA3012), severe hypoglycemic episodes were only observed in DIA3006. There was no significant baseline differences between these three trials that would suggest that subjects in DIA3006 are at a higher risk for hypoglycemic episodes.

From the pooled dataset (DIA3005, DIA3006, and DIA3012), the overall risk for hypoglycemia with canagliflozin appear to be increased even in subjects not on background of insulin or insulin secretagogues, as reflected in both the incidence of documented hyperglycemia and event rate per subject-year. However, the overall incidence of hypoglycemia with canagliflozin in studies where subjects were not on a background of insulin or insulin secretagogues was low.

The incidence of documnented hypoglycemic episodes reported in a subset of subjects who were not on a background of insulin or insulin secretagogues from DIA3008, DIA3010, and Moderate Renal Impairment Dataset (DS2) are presented in Table 78.

Table 78: Treatment-Emergent Documented Hypoglycemia in Subset of Subjects (%) Not on Insulin or Insulin Secretagogues - DIA3008, DIA3010, and DS2; Before Rescue (Safety Analysis Set)

	Placebo	Cana 100	Cana 300
DIA3008* (CV study)	235	210	202
Subjects with any documented hypoglycemia	4 (1.7)	9 (4.3)	6 (3.0)
Severe hypoglycemia	0	0	1 (0.5)
Total number of episodes	10	27	11
Event rate per subject-year exposure	0.13	0.38	0.16
DIA3010 (Older Adults Study)	62	60	63
Subjects with any documented hypoglycemia	2 (3.2)	4 (6.7)	3 (4.8)
Severe hypoglycemia	0	1	0
Total number of episodes	2	9	6
Event rate per subject-year exposure	0.07	0.31	0.20
Moderate Renal Impairment Dataset	50	37	41
Subjects with any documented hypoglycemia	1 (2.0)	3 (8.1)	1 (2.4)
Severe hypoglycemia	0	0	0
Total number of episodes	8	7	1
Event rate per subject-year exposure	0.45	0.47	0.06

*DIA3008 Interim Safety results until Week 18
Source: ISS, Table 174

The incidence of documented hypoglycemia in a subset of subjects from DIA3008 not on background insulin or insulin secretagogue was higher with canagliflozin (2-fold) compared to placebo: 4.3% with 100 mg, 3.0% with 300 mg, and 1.7% with placebo. The event-rate per subject-year was significant greater with canagliflozin 100 mg (0.38; 3-fold compared to placebo) compared to 300 mg (0.16) or placebo (0.13). One subject without any previous history of severe hypoglycemia had 2 severe hypoglycemic episodes after receiving canagliflozin 300 mg; no loss of consciousness or seizure occurred during either episode, and no precipitating factor or concurrent glucose measures were obtained.

In the subset of subjects from DIA3010 who were not on background insulin or insulin secretagogue, the incidence of documented hypoglycemia was also highest with canagliflozin 100 mg (6.7% with 100 mg and 4.8% with 300 mg), and higher than placebo (3.2%), with higher event-rate per subject-year (3-4 fold) with canagliflozin (0.31 with 100 mg and 0.20 with 300 mg) compared to placebo (0.07). One subject (without previous history of severe hypoglycemia) who received canagliflozin 100 mg reported a severe hypoglycemic episode requiring assistance and also led to loss of consciousness, which was thought to be related to decreased caloric intake.

The overall number of subjects from the Moderate Renal Impairment with documented hypoglycemia was too small for between treatment comparisons. Most likely this is due to a very small number of subjects who were not on a background of insulin or insulin secretagogue in this dataset.

Hypoglycemia in Studies with Subjects on a Background of Insulin or Insulin Secretagogues

Table 79 provides summary of the incidence of documented hypoglycemia in subjects on background of insulin or insulin secretagogues from DIA3012 (add-on to metformin/sulfonlyurea), DIA3008 Insulin Substudy, DIA3008 Sulfonylurea Substudy, and DIA3015 (active comparator, add-on to metformin/sulfonylurea). The total number of subjects and number of events in DIA3008 Sulfonylurea Substudy was too small to draw any conclusion, although the trend for higher event rate of hypoglycemia with canagliflozin was observed.

Table 79: Treatment-Emergent Documented Hypoglycemia in Phase 3 Trials in Subjects on a Background of Insulin or Insulin Secretagogue - Before Rescue (Safety Analysis Set)

	Placebo	Cana 100	Cana 300	Comparator
DIA3002 (add-on to metformin/sulfonlyurea)	156	157	156	
Subjects with any documented hypoglycemia	24 (15.4)	43 (27.4)	47 (30.1)	
Severe hypoglycemia	1 (0.6)	1 (0.6)	0	
Total number of episodes	69	184	239	
Event rate per subject-year exposure	1.04	2.58	3.38	
DIA3008 Insulin Substudy	565	566	587	
Subjects with any documented hypoglycemia	208 (36.8)	279 (49.3)	285 (48.6)	
Severe hypoglycemia	14 (2.5)	10 (1.8)	16 (2.7)	
Total number of episodes	945	1355	1629	
Event rate per subject-year exposure	5.26	7.21	8.44	
DIA3008 Sulfonylurea Substudy	69	74	72	
Subjects with any documented hypoglycemia	4 (5.8)	3 (4.1)	9 (12.5)	
Severe hypoglycemia	0	0	0	
Total number of episodes	8	14	14	
Event rate per subject-year exposure	0.37	0.58	0.59	
DIA3015 (add-on to metformin/sulfonlyurea)			377	378 (sitagliptin)
Subjects with any documented hypoglycemia			163 (43.2)	154 (40.7)
Severe hypoglycemia			15 (4.0)	13 (3.4)
Total number of episodes			1277	1143
Event rate per subject-year exposure			4.14	3.81

Source: ISS, Table 175

In DIA3002 (add-on to metformin/sulfonylurea), the incidence of documented hypoglycemic episodes were higher (2-fold) with canagliflozin (27.4% with 100 mg and 30.1% with 300 mg) compared to placebo (15.4%), and the event rate per subject-year was also higher (3-fold) with canagliflozin (2.58 with 100 mg and 3.38 with 300 mg) compared to placebo (1.04). One subject with canagliflozin and one subject with placebo experienced severe hypoglycemia; the subject

with canagliflozin had concurrent glucose level of 33 mg/dL thought to be due to decreased caloric intake.

Reviewer's comment: There is an increased incidence of hypoglycemia with canagliflozin in subjects on a background of insulin or insulin secretagogues.

In DIA3008 Insulin Substudy, the incidence of documented hypoglycemic episodes in the subset of subjects on a background dose of insulin ≥30 units/day was higher with canagliflozin (49.3% with 100 mg and 48.6% with 300 mg) compared to placebo (36.8%). Similarly, increased event rate per subject year was observed with canagliflozin (7.21 and 8.44 for 100 mg and 300 mg respectively) compared to placebo (5.26). The proportion of subjects with severe hypoglycemia was balanced between treatment groups, and the proportion of subjects who reported loss of consciousness or seizure was relatively low and similar across treatment groups (2 in each group).

In DIA3015 (add-on to metformin/sulfonylurea), the incidence of documented hypoglycemia was slightly higher with canagliflozin 300 mg (43.2%) compared to sitagliptin group (40.7%), with event rate per subject-year of 4.14 for canagliflozin and 3.81 for sitagliptin group. The proportion of subjects with severe hyperglycemia was similar between treatment groups.

The incidence of documented hypoglycemic episodes reported in a subset of subjects who were on a background of insulin or insulin secretagogues from DIA3008, DIA3010, and Moderate Renal Impairment Dataset (DS2) are presented in Table 78. These data were supportive of results seen in trials from Table 77, with higher incidence of documented hypoglycemia with canagliflozin compared to placebo group, and showed some dose-dependency.

Table 80: Treatment-Emergent Documented Hypoglycemia in Subset of Subjects (%)on Insulin or Insulin Secretagogues - DIA3008, DIA3010, and DS2; Before Rescue (Safety Analysis Set)

	Placebo	Cana 100	Cana 300
DIA3008* (CV study)	1206	1235	1239
Subjects with any documented hypoglycemia	307 (25.5)	388 (31.4)	429 (34.6)
Severe hypoglycemia	18 (1.5)	12 (1.0)	21 (1.7)
Total number of episodes	1339	1782	2179
Event rate per subject-year exposure	3.46	4.32	5.33
DIA3010 (Older Adults Study)	175	181	173
Subjects with any documented hypoglycemia	66 (37.7)	78 (43.1)	82 (47.4)
Severe hypoglycemia	7 (4.0)	2 (1.1)	1 (0.6)
Total number of episodes	323	371	389
Event rate per subject-year exposure	4.24	4.31	4.81
Moderate Renal Impairment Dataset	332	301	324
Subjects with any documented hypoglycemia	97 (29.2)	126 (41.9)	142 (43.8)
Severe hypoglycemia	4 (1.2)	9 (3.0)	7 (2.2)
Total number of episodes	642	623	832
Event rate per subject-year exposure	5.49	5.56	6.99

*DIA3008 Interim Safety results until Week 18
Source: ISS, Table 176

7.3.15 Submission Specific Primary Safety Concerns - Hepatic Safety

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

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

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

HEAC members, which included three external hepatology experts, remained blinded to treatment group assignment throughout the assessment process. The HEAC members classified causality to study drug using definitions provided in Table 81. Agreement between all three external experts for a single causality category was required; lack of consensus for causality required teleconference for HEAC members to determine final causality.

