CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

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RISK ASSESSMENT and RISK MITIGATION REVIEW(S)

Department of Health and Human Services
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Surveillance and Epidemiology
Office of Medication Error Prevention and Risk Management

Risk Evaluation and Mitigation Strategies (REMS) Review

Date:	February 5, 2013
Reviewer(s):	Amarilys Vega, M.D., M.P.H, Medical Officer Division of Risk Management (DRISK)
Team Leader:	Cynthia LaCivita, Pharm.D., Team Leader DRISK
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Subject:	Review evaluates if a risk evaluation and mitigation strategy (REMS) is needed
Drug Name(s):	Canagliflozin (Invokana™)
Therapeutic Class:	Inhibitor of sodium-glucose transporter 2 (SGLT2)
Dosage and Route:	100 mg or 300 mg, film-coated oral tablet, p.o. once daily
Application Type/Number:	NDA 204042
Submission Number:	1
Applicant/sponsor:	Janssen Pharmaceuticals
OSE RCM #:	2012-1441

CONTENTS

1 INTRODUCTION

This review by DRISK evaluates if a risk evaluation and mitigation strategy (REMS) is needed for canagliflozin (Invokana™). The proposed indication for canagliflozin is as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus.

1.1 BACKGROUND

Mechanism of action. Under normal circumstances, glucose is filtered at the glomerulus and 100% of the filtered glucose is reabsorbed in the proximal tubule of the nephron. Sodium-glucose cotransporters (SGLTs) have an important role in renal glucose reabsorption. SGLT2 in the proximal tubule of the kidney is responsible for the majority of glucose reabsorption and SGLT1, also expressed in the proximal tubule, is responsible to a lesser extent of renal tubular glucose reabsorption. Currently, there are no approved SGLT2 inhibitors. Canagliflozin is an inhibitor of SGLT2 (160-fold selectivity for SGLT2 over SGLT1) resulting in a significant decrease in renal glucose reabsorption and consequently, in an increase in urinary glucose excretion, osmotic diuresis, and lower plasma glucose levels.

Indication and dosage. The applicant is seeking approval of canagliflozin as adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus. Canagliflozin should not be used in patients with type 1 diabetes nor for treatment of diabetic ketoacidosis or in patients with severe renal impairment, end-stage renal disease (ESRD), or in patients on dialysis.

Canagliflozin is formulated as a film-coated tablet (100 mg and 300 mg) for oral administration. The recommended dose of canagliflozin is 100 mg or 300 mg once daily, preferably taken before the first meal of the day. A starting dose of 100 mg once daily should be considered for patients on a loop diuretic, patients with moderate renal impairment, or patients ≥75 years of age.

Other SGLT inhibitors. Dapagliflozin, another SGLT2 inhibitor, showed to be effective as monotherapy and in combination with other antidiabetic drugs but received a Complete Response action letter from FDA on January 17, 2012 due to safety concerns (hepatotoxicity and bladder cancer). Other risks associated with the use of dapagliflozin included: increased risk of urinary and genital infections, short-term risks to renal function related to hypovolemia and dehydration (the elderly and patients on diuretic and antihypertensive therapy), and concerns regarding bone health.

1.2 REGULATORY HISTORY

The applicant submitted NDA 204042 on May 31, 2012 for canagliflozin for the treatment of patients with type 2 diabetes mellitus.

The Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) met on January 10, 2013 to discuss the benefits and risks of canagliflozin.

2 MATERIALS REVIEWED

- Canagliflozin, Clinical Overview, Janssen Pharmaceuticals, May 20, 2012.
- Canagliflozin, Summary of Clinical Efficacy, Janssen Pharmaceuticals, May 17, 2012.
- Canagliflozin, Summary of Clinical Safety, Janssen Pharmaceuticals, May 19, 2012.
- Canagliflozin, Draft Label, Janssen Pharmaceuticals, submitted November 15, 2012.
- Canagliflozin, Advisory Committee Meeting FDA Briefing Document and slide presentation, January 10, 2013.

- Canagliflozin, Advisory Committee Meeting Janssen Pharmaceuticals slide presentation, January 10, 2013.

3 CLINICAL DEVELOPMENT PROGRAM

Janssen is developing canagliflozin globally, with the exception of the following countries: Japan, Taiwan, and Indonesia where they partner with Mitsubishi Tanabe Pharma Corporation (MTPC) and are conducting an independent clinical development program under different development timelines. The MTPC program provides only supportive data for the canagliflozin application submitted to FDA.[1]

The efficacy and safety of canagliflozin were evaluated for the treatment of subjects with type 2 diabetes mellitus (T2DM), including glycemic response and effects on other important endpoints reflecting the comorbidities of T2DM (i.e., body weight, blood pressure, serum lipids), in patients with T2DM with moderate renal function, and older adults. The clinical development program assessed the use of canagliflozin both as monotherapy and in combination with approved anti-diabetic agents – canagliflozin was given as an add-on to metformin, metformin plus sulfonylurea, metformin plus pioglitazone, and insulin.

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 (including three trials in special populations of subjects with T2DM, i.e., older adults, subjects with moderate renal impairment, and subject with or at high risk of cardiovascular disease). See Appendix 1 for a list of Phase 3 trials.

The primary evidence of the efficacy of canagliflozin in the target indication is derived from 9 pivotal Phase 3 studies (multinational, randomized, double-blind, parallel-group trials), supported by data from Phase 2 dose-finding studies.[2] Treatment differences (least-squares (LS) means and their two-sided 95% confidence intervals (CI)) between each canagliflozin group and the comparator(s) (either placebo or active comparator) were estimated from the model for each individual study.

The primary endpoint for all Phase 3 studies was the change in HbA1c from baseline to the end of the study. Major secondary endpoints included: changes in fasting plasma glucose (FPG) from baseline to the end of the study, changes in 2-hour post-prandial glucose (PPG) from baseline to the end of the study, proportion of subjects achieving an HbA1c target (<7.0%) at the end of the study, percent change from baseline to the end of the study in body weight, percent change from baseline to the end of the study in high density lipoprotein cholesterol (HDL-C), percent change from baseline to the end of the study in fasting triglycerides, and percent change from baseline to the end of the study in systolic blood pressure.

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[1] Canagliflozin, Clinical Overview, Janssen Pharmaceuticals, May 20, 2012.

[2] **Monotherapy** [DIA3005 (main study)]; **add-on anti hyperglycemic agent to monotherapy** [DIA3006 & DIA3009 (add-on to metformin monotherapy]; **add-on to dual combination therapy** [DIA3002 (add-on to metformin and sulfonylurea), DIA3012 (add-on to metformin and pioglitazone), DIA3015 (add-on to metformin and sulfonylurea)]; **special population studies** [DIA3010 (older adults ≥55 to ≤80 years), DIA3004 (moderate renal impairment)]; **cardiovascular assessment study with glycemic efficacy substudies** [DIA3008]. Note that one of nine Phase 3 trials, DIA3015, was not included in any of the pooled datasets because it was an active-controlled (sitagliptin) trial which included only one of two active canagliflozin groups (300 mg only).

A total of 7,803 subjects were randomized in Phase 3 clinical trials and received at least one dose of study drug. Of 7,803 subjects receiving study drug, 4,994 subjects were treated with canagliflozin (2,302 subjects with 100 mg and 2,692 subjects with 300 mg), 1,583 subjects were treated with placebo, and 1,226 subjects were treated with active comparator (744 with sitagliptin and 482 with glimepiride).

Four pooled datasets (DS) of Phase 3 trials were used to evaluate the safety of canagliflozin: DS1 (Placebo-Controlled Studies Dataset), DS2 (Moderate Renal Impairment Dataset), DS3 (Broad Dataset including all active- and placebo-controlled trials), and DS4 (Longer-term Exposure Broad Dataset all active- and placebo-controlled trials). See Appendix 2.