Table 81: Hepatic Event Causality Definitions

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

Source: ISS-Appendix 7

Mean Percent Change from Baseline

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

Predefined Limits of Change for Liver Function Tests

The predefined limits of change (PDLC) for ALT or AST elevations were based on any post-baseline double-blind treatment period and last on-treatment value (defined as a value up to two days after the last dose of study drug) meeting the PDLC criterion. The proportion of subjects

that had PDLC criteria for ALT or AST elevations at any or last values were low with no significant difference between treatment groups in the Placebo-controlled Studies Dataset (DS1) or Moderate Renal Impairment Dataset (DS2). Therefore, results from the Broad Dataset (DS3) are discussed to assess significant elevations in liver enzymes in the overall Phase 3 program.

The proportion of subjects and incidence rates in person-years for elevations in ALT, AST, and ALT or AST for DS3 are shown in Table 82, Table 83, and Table 84 respectively. Data in DS3 showed that the proportion of subjects meeting the PDLC criteria for ALT and/or AST >3x and >5x ULN in any post-baseline value was higher with canagliflozin 100 mg compared to canagliflozin 300 mg and non-canagliflozin. Similarly, the exposure adjusted incidence rate, calculated per 1000 person-years exposure, also demonstrated a higher incidence of ALT and/or AST elevations with canagliflozin 100 mg compared to canagliflozin 300 mg or non-canagliflozin. It is unclear why we observe a higher incidence of ALT and/or AST elevations with the lower dose of canagliflozin (100 mg) without similar or greater increased incidence with the higher dose of canagliflozin (300 mg).

Table 82: Number of Subjects with Serum ALT Elevations (Regardless of Rescue): ISS Phase 3 Broad Dataset (DS3) Safety Analysis Set

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

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

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

Source: ISS Table 177

Table 83: Number of Subjects with AST Elevations (Regardless of Rescue): ISS Phase 3 Broad Dataset (DS3) Safety Analysis Set

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

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

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

Source: ISS Table 178

Table 84: Number of Subjects with Serum ALT or Serum AST Elevations (Regardless of Rescue): ISS Phase 3 Broad Dataset (DS3) Safety Analysis Set

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

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

The proportion of subjects meeting the PDLC criteria for bilirubin was low and similar between treatment groups in DS1 and DS2. In DS3, 0.2% in the combined canagliflozin and 0.1% in non-canagliflozin group experienced any post-baseline value meeting PDLC criteria for bilirubin (>2x ULN), as shown in Table 85. Five subjects in combined canagliflozin group and no subjects in non-canagliflozin group had serum bilirubin value >2x ULN.

Table 85: Number of Subjects with Serum Bilirubin Elevations (Regardless of Rescue): ISS Phase 3 Broad Dataset (DS3) Safety Analysis Set

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

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

Events Adjudicated by HEAC

As of January 31, 2012, 56 subjects had hepatic events meeting adjudication criteria. Table 86 shows the distribution of events by adjudication criteria (excluding two subjects as noted). Forty-eight subjects met hepatic laboratory adjudication criteria and six subjects were reviewed based on hepatic adverse event terms. As noted, two subjects met the laboratory criteria but were not included in Table 86 since DIA3005 High Glycemic Cohort and Phase 1 trials were not included in the Safety Analysis Set. More hepatic events from canagliflozin 100 mg were submitted for adjudication compared to canagliflozin 300 mg or placebo groups.

Table 86: Summary of Cases Sent for HEAC Adjudication: Safety Analysis Set

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

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

HEAC categorized hepatic events in 56 events as shown in Table 87. One subject in the non-canagliflozin group was assessed as probably-related; this subject had elevations in both ALT and AST >5x ULN. Across all treatment groups, eight cases were assessed as possibly-related.

Table 87: Summary of Causality Determined by HEAC

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

Source: SCS, Table 137 [including subject 500260]

In order to assess the potential for canagliflozin to cause severe liver injury (e.g., irreversible liver injury), we identified cases of Biochemical Hy's law where aminotransferase elevation was accompanied by increased serum total bilirubin (TB). There were eight cases meeting the laboratory criteria for Hy's Law (ALT or AST ≥3x ULN with TB ≥2x ULN), all with canagliflozin at NDA submission. For all eight cases, the blinded HEAC determined the causality as either unlikely or excluded. In our review of these eight cases, we agreed with the HEAC's causality assessment in six cases where the event was determined to be unlikely-related to canagliflozin treatment since an alternative etiology for observed liver function changes were present in each of these cases (i.e., cholecystitis, adenocarcinoma, cholangiocarcinoma; Table 88).

Table 88: Eight Cases Meeting Adjudication Criteria of AST or ALT ≥3x ULN and Total Bililrubin ≥2x ULN

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

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

In addition, we asked Dr. Seeff to provide an assessment on additional 18 cases who did not meet Biochemical Hy's law but had significant elevation in aminotransferase at some point during the trials and where narratives lacked the necessary clinical information (i.e., serology) to

completely exclude a role of canagliflozin in the reported hepatic events. Dr. Seeff concluded that two of 18 cases represented 'possible' DILI (602764 and 602830) based on the lack of complete clinical data.

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

- Subject T062301 is a 64-year old male with T2DM on mitiglinide and received canagliflozin 100 mg daily. At Week 28 visit, subject reported brown urine, itching, and lack of energy. Laboratory values showed elevated liver enzymes, with ALT 545 U/L, AST 132 U/L, total bilirubin 18.7 mg/dL and alkaline phosphatase 1084 U/L. The subject was diagnosed with portal hepatitis bile duct cancer by CT scan and was hospitalized.
- Subject T060404 is a 68-year old male with T2DM on glimepiride and received canagliflozin 200 mg daily. At Week 24 visit, ALT was elevated at 296 U/L, AST was elevated at 105 U/L, total bilirubin was 0.7 mg/dL, and alkaline phosphatase was 481 U/L. Intrahepatic duct dilation was suspected by abdominal echography. Subject was diagnosed with autoimmune hepatitis based on serologic testing (elevated IgG4), CT findings such as narrowing of pancreatic duct, retroperitoneal fibrosis and interstitial nephritis.

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

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

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

7.3.16 Submission Specific Primary Safety Concerns - Malignancies

In the long-term carcinogenicity study in rats, orally administered canagliflozin caused an increase in Leydig cell tumors (LCT) at all doses, and increase in renal tubular tumors (RTT) and pheochromocytomas in both gender at the highest dose studied (100 mg/kg/day, 12x clinical exposure from 300 mg maximal clinical dose). The applicant proposes that a rat-specific hormonal mechanism (increased luteinizing hormone) underlies the LCT formation. The applicant also proposes that a rat-specific mechanism (i.e., carbohydrate malabsorption) explains the imbalance in observed RTT and pheochromocytoma in rats treated with canagliflozin. Further details of nonclinical carcinogenicity studies can be found in Dr. Fred Alavi's review.

Based on this nonclinical finding, pheochromocytomas, RCC, and LCT were evaluated throughout Phase 3 program for canagliflozin.

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

Pharmacodynamic Results in Phase 1 and 2 Trials

Because increase in LCTs in rats were related with decreases in testosterone and increases in luteinizing hormone (LH), archived specimens in subjects from DIA2001 were used to measure LH and testosterone levels. There was a slight, non-dose related reduction in LH without meaningful change in testosterone (Table 89).

Table 89: Change from Baseline to Week 12 from DIA2001: Testosterone and Luteinizing Hormone

	Placebo	Cana 100	Cana 300
Testosterone LS mean change from baseline (nmol/L)	-0.58 (N=26)	-1.11 (N=27)	-0.97 (N=29)
Luteinizing Hormone LS mean change from baseline (IU/L)	0.60 (N=24)	-0.69 (N=30)	-0.28 (N=30)

Source: ISS, Table 165, 166

Also, in DIA2001, there was no meaningful effects on the overnight urinary samples for calcium/creatinine ratio after 12 weeks of treatment with canagliflozin (data not shown).

In DIA1007, a hydrogen breath test was done before (Day -2) and after four weeks (Day 26) of treatment with placebo or canagliflozin (100 mg and 300 mg twice daily). Carbohydrate malabsorption was predefined as an increase of at least 10 parts per million (ppm) in breath hydrogen and methane excretion at 2-hours after a 75-gram oral glucose tolerance test. There was no consistent increases in the hydrogen breath test values on Day 26 with canagliflozin compared to placebo, and the maximum values at 2-hours did not exceed 10 ppm (Table 89).