3.1 EFFICACY FINDINGS

Glycemic Control. All superiority comparisons of canagliflozin (100 mg and 300 mg) vs. placebo in glycosylated hemoglobin (HbA1c) change from baseline were significant in all studies (see Appendix 3). Canagliflozin 300 mg was also shown to be superior to glimepiride (DIA3009, p=0.016) although the mean treatment difference was small (-0.12%). In addition, canagliflozin (100 mg and 300 mg) demonstrated to be non-inferior to glimepiride (DIA3009) and to sitagliptin (DIA3015). In patients with moderate renal impairment (DIA3004), canagliflozin (100 mg and 300 mg) were both statistically superior to placebo; however, the change in HbA1c from baseline was modest when compared to that observed in other placebo controlled trials. The observed LS mean decreases in FPG were dose-dependent and statistically significant for all comparisons (canagliflozin 100 mg ranging from -22.4 to -37.4 mg/dL, canagliflozin 300 mg ranging from -27.7 to -48.1 mg/dL). In study subjects with renal impairment, the mean changes relatively to placebo were smaller (canagliflozin 100 mg = -12.2 mg/ dL, canagliflozin 300 mg = -15.4 mg/ dL). The LS mean reduction in 2-hour PPG (DIA3005 and DIA3006) was statistically significant compared to placebo for the canagliflozin 100 mg and 300 mg groups ($p<0.001$ for both comparisons).

Effect on Blood Pressure. There was a significant, dose-dependent reduction in systolic blood pressure (SBP) except for studies DIA3002 and DIA3008 (sulphonylurea (SU) substudy) where the changes in blood pressure did not reach statistical significance with both doses of canagliflozin (see Appendix 4). The LS mean SBP changes from baseline ranged from -3.27 to -6.05 mmHg with the canagliflozin 100 mg dose, from -4.27 to -6.87 mmHg with the canagliflozin 300 mg dose, and from +1.52 to -3.38 mmHg for placebo groups.

Effect on Body Weight. Also, there was a statistically significant, dose-dependent reduction in body weight from baseline across the placebo-controlled studies except with the 100 mg dose of canagliflozin in DIA3008 SU substudy where it did not reach statistical significance (see Appendix 4). The percent changes from baseline in body weight were from -1.4% to -2.7% with the canagliflozin 100 mg dose and -1.8% to -3.7% with the canagliflozin 300 mg dose.

Effects on Lipid Metabolism. There was a statistically significant increase in HDL-C with canagliflozin in four of eight placebo-controlled Phase 3 trials (DIA3005, DIA3006, DIA3012, and DIA3010). The percent changes from baseline in HDL-C ranged from 4.8% to 6.8% with the canagliflozin 100 mg dose and from 4.7% to 8.4% with the canagliflozin 300 mg dose (at the time of primary assessment timepoint). A small but statistically significant decrease in triglycerides with canagliflozin was observed in only one of eight placebo-controlled trials (DIA3012). Changes in calculated low density lipoprotein cholesterol (LDL-C) were variable

across studies; the percent increases for with canagliflozin 100 mg ranged from 2.0% to 7.9% and from 4.6% to 12.2% with canagliflozin 300 mg.

3.2 KEY SAFETY FINDINGS

The primary analyses of safety were based on data from the Placebo-controlled Studies Dataset (DS1); supporting information was obtained from DS2, DS3, and DS4. The DS3 dataset includes all subjects from DS1. There were no significantly meaningful differences in the safety profile of canagliflozin identified in DS4.

The Placebo-controlled Studies Dataset (DS1) included a broad range of patients with T2DM while the Broad Dataset (DS3) represents a more vulnerable population given it included older subjects and subjects with a higher prevalence of comorbidities and diabetic complications. The following sections present key safety findings identified in the canagliflozin development program.

Placebo-controlled Studies Dataset (DS1). In the DS1 dataset, most of the reported adverse events were mild to moderate in severity and the incidence of severe adverse events was relatively low and similar across treatment groups. The incidence of adverse events was similar in all study groups (canagliflozin 100 mg = 60.0%, canagliflozin 300 mg = 59.2%, placebo = 57.4%). However, the incidence of adverse events considered related to study drug (canagliflozin 100 mg = 20%, canagliflozin 300 mg = 23%, placebo = 13%) and the incidence of adverse events leading to discontinuation (canagliflozin 100 mg = 2.6%, canagliflozin 300 mg = 2.5%, placebo = 1.5%) were higher in the canagliflozin groups. The incidence of serious adverse events was low in all treatment groups (canagliflozin 100 mg/300 mg = 0.4%, placebo = 0.2%).[3] There were four deaths in DS1 (2 in the placebo group and one in each of the canagliflozin groups) but none were considered related to canagliflozin.[4]