Table 90: Hydrogen Breath Test Values: Mean Differences and 90% CI in Change from Baseline Between Each Canagliflozin Dose and Placebo

Analysis Set: SAFETY
Parameter: HYDROGEN BREATH TEST, ppm

Visit - Timepoint	--- JNJ-28431754 100 MG Q.D. versus Placebo -- Mean	SE	90% CI	-- JNJ-28431754 300 MG B.I.D. versus Placebo - Mean	SE	90% CI
DAY 26 Predose	11.84	21.538	(-25.915; 49.601)	14.04	14.260	(-10.956; 39.041)
DAY 26 5 min	-0.29	9.778	(-17.427; 16.856)	6.81	5.188	(-2.280; 15.909)
DAY 26 10 min	8.00	15.057	(-18.395; 34.395)	18.50	10.961	(-0.715; 37.715)
DAY 26 15 min	6.10	14.927	(-20.069; 32.269)	12.20	11.332	(-7.666; 32.066)
DAY 26 20 min	-1.31	15.256	(-28.059; 25.431)	9.89	9.154	(-6.162; 25.933)
DAY 26 0.5 h	-3.47	18.422	(-35.766; 28.823)	11.83	10.170	(-6.000; 29.657)
DAY 26 40 min	3.64	15.359	(-23.281; 30.567)	20.94	11.287	(1.156; 40.729)
DAY 26 50 min	10.19	14.454	(-15.153; 35.525)	20.09	12.287	(-1.454; 41.626)
DAY 26 1 h	1.89	14.878	(-24.196; 27.968)	8.49	14.418	(-16.789; 33.761)
DAY 26 70 min	20.87	13.583	(-2.941; 44.683)	28.07	13.726	(4.010; 52.133)
DAY 26 80 min	23.49	13.409	(-0.021; 46.992)	24.19	13.812	(-0.027; 48.398)
DAY 26 1.5 h	2.06	11.141	(-17.474; 21.588)	2.86	11.356	(-17.050; 22.764)
DAY 26 100 min	-10.07	16.388	(-38.801; 18.658)	-10.67	16.512	(-39.618; 18.276)
DAY 26 110 min	-0.49	9.760	(-17.595; 16.623)	1.41	9.195	(-14.704; 17.533)
DAY 26 2 h	-8.19	10.256	(-26.164; 9.793)	-5.79	9.300	(-22.089; 10.518)

Source: DIA1007 CSR, Att 3.1.2

Phase 3 Trials

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

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

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

The incidences of renal, bladder, and breast cancers with the exposure adjusted incidence rate, with data cutoff date of November 15, 2012, are presented in Table 91 by treatment group. The overall incidence of these cancers was low in the clinical program for canagliflozin, and did not show an increased incidence of these cancers in the canagliflozin treatment groups compared to the non-canagliflozin treatment group as of November 15, 2012.

Table 91: Renal, Bladder, and Breast Cancer in All Phase 3 Trials of Canagliflozin through November 15, 2012 - Regardless of Rescue

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

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

7.3.17 Submission Specific Primary Safety Concerns - Photosensitivity Skin Adverse Events

Canagliflozin absorbs light in the UV range with absorption peak around 290 nm. The US FDA Guidance for Industry Photosafety Testing recommend testing for photoirritation if drug product absorbs light between 290 to 700 nm. In vitro testing result showed that canagliflozin was considered to be photosensitizing. In pigmented rats, canagliflozin caused skin photosensitization (mild to moderate erythema and edema) with UVA and UVB light exposure. See Dr. Fred Alavi's review for full details of preclinical studies.

Initial Single- and Multiple Dose Photosensitivity Studies

A single dose study of canagliflozin (200 mg and 400 mg) in healthy subjects (NAP1005) showed that canagliflozin had no effects on either delayed or immediate photosensitivity responses at any of the wavebands tested. A subsequent multiple-dose study (DIA1011) of canagliflozin (300 mg QD or BID) for 6 days showed a mild, UVA-dependent, delayed photosensitivity responses with canagliflozin 300 mg BID and not with QD. However, an immediate photosensitivity response was observed with both 300 mg QD and BID doses. Since the irradiance used in the phototesting was 30-fold above natural sunlight, two additional phototoxicity studies were done, DIA1019 and DIA1020.

DIA1020 further studied immediate photosensitivity response in 6 healthy subjects who experienced immediate photosensitivity in DIA1011. When the irradiance level was reduced up to $1/10^{th}$ (3-fold above natural sunlight) of the standard irrandiance level (30-fold above natural sunlight), the immediate photosensitivity responses was not seen.

In DIA1019, multiple doses of canagliflozin (100 mg and 300 mg QD for 6 days) in healthy subjects did not result in delayed photosensitivity response. Immediate photosensitivity

responses were seen in none of 12 subjects with canagliflozin 100 mg QD, 3 of 12 subjects with 300 mg QD, and one of 12 subjects in each ciprofloxacin and placebo groups. All immediate photosensitivity responses were seen at 335+/-30 nm UVA waveband, within 30 minutes of light exposure.

Phase 2 Trials

In two 12-week Phase 2b trials (DIA2001 and OBE2001), subjects were advised to avoid excessive exposure to sunlight and to use appropriate sunscreen if exposed to sunlight.

In DIA2001, photosensitivity-related skin events were reported in 3 subjects, 2 with placebo and one with canagliflozin 300 mg daily. The canagliflozin-treated subject reportedly had "polymorphic light eruption" on Day 72 that was not serious and did not lead to study discontinuation.

In OBE2001, three subjects had photosensitivity-related skin adverse events, one with placebo on Day 82, one with canagliflozin 50 mg daily with "post dose photosensitivity" on Day 1, and one with canagliflozin 100 mg daily with "sunlight sensitivity" on Day 39. None were serious and none led to study discontinuation.

Phase 3 Trials

Except for DIA3009, the protocol for other Phase 3 trials in the canagliflozin program did not provide instructions for subjects regarding the use of sun protection, with sun protection left at the investigator's discretion. Subjects in DIA3009 were counseled before randomization to avoid excessive sunlight or artificial ultraviolet light and use sunprotective measures such as topical sunscreen or clothing as appropriate. A supplemental eCRF was used to collect skin adverse events in Phase 3 trials. To clinical database was searched on a regular basis with a list of following Preferred Terms associated with skin photosensitivity to make sure that any reported skin AE with light or sun-exposure as potential precipitant have a supplemental eCRF page completed: Hutchinson's summer prurigo, Juvenile spring eruption, Photodermatosis, Photosensitivity allergic reaction, Photosensitivity reaction, Polymorphic light eruption, Sunburn.

Since the incidence of photosensitivity adverse event is expected to be low, the Longer-term Exposure Broad Dataset (DS4) was used to analyze photosensitivity events, and is summarized in Table 92. Although the overall incidence was low, the incidence of photosensitivity skin events was higher with canagliflozin (0.3% in both groups) compared to non-canagliflozin (0.2%). When the incidence was adjusted for subject-exposure, canagliflozin treatment had 1.5 to 2-fold increase in the incidence rate compared to placebo group (2.7 and 2.4 with 100 mg and 300 mg compared to 1.5 with placebo per 1000 subject-years).

Table 92: Photosensitivity Skin Adverse Events - DS4, Regardless of Rescue (Safety Analysis Set)

	Cana 100 (N=3092)	Cana 300 (N=3085)	Non-Cana (N=3262)
Total number of subject with photosensitivity event	9 (0.3%)	8 (0.3%)	5 (0.2%)
Incidence Rate Per 1000 Subject-Year Exposure	2.7	2.4	1.5
Photodermatosis	0	1	0
Photosensitivity Reaction	6	4	2
Polymorphic Light Eruption	0	1	0
Sunburn	3	3	3

Source: ADAE

Two subjects with an adverse event of photosensitivity discontinued study drug due to adverse event, and are summarized here:

- Subject (b) (4) (DIA3008), a 55-year-old man with history of diabetic nephropathy and neuropathy, cellulitis of the lower limb and varicose veins received canagliflozin 100 mg. On Day 60, he had a 2x2 centimeter clear ulcer with granular tissue on the left foot, and was diagnosed with skin ulcer (recurrence of left foot ulcer). He was treated with lincomycin and mupirocin and study drug was interrupted. On Day 111, he developed itching, with pus-filled lesions with central crusting on the anterior surface of bilateral legs, and he was diagnosed with **erythema multiforme**. He received amoxicillin, rupatadine, betamethasone, and sunscreen lotion for this event. Study drug was interrupted, and erythema multiforme resolved on Day 172. On Day 172, he experienced itching with multiple pigmented scars on the feet and anterior surface of legs, and was diagnosed with **photosensitivity reaction**. Study drug was discontinued on Day 172, and without any treatment, the photosensitivity reaction resolved on Day 203. **[Reviewer's comment: Although the AE leading to discontinuation was photosensitivity reaction in this subject, he also had a non-serious event of erythema multiforme that appear to be related to canagliflozin]**

- Subject 900717 (DIA3009), a 60-year-old man with history of allergy to gabapentin and allergic rhinitis received canagliflozin 300 mg. About 60 days later, he developed **photodermatosis** (appearing as red splotches and bumps; reported term was dermatitis due to sun exposure). He was reportedly exposed to a large amount of sunlight and hot summer heat during his cruise vacation and travel to San Diego. He was treated with desloratadine, triamcinolone, and aloe vera. Study drug was discontinued on Day 350 and he was withdrawn from the study on Day 357 due to photodermatosis. On Day 441, photosensitivity was resolved, and he was diagnosed with rosacea and was treated with metronidazole. Rosacea was reported as resolving.

7.4 Supportive Safety Results

7.4.1 Common Adverse Events

Placebo-Controlled Studies Dataset (DS1)

Adverse events that were reported in at least 2% of subjects in any treatment group before rescue are summarized in Table 93. Nasopharyngitis and urinary tract infection were common with >5% incidence in one or both canagliflozin groups. Howeverr, the incidence of nasopharyngitis was not higher with canagliflozin compared to placebo. Urinary tract infections are further reviewed in section 7.3.11.

Of note, constipation and nausea under Gastrointestinal Disorders occurred slightly higher with canagliflozin in DS1. Constipation occurred in 1.8% with canagliflozin and 2.3% with 300 mg compared to 0.9% with placebo. Nausea occurred in 2.2% with each canagliflozin dose group and 1.4% with placebo.

Table 93: Adverse Events in At Least 2% of Subjects in Any Treatment Group by SOC and PT in DS1 - Before Rescue

Body System Or Organ Class Dictionary-Derived Term	Placebo (N=646) n (%)	Cana 100 mg (N=833) n (%)	Cana 300 mg (N=834) n (%)	All Cana (N=1667) n (%)
Total no. subjects with the AEs	371 (57.4)	500 (60.0)	494 (59.2)	994 (59.6)
Gastrointestinal Disorders	88 (13.6)	124 (14.9)	128 (15.3)	252 (15.1)
Constipation	6 (0.9)	15 (1.8)	19 (2.3)	34 (2.0)
Diarrhoea	28 (4.3)	26 (3.1)	37 (4.4)	63 (3.8)
Nausea	9 (1.4)	18 (2.2)	18 (2.2)	36 (2.2)
Infections and Infestations	180 (27.9)	247 (29.7)	241 (28.9)	488 (29.3)
Influenza	20 (3.1)	19 (2.3)	16 (1.9)	35 (2.1)
Nasopharyngitis	30 (4.6)	37 (4.4)	44 (5.3)	81 (4.9)
Sinusitis	11 (1.7)	17 (2.0)	8 (1.0)	25 (1.5)
Upper Respiratory Tract Infection	31 (4.8)	38 (4.6)	38 (4.6)	76 (4.6)
Urinary Tract Infection	23 (3.6)	45 (5.4)	33 (4.0)	78 (4.7)
Vulvovaginal Mycotic Infection	4 (0.6)	25 (3.0)	23 (2.8)	48 (2.9)
Metabolism and Nutrition Disorders	41 (6.3)	51 (6.1)	41 (4.9)	92 (5.5)
Hyperglycaemia	16 (2.5)	6 (0.7)	1 (0.1)	7 (0.4)
Hypoglycaemia	13 (2.0)	21 (2.5)	19 (2.3)	40 (2.4)
Musculoskeletal and Connective Tissue Disorders	83 (12.8)	93 (11.2)	104 (12.5)	197 (11.8)
Arthralgia	23 (3.6)	23 (2.8)	19 (2.3)	42 (2.5)
Back Pain	16 (2.5)	23 (2.8)	34 (4.1)	57 (3.4)
Nervous System Disorders	47 (7.3)	74 (8.9)	65 (7.8)	139 (8.3)
Headache	27 (4.2)	34 (4.1)	29 (3.5)	63 (3.8)
Renal and Urinary Disorders	13 (2.0)	61 (7.3)	52 (6.2)	113 (6.8)
Pollakiuria	4 (0.6)	35 (4.2)	26 (3.1)	61 (3.7)
Respiratory, Thoracic and Mediastinal Disorders	41 (6.3)	42 (5.0)	42 (5.0)	84 (5.0)
Cough	15 (2.3)	12 (1.4)	13 (1.6)	25 (1.5)

Note: Percentages calculated with the number of subjects in each group as denominator. Incidence is based on the number of subjects experiencing at least one adverse event, not the number of events, prior to use of rescue medication.
Source: ISS, Table 48

Broad Dataset (DS3)

Adverse events that were reported in at least 2% of subjects in any treatment group regardless of rescue are summarized in Table 94. Nasopharyngitis and hypoglycemia were common with >5% incidence in one or both canagliflozin groups, but the incidence of both events was not higher with canagliflozin compared to placebo. Hypoglycemia with canagliflozin are discussed in section 7.3.14. Increased incidence of constipation and nausea with canagliflozin seen in DS1 was also observed in DS3.

Table 94: Adverse Events in verse Events in At Least 2% of Subjects in Any Treatment Group by SOC and PT in DS3 - Regardless of Rescue

Body System Or Organ Class Dictionary-Derived Term	Cana 100 mg (N=3092) n (%)	Cana 300 mg (N=3085) n (%)	All Cana (N=6177) n (%)	All Non-Cana (N=3262) n (%)
Total no. subjects with the AEs	2083 (67.4)	2133 (69.1)	4216 (68.3)	2160 (66.2)
Gastrointestinal Disorders	557 (18.0)	582 (18.9)	1139 (18.4)	538 (16.5)
Constipation	71 (2.3)	76 (2.5)	147 (2.4)	47 (1.4)
Diarrhoea	118 (3.8)	167 (5.4)	285 (4.6)	161 (4.9)
Nausea	75 (2.4)	94 (3.0)	169 (2.7)	68 (2.1)
General Disorders and Administration Site Conditions	308 (10.0)	334 (10.8)	642 (10.4)	301 (9.2)
Fatigue	67 (2.2)	63 (2.0)	130 (2.1)	57 (1.7)
Oedema Peripheral	34 (1.1)	32 (1.0)	66 (1.1)	77 (2.4)
Thirst	42 (1.4)	64 (2.1)	106 (1.7)	2 (0.1)
Infections and Infestations	1046 (33.8)	1029 (33.4)	2075 (33.6)	1036 (31.8)
Bronchitis	76 (2.5)	66 (2.1)	142 (2.3)	84 (2.6)
Influenza	92 (3.0)	83 (2.7)	175 (2.8)	83 (2.5)
Nasopharyngitis	216 (7.0)	202 (6.5)	418 (6.8)	230 (7.1)
Sinusitis	55 (1.8)	62 (2.0)	117 (1.9)	58 (1.8)
Upper Respiratory Tract Infection	157 (5.1)	143 (4.6)	300 (4.9)	204 (6.3)
Urinary Tract Infection	145 (4.7)	149 (4.8)	294 (4.8)	124 (3.8)
Vulvovaginal Mycotic Infection	64 (2.1)	67 (2.2)	131 (2.1)	16 (0.5)
Metabolism and Nutrition Disorders	330 (10.7)	346 (11.2)	676 (10.9)	427 (13.1)
Hyperglycaemia	31 (1.0)	26 (0.8)	57 (0.9)	92 (2.8)
Hypoglycaemia	185 (6.0)	207 (6.7)	392 (6.3)	226 (6.9)
Musculoskeletal and Connective Tissue Disorders	484 (15.7)	492 (15.9)	976 (15.8)	526 (16.1)
Arthralgia	95 (3.1)	85 (2.8)	180 (2.9)	118 (3.6)
Back Pain	110 (3.6)	137 (4.4)	247 (4.0)	113 (3.5)
Pain in Extremity	70 (2.3)	50 (1.6)	120 (1.9)	72 (2.2)
Nervous System Disorders	325 (10.5)	358 (11.6)	683 (11.1)	356 (10.9)
Headache	111 (3.6)	126 (4.1)	237 (3.8)	147 (4.5)
Renal and Urinary Disorders	275 (8.9)	296 (9.6)	571 (9.2)	150 (4.6)
Pollakiuria	105 (3.4)	125 (4.1)	230 (3.7)	26 (0.8)
Reproductive System and Breast Disorders	190 (6.1)	255 (8.3)	445 (7.2)	85 (2.6)
Balanitis	61 (2.0)	59 (1.9)	120 (1.9)	11 (0.3)
Respiratory, Thoracic and Mediastinal Disorders	230 (7.4)	223 (7.2)	453 (7.3)	290 (8.9)
Cough	78 (2.5)	65 (2.1)	143 (2.3)	101 (3.1)
Vascular Disorders	131 (4.2)	163 (5.3)	294 (4.8)	176 (5.4)
Hypertension	44 (1.4)	45 (1.5)	89 (1.4)	99 (3.0)

Source: ISS, Table 55

In the Longer-term Exposure Broad Dataset (DS4), adverse events that was common with >5% incidence in one or both canagliflozin groups and higher with canagliflozin compared to placebo were urinary tract infection, back pain. See section 7.3.11 for urinary tract infection. The adverse event of back pain occurred slightly higher with canagliflozin (5.4% with 300 mg and 4.5% with 100 mg) compared to placebo (4.4%).

Increased incidence of constipation and nausea with canagliflozin compared to placebo observed in DS1 and DS3 datasets were also seen in DS4. Constipation occurred in 2.7% with each canagliflozin group compared to 2.1% with placebo. Nausea occurred in 2.7% with canagliflozin 100 mg and 3.2% with 300 mg compared to 2.5% with placebo.

7.4.2 Laboratory Findings

The mean change in laboratory values over time is based on data from Placebo-controlled Studies (DS1), since trials in DS2 and DS3 had different time and event schedule for laboratory assessments. Many of the laboratory findings from the clinical program are discussed in clinically relevant sections of this review. For example, changes related to liver function tests were already discussed in section 7.3.15 (Hepatic Safety), changes related to calcium and phosphate were already discussed in section 7.3.9 (Bone Safety), and changes related to renal function were already discussed in section 7.3.7 (Changes in Renal Function). Here, I mainly discuss changes in electrolytes since canagliflozin acts as an osmotic diuretic.

The mean change in serum electrolytes are summarized in Table 95. As noted, magnesium levels with canagliflozin had the most elevations (7.3 and 8.8% with 100 mg and 300 mg) at the end of 26 weeks of study period, compared to placebo (-1%). The change in magnesium occur by Week 6 with canagliflozin, and remained elevated at similar magnitude throughout 26 weeks of study period.

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

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

Table 95: Changes in Serum Electrolytes: Mean and Mean Percent Change from Baseline at Week 26, Regardless of Rescue, DS1

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

Source: ISS, DLAB01C_01

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

Hypermagnesemia

The mean changes in magnesium in DIA3004 and DIA3008 are summarized in Table 96. Compared to DS1, there was a slight higher mean change in magnesium with canagliflozin among subjects enrolled in DIA3004 and DIA3008 at the end of Week 26, as summarized in Table 96.

Table 96: Changes in Magnesium (mg/dL) in DIA3004 and DIA3008

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

Source: DIA3008 CSR, DLAB51R_CNV; DIA3004 CSR, DLAB01RM_CORE_CNV

No subjects met the PDLC criteria for serum magnesium elevations with canagliflozin in DS1, but more subjects met the PDLC criteria for serum magnesium elevations in DS2 and DS3, as shown in Table 97. In DS3, the incidence of subjects with PDLC of magnesium with canagliflozin 100 mg were comparable to placebo, and the highest incidence was observed with canagliflozin 300 mg. However, the incidence of consistent elevations (reflected in the last post-baseline value) appear to be low overall.