Broad Dataset (DS3). The safety profile of canagliflozin identified in the DS3 dataset is similar to that observed in the DS1 dataset. Most adverse events were mild or moderate in severity and the incidence of serious adverse events and deaths was relatively low and similar in the canagliflozin and non-canagliflozin groups. However, the incidence of any adverse event and adverse events leading to discontinuation was higher in the canagliflozin 300 mg group compared to canagliflozin 100 mg and non-canagliflozin groups. Also, the incidence of adverse events considered related to canagliflozin was higher in the canagliflozin groups compared with the non-canagliflozin group (canagliflozin 100 mg = 24.7%, canagliflozin 300 mg = and 29.6%, non-canagliflozin = 17.9%). The incidence of adverse events was higher for canagliflozin in the Renal and urinary disorders (pollakiuria, polyuria, micturition urgency, urinary incontinence), Reproductive and breast disorders (balanitis, balanoposthitis, vulvovaginal pruritus), and Gastrointestinal disorders (constipation, dry mouth) MedDRA SOCs.[5] There were 25 (0.4%) deaths in the combined canagliflozin group and 18 (0.6%) in the non-canagliflozin group; none of the deaths was considered related to canagliflozin. Most deaths in the canagliflozin as well as in the non-canagliflozin groups occurred in study DIA3008 which enrolled subjects with a history or high risk of cardiovascular disease.

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[3] Serious adverse events considered as related to the canagliflozin group were urinary tract infection (2 subjects) and bacterial prostatitis, urticaria, pulmonary embolism, deep vein thrombosis, and thrombosis (1 subject each).

[4] One death was related to an adverse event of pneumonia, complicated by septic shock, acute renal failure, and acute ischemic hepatitis) and the other death was related to an adverse event of stroke.

[5] MedDRA SOC – Medical Dictionary for Regulatory Activities System Organ Class

3.2.1 Adverse Events

3.2.1.1 Adverse Drug Reactions ≥2% in Incidence (DS1)

Adverse reaction occurring in ≥2% of subjects treated with canagliflozin in the DS1 dataset included: genital mycotic infections (vulvovaginal candidiasis[6] and balanitis/balanoposthitis[7]); osmotic diuresis-related adverse drug reactions (pollakiuria/polyuria[8] and thirst[9]); urinary tract infections[10]; and constipation[11].

Vulvovaginal adverse events mostly occurred in the first 4 months of therapy, were not dose-dependent, and were mild to moderate in severity; there were no serious adverse event reported. Women who developed vulvovaginal adverse events tended to be younger, more likely to be pre-menopausal, and to have a prior history of vulvovaginitis. The majority of women reporting vulvovaginitis had a single event; only 2.4% of women in the canagliflozin group had more than1 episode of vulvovaginitis.

Balanitis and balanoposthitis were mild to moderate in severity, occurring more commonly in uncircumcised men and in men who had a prior history of such infections. The majority of the men experiencing these adverse events had a single event; 0.9% subjects in the canagliflozin group reported more than 1 event.

Canagliflozin-induced osmotic diuresis was associated with an increase in the incidence of adverse events reflecting changes in the pattern of urination (pollakiuria, polyuria) or the desire to increase fluid intake (thirst and related terms). These adverse events were mild to moderate in severity and typically occurred early after the treatment initiation (within days to weeks), persisting in some subjects while in others these adverse events were self-limited. See section 3.2.4.2 Renal Safety for additional information.

The increase in the incidence of urinary tract infections was observed in both males and females but it was more common among females. The most common adverse event terms were urinary tract infection and cystitis. Serious adverse events and upper urinary tract infections were infrequent.

3.2.1.2 Other Important Adverse Drug Reactions (all safety datasets)

Other important adverse events include: hypoglycemia, urticarial/rash, decreased serum urate (see section 3.2.2.1 Renal Safety), volume depletion-related events (see section 3.2.2.1 Renal Safety), hyperkalemia (see section 3.2.2.1 Renal Safety), increased hemoglobin (see section 3.2.2.5 Cardiovascular Safety), and increased LDL-C (see section 3.2.2.5 Cardiovascular Safety).