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

Table 97: Subjects (N [%]) with Serum Magnesium Outside Pre-Defined Limits - Regardless of Rescue

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

Source: ISS, DLAB02BCNV_02, DLAB02BCNV_03

Hyperkalemia

The mean changes in potassium in DIA3004 and DIA3008 are summarized in Table 98. The changes in potassium levels in DIA3004 over 26 weeks were inconsistent between two canagliflozin groups. Compared to DS1, there was a slight higher mean change in potassium with canagliflozin at the end of Week 26 among subjects enrolled in DIA3008.

Table 98: Changes in Potassium (mEq/L) in DIA3004 and DIA3008

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

Source: DIA3008 CSR, DLAB51R_CNV; DIA3004 CSR, DLAB01RM_CORE_CNV

As previously noted, the maximal increase for potassium occurs early post dose, so PDLC analysis would be more relevant to evaluate any clinically significant changes that may occur with potassium levels during canagliflozin therapy. Summary of subjects who met PDLC criteria for serum potassium in DS1, DS2, and DS3 is presented in Table 99. Although there a higher incidence of subjects with serum potassium elevations meeting PDLC criteria with canagliflozin 300 mg compared to the other groups, the incidence was comparable between canagliflozin 100 mg and placebo.

Table 99: Subjects (N [%]) with Serum Potassium Outside Pre-Defined Limits - Regardless of Rescue

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

Source: ISS, DLAB02B_01, DLAB02BCNV_02, DLAB02BCNV_03

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

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

In DS3, a higher incidence of hyperkalemia occurred in canagliflozin 300 mg group compared to non-canagliflozin group, although the difference between treatment groups was not large. Three hyperkalemia events were serious (one in 100 mg and two in 300 mg). All three had baseline moderate renal impairment. Two of these subjects were also on diuretics and renin-angiotensin agents, and experienced severe hyperkalemia (>7 mEq/L). Third subject also had mild renal function (eGFR 55 mL/min/17.3m2) and was on ACE inhibitor, and developed worsening renal insufficiency with potassium of 5.8 mEq/L. Two events of hyperkalemia also led to discontinuation, both with canagliflozin 300 mg. A significantly higher incidence of blood potassium increased also occurred in DS3; three events led to discontinuation (two with canagliflozin 300 mg and one with non-canagliflozin).

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

Table 100: Hyperkalemia-related Adverse Events - Regardless of Rescue

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

Source: ISS, DAE01R_01, DAE01RB_02, DAE01RC_03, DAE01R_04

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

Serum Urate

In DS1, decreases in the mean percent change from baseline in serum urate was seen with canagliflozin (-10.1% with 100 mg and -10.6% with 300 mg) compared to placebo (1.9%) at Week 26. Decreases in serum urate with canagliflozin was maximal or near maximal at the first ascertained timepoint, Week 6, and remained stable through Week 26. For decreases in serum urate, the incidence of subjects meeting the PDLC criteria of any value (<lower limit of normal and decreased >25% from baseline) was 1.9% in the combined canagliflozin group compared to

0.2% in the placebo group in DS1, and the 95% CI for between group differences compared to placebo excluded "0". Similar results were observed in DS3.

In DIA3008, the mean percent decreases from baseline in serum urate at Week 52 with canagliflozin was -6.8% with 100 mg and -5.8% with 300 mg, compared to placebo which had a small increase from baseline (3.0%). The maximal decreases in serum urate was observed by Week 6 in DIA3008 as well.

Nephrolithiasis is a concerning adverse event that may result with decrease in serum urate. In DS4, the incidence of nephrolithiasis (using the Preferred Term 'Nephrolithiasis') was not increased with canagliflozin. Nephrolithiasis occurred in 0.7% (21/3092) in canagliflozin 100 mg, 0.2% (6/3085) in canagliflozin 300 mg, and 0.6% (18/3262) in non-canagliflozin group.

7.4.3 Vital Signs

The mean change in vital signs from baseline to Week 26 in the Placebo-controlled studies dataset (DS1), Moderate Renal Impairment Dataset (DS2), and Broad Dataset (DS3) are summarized in Table 101. As discussed in section 6.1.6, canagliflozin reduce systolic and diastolic blood pressure. As a result, there was a dose-dependent decrease in systolic blood pressure and diastolic blood pressure in all three dataset, with similar magnitude of placebo-subtracted change from baseline with canagliflozin. There was a slight mean reduction of pulse in DS1 and DS3 with canagliflozin, with placebo-subtracted change in pulse ranging from -0.2 to -0.6. In DS2, the reduction in pulse with canagliflozin was similar with placebo.

Table 101: Vital Signs: Mean Change from Baseline to Week 26 in DS1, DS2, and DS3 - Regardless of Rescue

	Placebo	Cana 100	Cana 300
Placebo-Controlled Studies Dataset (DS1), N	**531**	**724**	**726**
Systolic blood pressure (mmHg)	-0.1	-3.9	-5.3
Diastolic blood pressure (mmHg)	-0.3	-2.1	-2.5
Pulse (bpm)	-0.0	-0.6	-0.4
Moderate Renal Impairment Dataset (DS2), N	**323**	**291**	**314**
Systolic blood pressure (mmHg)	-1.6	-4.7	-6.3
Diastolic blood pressure (mmHg)	-0.9	-2.0	-3.1
Pulse (bpm)	-1.0	-1.0	-1.1
Broad Dataset (DS3), N	**2786***	**2739**	**2691**
Systolic blood pressure (mmHg)	-1.4	-5.2	-6.7
Diastolic blood pressure (mmHg)	-0.9	-2.4	-3.2
Pulse (bpm)	-0.3	-0.7	-0.5

Note: Mean change showing change in subjects who had both baseline and Week 26 values.
*Non-Canagliflozin group for DS3
Source: ISS, Table 229, 234, 238

The incidence of subjects with decrease in SBP and increase in pulse that met the PDLC criteria are summarized in Table 102. The incidence of subjects with vital signs that met the PDLC criteria for increase in SBP, increase in pulse, or related to DBP were low and not significant and are not described.

As expected, the incidence of subjects with the PDLC criteria for decrease in SBP was higher with canagliflozin compared to placebo, but the overall incidence was low in each pooled dataset. Compared to placebo, the incidence of subjects that met the criteria for decrease in pulse in canagliflozin groups was largest in DS2.

Table 102: Number of Subjects (%) with Vital Signs outside Pre-Defined Limits - DS1, DS2, DS3 Regardless of Rescue

	Placebo	Cana 100	Cana 300
Placebo-Controlled Studies Dataset (DS1), N	625	808	808
Systolic blood pressure (mmHg)			
Any average SBP decrease from baseline ≥20 mmHg and ≤90 mmHg	1 (0.2)	5 (0.6)	1 (0.1)
Last average SBP decrease from baseline ≥20 mmHg and ≤90 mmHg	0	4 (0.5)	0
Pulse rate (bpm)			
Any pulse ≤50 bpm	14 (2.2)	6 (0.7)	12 (1.5)
Last pulse ≤50 bpm	7 (1.1)	3 (0.4)	4 (0.5)
Moderate Renal Impairment Dataset (DS2), N	369	332	352
Systolic blood pressure (mmHg)			
Any average SBP decrease from baseline ≥20 mmHg and ≤90 mmHg	2 (0.5)	3 (0.9)	4 (1.1)
Last average SBP decrease from baseline ≥20 mmHg and ≤90 mmHg	12 (3.3)	2 (0.6)	1 (0.3)
Pulse rate (bpm)			
Any pulse ≤50 bpm	19 (5.1)	28 (8.4)	27 (7.7)
Last pulse ≤50 bpm	12 (3.3)	17 (5.1)	7 (2.0)
Broad Dataset (DS3), N	3159*	3020	2979
Systolic blood pressure (mmHg)			
Any average SBP decrease from baseline ≥20 mmHg and ≤90 mmHg	7 (0.2)	13 (0.4)	19 (0.6)
Last average SBP decrease from baseline ≥20 mmHg and ≤90 mmHg	1 (<0.1)	5 (0.2)	5 (0.2)
Pulse rate (bpm)			
Any pulse ≤50 bpm	91 (2.9)	93 (3.1)	102 (3.4)
Last pulse ≤50 bpm	39 (1.2)	50 (1.7)	34 (1.1)

*Non-Canagliflozin group for DS3
Source: ISS, Table 230, 235, 239

7.4.4 Electrocardiograms (ECGs)

Table 103 summarizes the mean change from baseline in ECG parameters for DS1, DS2, and DS3. There was a change of >5msec in supine RR interval for DS1 and DS2. This is likely due to the change in pulse, since RR interval represents the amount of time between heart beats. The mean change in ECG intervals for other ECG parameters was < 5 msec and there did not appear to be a dose-relationship to canagliflozin dose. Therefore, canagliflozin has minor effects, if any, on ECG parameters using central tendency analysis. Also, it should be noted that the applicant

had previously conducted cardiac eletrophysiology study, and did not detect any meaningful change in the ECG parameter.

Table 103: ECG: Mean Changes from Baseline to Week 26 in DS1 and DS2 - Regardless of Rescue

	Placebo	Cana 100	Cana 300
Placebo-Controlled Studies Dataset (DS1), N	**517**	**700**	**704**
Supine heart rate (beats/min)	0.38	-1.00	-0.99
Supine PR interval (msec)	0.71	1.04	0.20
Supine QRS interval (msec)	-0.01	0.6	0.5
Supine QT interval (msec)	0.07	3.13	3.05
Supine QTc interval Fredericia (msec)	0.81	1.15	1.56
Supine RR interval (msec)	-5.53	13.68	10.34
Moderate Renal Impairment Dataset (DS2), N	**109**	**104**	**100**
Supine heart rate (beats/min)	-2.11	-1.45	-1.75
Supine PR interval (msec)	0.15	1.96	3.25
Supine QRS interval (msec)	1.39	1.67	-0.35
Supine QT interval (msec)	7.11	4.49	4.73
Supine QTc interval Fredericia (msec)	3.07	1.52	1.07
Supine RR interval (msec)	22.88	21.60	25.30

Note: Mean change showing change in subjects who had both baseline and Week 26 values.
*Non-Canagliflozin group for DS3
Source: ISS, Table 231, DECG01D2_02

The incidence of subjects with QTcF values >450 msec or with changes from baseline in QTcF of >30 msec was similar across treatment groups in DS1 and DS2, as summarized in Table 104.

Table 104: Proportion of Subjects with Change in QTcF Value in DS1 and DS2 - Regardless of Rescue

	Placebo	Cana 100	Cana 300
DS1			
Supine QTcF >450 msec: Maximum during study	4.7 (28/592)	4.1 (32/778)	3.1 (24/760)
Supine QTcF Change >30 msec: Maximum during study	2.1 (12/591)	2.8 (22/777)	2.5 (19/757)
DS2			
Supine QTcF >450 msec: Maximum during study	15.3 (28/182)	14.7 (24/177)	13.5 (25/185)
Supine QTcF Change >30 msec: Maximum during study	5.0 (9/181)	6.8 (12/176)	2.7 (5/184)

Source: ISS, Table 232, 233

7.4.5 Special Safety Studies/Clinical Trials

The available results of special safety study to evaluate bone safety in elderly, DIA3010, was discussed in section 7.3.9. Refer to Dr. Andraca-Carrera for discussion of cardiovascular meta-analysis to evaluate the overall cardiovascular risk with canagliflozin.

7.4.6 Immunogenicity

Canagliflozin is a small molecule, not a protein, and therefore not expected to be immunogenic.

7.5 Other Safety Explorations

7.5.1 Dose Dependency for Adverse Events

Dose-dependency for adverse events were noted for volume-depletion events, changes in renal function and renal adverse events, where there was an increased incidence of these events with the higher dose (300 mg) of canagliflozin compared to the lower dose (100 mg) of canagliflozin studied. This was discussed in sections 7.3.6 (Volume Depletion Events) and 7.3.7 (Changes in Renal Function).

A higher proportion of subjects having significant elevations of LFTs were seen with the lower dose of canagliflozin compared to the higher dose, as discussed in section 7.3.15.

7.5.2 Time Dependency for Adverse Events

Most adverse events that are significant and appear to be related with canagliflozin appear to occur early after treatment initiation, within 2-3 months. These include volume depletion events, renal function changes, mycotic infections, and also fractures. Similar to these adverse events, there was also an imbalance in early cardiovascular events (within 30 days) not favoring canagliflozin compared to placebo, as discussed in section 7.3.13.

Similar to volume and renal function changes seen with canagliflozin, the most significant changes in electrolytes were seen early with canagliflozin at the earliest ascertained timepoint (3 weeks or 6 weeks), with some returning to baseline over the course of treatment (e.g., potassium). See section 7.4.2 for discussion of time dependency for electrolytes.

Most hypersensitivity related skin events with canagliflozin appear to occur immediately (1-7 days), although some rash development was delayed; skin and hypersensitivity events are summarized in section 7.3.3.

7.5.3 Drug-Demographic Interactions

As previously discussed, elderly subjects (≥65 or 75 years of age) were at an increased risk for volume depletion-related events with apparent dose relationship (see section 7.3.6).

A higher incidence of upper extremity fractures with canagliflozin was observed in women (see section 7.3.9).

7.5.4 Drug-Disease Interactions

Since the efficacy of canagliflozin depends on renal function, its efficacy is modest in subjects with moderate renal function (see section 6.1.7), and canagliflozin has not been studied and should not be used in those with severe renal impairment (e.g., ≤30 mL/min/1.73m^2). In addition, subjects with moderate renal impairment experienced more significant changes in renal function as estimated by eGFR and had more renal-related events (see section 7.3.7).

7.5.5 Drug-Drug Interactions

Please see section 4.4.3 Pharmacokinetics, for details on studies of drug-drug interactions. Please refer to Dr. Jaya Vaidyanathan's review for full details.

7.6 Additional Safety Evaluations

7.6.1 Human Carcinogenicity

Despite preclinical signal for renal tubular tumors, pheochromocytomas, and Leydig cell tumors, the incidence of malignancies were not increased with canagliflozin treatment (see section 7.3.16) as of November 15, 2012. However, it should be noted that most clinical program is never big or long enough to detect malignancy potential for a drug product at the time of NDA submission.

7.6.2 Human Reproduction and Pregnancy Data

Canagliflozin has not been studied in pregnant women or nursing mothers. There was one reported pregnancy in a 39-year-old woman who received canagliflozin 300 mg during the trial (602889), at which time the subject was withdrawn from the trial. The outcome of the pregnancy is unknown.

Given the paucity of pregnancy data, canagliflozin should be used during pregnancy only if clearly needed.

7.6.3 Pediatrics and Assessment of Effects on Growth

Studies in pediatric patients have not been performed. The applicant is proposing partial waiver of pediatric studies in those less than 10 years of age, and deferral in those 10 to <18 years of age. The applicant is proposing the following pediatric plan after approval:

- (b) (4)
-

The applicant's pediatric plan will be discussed at the PeRC meeting on February 13, 2013.

7.6.4 Overdose, Drug Abuse Potential, Withdrawal and Rebound

During controlled clinical studies in healthy subjects, single doses up to 1600 mg of canagliflozin did not show dose-related adverse drug reactions.

In the event of overdose, it is reasonable to use the usual measure to remove the unabsorbed drug from the stomach, monitor patients, and give supportive treatment as needed based on the patient's status. Canagliflozin was negligibly removed during a 4-hour hemodialysis session. It is unknown whether canagliflozin is dialyzable by peritoneal dialysis.

No potential for drug dependence or drug abuse was seen with canagliflozin.

No information is available on withdrawal or rebound effects with canagliflozin.

7.7 Additional Submissions / Safety Issues

Not applicable.

8 Postmarket Experience

Not applicable.

9 Appendices

9.1 Literature Review/References

Relevant literatures are referenced throughout the review.

9.2 Labeling Recommendations

I recommend the following labeling changes, with the final changes pending further discussion with the applicant:

- Do not recommend canagliflozin in patients with eGFR of <45 mL/min/1.73m^2.
- Do not recommend 300 mg canagliflozin in elderly who are ≥75 years of age and those with moderate renal impairment with eGFR of <60 mL/min/1.73m^2.
- (b) (4)
- (b) (4)
- Recommend adding pancreatitis information to the label.
- Recommend adding skin and hypersensitivity reaction to the label.
- Recommend adding photosensitivity skin adverse events to the label.
- Recommend adding imbalance in fracture to the label.
- Recommend adding imbalance of significant elevations of liver enzymes to the label.
- Recommend adding renal section under Warnings and Precauations, which should include information about changes in renal function and renal-related adverse events, as worsening renal function is an important safety information that should be warned to patients. Information about increases in serum creatinine and BUN from Laboratory Tests should be

[6] Draft ICH Consensus Principle, Principles for Clinical Evaluation of New Antihypertensive Drugs, March 2, 2000

moved to this section. I would also recommend that prescribers monitor for renal function during therapy with canagliflozin.
- Recommend adding the imbalance of early CV events observed in DIA3008 in Cardiovascular Safety

9.3 Advisory Committee Meeting

This NDA was discussed at an Endocrinologic and Metabolic Drugs Advisory Committee Meeting on January 10, 2013.

Quick minutes prepared by Dr. Caleb Briggs, Acting Designated Federal Officer for the meeting, including questions posed to the committee members at the meeting, and highlighting the discussion and voting results, are summarized here. I've also included few comments where applicable:

Questions to the Advisory Committee:

1) **Discussion:** Based on the information provided in the briefing materials and presentations at today's meeting, please weigh the benefit-risk profile of canagliflozin in the population of patients with type 2 diabetes and moderate renal impairment.

   In your discussion consider and comment on the following:

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

   Committee Discussion: *The committee members generally agreed that the benefit-risk profile of canagliflozin in patients with type 2 diabetes and moderate renal impairment should be considered differently from the general population. The committee members expressed concern about usage in these patients, owing to a decreased efficacy, especially when combined with an increased incidence of side effects. The committee members further discussed a discomfort with the relatively small volume of data to support use in this population. Some committee members did suggest a need for separate consideration of renal function in the elderly, as exclusion based only on eGFR could eliminate patients who may actually be suitable candidates for treatment with canagliflozin. One committee member also mentioned a concern over the cardiovascular risks of the drug, given an existing elevated cardiovascular risk in patients with renal impairment. Please see the transcript for details of the committee's discussion.*

Reviewer's comment: Dr. Palevsky (nephrologist) stated that he did not find electrolyte changes and volume depletion as concerning, and both Drs Palevsky and Lewis (also nephrologist) was okay with declining renal function since it was most likely hemodynamically mediated. Dr. Lewis was specifically concerned about using canagliflozin in patients with low GFR (<45 mL/min/1.73m^2), and also expressed concern that elderly will be unable to receive canagliflozin if usage was restricted to patients with eGFR >60 mL/min/1.73m^2 since GFR calculation include age and these patients may have lower calculated eGFR with normal renal function.

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

Comment on the clinical significance of this finding on your overall assessment of safety.

In your discussion consider the following:

- The relevance of observed changes in calcium, phosphorus, parathyroid hormone and 1,25 dihydroxy vitamin D levels
- The relevance of changes to bone turnover markers
- The relevance of the bone mineral density changes at 52 weeks in the dedicated study in elderly individuals (DIA-3010)
- The clinical importance of bone and calcium metabolism-related effect associated with canagliflozin use to the overall safety of this population and in the renally-impaired population

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

3) **Discussion:** The cardiovascular risk associated with canagliflozin use was assessed in a prespecified meta-analysis of adjudicated cardiovascular events across nine Phase 2 and 3 clinical trials using a composite endpoint (MACE+) that combines cardiovascular death, non-fatal myocardial infarction, non-fatal stroke and hospitalization for unstable angina.

   Based on the information provided in the briefing materials and the presentations at today's meeting, please discuss the following:

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

   NOTE: It was noted during the meeting that question #3 inaccurately states a hazard ratio for nonfatal stroke which exceeds 1.0. This hazard ratio actually applies to both fatal and nonfatal stroke.

   Committee Discussion: *Several committee members discussed their comfort in the reliability of the results of the pre-specified Cox proportional hazards model, though others did cite certain areas of concern, particularly with long-term impact. The committee generally agreed that long-term follow up would be necessary to properly assess the clinical relevance of changes in blood pressure, weight and low density cholesterol levels. The committee members also described some level of concern with the imbalance of MACE+ events at thirty days in the DIA-3008 trial, but many members reiterated that this was not a result of a pre-specified analysis, and encouraged caution in assigning too much significance to this occurrence. One member did question whether this could possibly be an indication of a subgroup with higher risk. One committee member stated that, because this drug acts as an osmotic diuretic, there could be a wider impact on the function of the kidneys than is easily understood. The committee members also discussed concern with the potential of type 1 error with an interim analysis in the cardiovascular outcomes trial and the need to balance this risk with the need to bring drugs to market more quickly. Please see the transcript for details of the committee's discussion.*

4) **Vote:** In accordance with FDA's Guidance for Industry titled "Diabetes Mellitus – Evaluating CV Risk in New Anti-diabetic Therapies to Treat Type 2 Diabetes", at the time of NDA submission, all applicants are to compare the incidence of important CV events occurring with their investigational agent to the incidence of the same types of events occurring with the control group to show that the upper bound of the 2-sided 95% confidence interval for the estimated risk ratio is less than 1.8.

Based on the data submitted and considering the points of discussion in question 3, do you have any concern regarding a conclusion that a risk margin of 1.8 has been excluded for canagliflozin?

Yes: 8 No: 7 Abs: 0

a. If you voted "Yes" to question #4, please provide your rationale.

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

b. If you voted "No" to question #4, please provide your rationale.

Committee Discussion: *The committee members who voted "no" did not differ significantly from the perspective of those who voted "yes". These members expressed some level of concern over the increased stroke incidence, low-density cholesterol, and MACE+ events at thirty days, but described a general comfort with the data overall. These committee members also described a desire for more data to help inform the cardiovascular risks, but stated that the currently-available data is not especially alarming. Please see the transcript for details of the committee's discussion.*

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

Yes: 10 No: 5 Abs: 0

a. If you voted "Yes" to question #5, please provide your rationale and whether you recommend any additional studies post-approval.

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.

b. If you voted "No" to question #5, please provide your rationale and discuss what additional data are necessary to potentially support approval.

Committee Discussion: *The committee members who voted "no" cited similar concerns over unknown cardiovascular risk and usage in moderate renal impairment, which were frequently stated as overriding concerns. One committee member who voted "no" expressed comfort with the benefit-risk profile in combination therapy, but described a lack of comfort with usage as monotherapy. An additional committee member voiced concerns over the potential for renal damage, and suggested a possibility of prolonging hypoglycemia in the elderly. Please see the transcript for details of the committee's discussion.*

Reviewer's comment: Several panel members who voted yes and no discussed discomfort of using canagliflozin in patients with moderate renal impairment, where the benefit risk is unfavorable and safety issues are concerning. Dr. Palevsky again expressed concerns about patients with eGFR <45 mL/min/1.73m^2. Several panel members also expressed concern about the need for obtaining long-term cardiovascular and other safety data post-approval.

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/s/

HYON J KWON
02/11/2013

JEAN-MARC P GUETTIER
02/11/2013

MEMORANDUM

Filing Meeting: July 31, 2012
NDA 204042
Drug: Canagliflozin, SGLT2 inhibitor
Sponsor: Janssen Research & Development, LLC (previously Johnson & Johnson Pharmaceutical Research & Development, LLC)
Clinical Reviewer: Hyon J. Kwon, PharmD, MPH
Date Received: May 31, 2012
PDUFA Date: March 31, 2013

Assessment:

From the clinical standpoint, the NDA is fileable.

Background:

Janssen Research & Development, LLC developed an orally active antihyperglycemic agent (AHA) canagliflozin, a sodium glucose co-transporter 2 (SGLT2) inhibitor, for treatment of type 2 diabetes in adults. The SGLT2 is located in the proximal renal tubule and reabsorbs most of the filtered glucose. Inhibition of SGLT2 decreases renal glucose re-absorption, thereby increasing urinary glucose excretion and lowering plasma glucose.

The proposed dose for canagliflozin is 100 mg or 300 mg QD, preferably before the first meal of the day. Starting dose of 100 mg QD is to be considered in patients on a loop diuretic, patients with moderate renal impairment, or patients ≥75 years of age due to higher occurrence of adverse reactions related to reduced intravascular volume (e.g., postural dizziness, orthostatic hypotension, or hypotension).

The applicant submitted data from 52 completed or ongoing clinical studies of canagliflozin, including data from 10,285 subjects in nine Phase 3 studies, 1,210 subjects in three Phase 2 studies, and 1,300 subjects in 40 Phase 1 studies. Overall, 6645 subjects were exposed to canagliflozin (both 100 mg and 300 mg dose), with 4723 subjects exposed to canagliflozin for at least one year and 144 subjects for at least 2 years.

Nine Phase 3 studies established the clinical efficacy and safety of canagliflozin in adults with type 2 diabetes:

Canagliflozin as Monotherapy:

- DIA3005 (N=587) - Placebo-controlled study of canagliflozin as monotherapy. Includes non-placebo controlled High Glycemic Substudy in subjects with baseline HbA1c >10 to ≤12%.

Canagliflozin as Add-on to AHA Monotherapy:

- DIA3006 (N=1284) - Placebo and active (sitagliptin)-controlled study as add-on to metformin monotherapy

- DIA3009 (N=1452) - Active comparator (glimepiride)-controlled study as add-on to metformin monotherapy
- DIA3008 Sulfonylurea (SU) Substudy (N=127) - Placebo-controlled substudy as add-on to SU monotherapy

Canagliflozin as Add-on to Dual Combination AHA Therapy:

- DIA3002 (N=469) - Placebo-controlled study as add-on to metformin + SU
- DIA3012 (N=344) - Placebo-controlled study as add-on to metformin + pioglitazone
- DIA3015 (N=756) - Active comparator (sitagliptin)-controlled study as add-on to metformin + SU

Canagliflozin as Add-on to Insulin:

- DIA3008 Insulin Substudy (N=1718) - Placebo-controlled substudy as add-on to insulin (given as monotherapy, in combination with metformin, or in combination with another AHA)

Canagliflozin in Special Population:

- DIA3004 (N=279) - Placebo-controlled study in T2DM with moderate renal impairment (eGFR ≥ 30 to <50 mL/min)
- DIA3010 (N=716) - Placebo-controlled study in older adults (≥ 55 to ≤80 years of age) with T2DM on AHA therapy; included dual energy X-ray absorptiometry (DXA) bone density assessments and evaluation of bone markers
- DIA3008 (N=4330) - Cardiovascular Safety Study (CANVAS)

In all Phase 3 studies, except for DIA3015 (where only canagliflozin 300 mg QD dose was studied), treatment arms included both proposed doses of canagliflozin (100 mg and 300 mg QD).

The primary endpoint for efficacy was the change in HbA1c from baseline to 26 Weeks for all Phase 3 studies except for active comparator studies (DIA3009 and DIA3015, at 52 Weeks) and 3008 substudies (DIA 3008 Insulin and SU Substudies, at 18 Weeks).

Aside from deaths, serious adverse events, and adverse events leading to study discontinuation, the applicant evaluated the following safety issues:

- Genital mycotic infections
- Urinary tract infections
- Osmotic diuresis-related adverse events
- Volume depletion adverse events related to reduced intravascular volume
- Hypoglycemia in combination with insulin or insulin secretagogue
- Changes in renal function and renal adverse events
- Bone safety - Bone turnover markers were assessed in three 12-week Phase 2 studies (OBE2001, DIA2001, and TA-7284) and one Phase 3 study (DIA3010). Bone density was measured by DXA in DIA3010 study.

- Photosensitivity skin adverse events
- Venous thromboembolic events
- Hepatic adverse events
- Malignancies - No pheochromocytoma or Leydig cell tumors in Phase 3 program. Three bladder cancers were reported, 1 in cana 100 mg group and 2 in non-cana group. Breast cancer was reported in 9 all cana group (0.35%, or 3.32/1000 PY; 5 in cana 300 mg and 4 in cana 100 mg) compared to 3 all non-cana group (0.22%, or 2.26/1000 PY). Three cases of renal cancer reported: 2 in cana 300 mg compared to 1 in non-cana group.

The primary CV meta-analysis for MACE-plus endpoint (included MACE plus hospitalization for unstable angina) for the hazard ratio (HR) of the combined canagliflozin to the non-canagliflozin excluded 1.8 (HR 0.91, 95% CI: 0.68, 1.2). The HR was 1.00 in CANVAS (95% CI: 0.72, 1.39) and 0.65 in studies other than CANVAS (95% CI: 0.35, 1.21).

Across the placebo-controlled Phase 3 studies, treatment with canagliflozin resulted in dose-related increases in LDL-C, with placebo-subtracted LS mean change from baseline of 4.4 mg/dL and 8.2 mg/dL with canagliflozin 100 mg and 300 mg respectively.

CLINICAL FILING CHECKLIST FOR NDA

NDA/BLA Number: 204042 **Applicant: Janssen Research & Development, LLC** **Stamp Date: 5/31/2012**

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

On initial overview of the NDA/BLA application for filing:

	Content Parameter	Yes	No	NA	Comment
FORMAT/ORGANIZATION/LEGIBILITY					
1.	Identify the general format that has been used for this application, e.g. electronic CTD.				electronic CTD
2.	On its face, is the clinical section organized in a manner to allow substantive review to begin?	x			
3.	Is the clinical section indexed (using a table of contents) and paginated in a manner to allow substantive review to begin?	x			
4.	For an electronic submission, is it possible to navigate the application in order to allow a substantive review to begin (*e.g.*, are the bookmarks adequate)?	x			
5.	Are all documents submitted in English or are English translations provided when necessary?	x			
6.	Is the clinical section legible so that substantive review can begin?	x			
LABELING					
7.	Has the applicant submitted the design of the development package and draft labeling in electronic format consistent with current regulation, divisional, and Center policies?	x			
SUMMARIES					
8.	Has the applicant submitted all the required discipline summaries (*i.e.,* Module 2 summaries)?	x			
9.	Has the applicant submitted the integrated summary of safety (ISS)?	x			
10.	Has the applicant submitted the integrated summary of efficacy (ISE)?	x			
11.	Has the applicant submitted a benefit-risk analysis for the product?	x			In the Clinical Overview
12.	Indicate if the Application is a 505(b)(1) or a 505(b)(2). If Application is a 505(b)(2) and if appropriate, what is the reference drug?				505(b)(1)
DOSE					
13.	If needed, has the applicant made an appropriate attempt to determine the correct dosage and schedule for this product (*i.e.*, appropriately designed dose-ranging studies)? Study Number: DIA2001 Study Title: A Randomized, Double-Blind, Placebo-Controlled, Double-Dummy, Parallel-Group, Multicenter, Dose-Ranging Study in Subjects With Type 2 Diabetes Mellitus to Evaluate the Efficacy, Safety, and Tolerability of Orally-Administered SGLT2 Inhibitor JNJ-28431754 With Sitagliptin as a Reference Arm Sample Size: 451 Arms: 7	x			

	Content Parameter	Yes	No	NA	Comment
	Location in submission: Module 5.3.3.1				
EFFICACY					
14.	Do there appear to be the requisite number of adequate and well-controlled studies in the application? There are nine Phase 3 studies in this application: <u>Monotherapy:</u> DIA3005 (includes High Glycemic Substudy) <u>Add-on to AHA Monotherapy:</u> • DIA3006 - add-on to metformin monotherapy • DIA3009 - add-on to metformin monotherapy, active comparator (glimepiride) • DIA3008 Sulfonylurea (SU) Substudy - add-on to SU <u>Add-on to Dual Combination AHA Therapy:</u> • DIA3002 - add-on to metformin + SU • DIA3012 - add-on to metformin + pioglitazone • DIA3015 - add-on to metformin + SU, active comparator (sitagliptin) <u>Add-on to Insulin:</u> DIA3008 Insulin Substudy - add-on to insulin <u>Special Population:</u> • DIA3004 - Moderate Renal Impairment Study (eGFR ≥ 30 to <50 mL/min) • DIA3010 - Older adults (≥ 55 to ≤80 years of age) • DIA3008 - Cardiovascular Safety Study (CANVAS)	x			
15.	Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	x			
16.	Do the endpoints in the pivotal studies conform to previous Agency commitments/agreements? Indicate if there were not previous Agency agreements regarding primary/secondary endpoints.	x			
17.	Has the application submitted a rationale for assuming the applicability of foreign data to U.S. population/practice of medicine in the submission?		x		
SAFETY					
18.	Has the applicant presented the safety data in a manner consistent with Center guidelines and/or in a manner previously requested by the Division?	x			
19.	Has the applicant submitted adequate information to assess the arythmogenic potential of the product (*e.g.*, QT interval studies, if needed)?	x			
20.	Has the applicant presented a safety assessment based on all current worldwide knowledge regarding this product?	x			

	Content Parameter	Yes	No	NA	Comment
21.	For chronically administered drugs, have an adequate number of patients (based on ICH guidelines for exposure[1]) been exposed at the dose (or dose range) believed to be efficacious?	x			6645 exposed to canagliflozin 100 mg or 300 mg; of these, 4723 for 1 year and 144 for 2 years
22.	For drugs not chronically administered (intermittent or short course), have the requisite number of patients been exposed as requested by the Division?			x	
23.	Has the applicant submitted the coding dictionary[2] used for mapping investigator verbatim terms to preferred terms?	x			
24.	Has the applicant adequately evaluated the safety issues that are known to occur with the drugs in the class to which the new drug belongs?	x			Genital mycotic infections, urinary tract infections, osmotic diuresis-related, volume depletion-related, bone safety, hepatic and renal events, malignancies, cardiovascular safety
25.	Have narrative summaries been submitted for all deaths and adverse dropouts (and serious adverse events if requested by the Division)?	x			also provided narratives for serious adverse events, confirmed adjudicated VTE events, hepatic events, and bladder, breast, and renal cancers
OTHER STUDIES					
26.	Has the applicant submitted all special studies/data requested by the Division during pre-submission discussions?				Yes from clinical standpoint, otherwise defer to other disciplines
27.	For Rx-to-OTC switch and direct-to-OTC applications, are the necessary consumer behavioral studies included (*e.g.*, label comprehension, self selection and/or actual use)?			x	
PEDIATRIC USE					
28.	Has the applicant submitted the pediatric assessment, or provided documentation for a waiver and/or deferral?	x			Waiver for <10 years, deferral for 10-17 years of age
ABUSE LIABILITY					
29.	If relevant, has the applicant submitted information to assess the abuse liability of the product?		x		
FOREIGN STUDIES					
30.	Has the applicant submitted a rationale for assuming the		x		

[1] For chronically administered drugs, the ICH guidelines recommend 1500 patients overall, 300-600 patients for six months, and 100 patients for one year. These exposures MUST occur at the dose or dose range believed to be efficacious.

[2] The "coding dictionary" consists of a list of all investigator verbatim terms and the preferred terms to which they were mapped. It is most helpful if this comes in as a SAS transport file so that it can be sorted as needed; however, if it is submitted as a PDF document, it should be submitted in both directions (verbatim -> preferred and preferred -> verbatim).

	Content Parameter	Yes	No	NA	Comment
	applicability of foreign data in the submission to the U.S. population?				
DATASETS					
31.	Has the applicant submitted datasets in a format to allow reasonable review of the patient data?	x			
32.	Has the applicant submitted datasets in the format agreed to previously by the Division?	x			
33.	Are all datasets for pivotal efficacy studies available and complete for all indications requested?	x			
34.	Are all datasets to support the critical safety analyses available and complete?	x			
35.	For the major derived or composite endpoints, are all of the raw data needed to derive these endpoints included?			x	No composite endpoint in the pivotal study
CASE REPORT FORMS					
36.	Has the applicant submitted all required Case Report Forms in a legible format (deaths, serious adverse events, and adverse dropouts)?	x			
37.	Has the applicant submitted all additional Case Report Forms (beyond deaths, serious adverse events, and adverse drop-outs) as previously requested by the Division?	x			Submitted Case Report Forms for confirmed adjudicated hepatic events, and bladder, breast, and renal cancers
FINANCIAL DISCLOSURE					
38.	Has the applicant submitted the required Financial Disclosure information?	x			
GOOD CLINICAL PRACTICE					
39.	Is there a statement of Good Clinical Practice; that all clinical studies were conducted under the supervision of an IRB and with adequate informed consent procedures?	x			

IS THE CLINICAL SECTION OF THE APPLICATION FILEABLE? __Yes_____

If the Application is not fileable from the clinical perspective, state the reasons and provide comments to be sent to the Applicant.

Please identify and list any potential review issues to be forwarded to the Applicant for the 74-day letter.

- Provide unique subject identifier by the Hepatic Event Assessment Committee (HEAC) Adjudication Criteria and treatment group as shown in the Table provide below for 56 subjects who were adjudicated for hepatic events. For 'Other' criteria, provide the liver injury-related preferred terms that led to adjudication for each subject.

Table: List of Subject Identifier by HEAC Adjudication Criteria and Treatment Group

HEAC Adjudication Criteria	Control	Cana 100 mg	Cana 300 mg
ALT ≥5x ULN			
AST ≥5x ULN			
ALT or AST ≥5x ULN or TB ≥2x ULN			
Other			

- Clarify why there were 56 subjects who had liver events meeting adjudication criteria, and only 48 subjects are summarized in Table 136 and 138 in the Summary of Clinical Safety.

Hyon Kwon, PharmD, MPH

Reviewing Medical Officer Date

Jean-Marc Guettier, MD

Clinical Team Leader Date

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

/s/

HYON J KWON
08/10/2012

JEAN-MARC P GUETTIER
08/10/2012