Hypoglycemia. The incidence of hypoglycemia was increased in subjects receiving treatment with canagliflozin in combination with insulin and/or a non-glucose dependent insulin secretagogue.[12] The sponsor contends that canagliflozin has a low intrinsic risk for

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[6] Canagliflozin 100 mg = 10.4%, canagliflozin 300 mg = 11.4%, placebo = 3.2%
[7] Canagliflozin 100 mg = 4.2%, canagliflozin 300 mg = 3.7%, placebo = 0.6%
[8] Canagliflozin 100 mg = 5.3%, canagliflozin 300 mg = 4.6%, placebo = 0.8%
[9] Canagliflozin 100 mg = 2.8%, canagliflozin 300 mg = 2.3%, placebo = 0.2%
[10] Canagliflozin 100 mg = 5.9%, canagliflozin 300 mg = 4.3%, placebo = 4.0%
[11] Canagliflozin 100 mg = 1.8%, canagliflozin 300 mg = 2.3%, placebo = 0.9
[12] Event rate per subject-year exposure in subjects with any documented hypoglycemia:
DIA3002 (add-on to metformin/sulphonylurea): Total canagliflozin = 2.98, placebo = 1.04;
DIA3008 Insulin Substudy: Total canagliflozin = 7.84, placebo = 5.26;

hypoglycemia given the similar incidence of hypoglycemic episodes observe in the canagliflozin compared to that of sitagliptin, which is not associated with hypoglycemia.[12]

Urticaria and rash. In DS1, there was slight increase of urticaria (combined canagliflozin group = 0.3%, placebo = 0.2%) and rash (combined canagliflozin group = 0.7%, placebo = 0.3%) in the canagliflozin-treated group. There were no events suggestive of anaphylaxis, severe angioedema, mucosal involvement or Stevens - Johnson syndrome.

Reduced Intravascular Volume-related Adverse Events. Overall, these adverse events associated to decreased intravascular volume (e.g., hypotension, orthostatic hypotension, postural dizziness) were mild or moderate in severity. Analyses of these events showed that the following 3 risk factors appeared to lead to a notable increase in the risk of reduced intravascular volume-related factors: moderate renal impairment (eGFR <60 mL/min/1.73 m^2), treatment with loop diuretic, and age $\geq$75 years. See section 3.2.2.1 Renal Safety.

3.2.2 Safety of Relevant Body Systems

3.2.2.1 Malignancies

Animal data suggested an increase in the risk of Leydig cell tumors and in renal tubular tumors and pheochromocytomas. The applicant attributed these findings to rat-specific mechanisms. Also, the clinical development program dapagliflozin identified and imbalance in breast and bladder cancer among subjects exposed to this product. Consequently, the occurrence of Leyding cell tumors, renal tubular tumors, pheochromocytomas, breast, and bladder cancers were assessed in canagliflozin development program.

There were no cases of pheochromocytoma or malignant adrenal tumors reported in the canagliflozin development program. There was one case of a seminoma (a germ cell tumor of the testes) reported to the MTPC program but the patient's clinical presentation was not consistent with a drug-related event.[13] The incidence of renal, bladder, and breast cancers per 1,000 person-years was low in the clinical program and comparable to that in the non-canagliflozin treatment groups: renal cancer (canagliflozin 100 mg = 0.44, canagliflozin 300 mg = 0.63, and non-canagliflozin users = 0.63), bladder cancer (canagliflozin 100 mg = 0.44, canagliflozin 300 mg = 0.63, and non-canagliflozin users = 0.84), and breast cancer (canagliflozin 100 mg = 2.61, canagliflozin 300 mg = 3.39, and non-canagliflozin users = 3.05).

In summary, the available data do not suggest an increased risk of malignancies associated to exposure to canagliflozin.

3.2.2.2 Renal Safety

Osmotic Diuresis. Canagliflozin produces osmotic diuresis due to an increase in urinary excretion of glucose. In the Placebo-Controlled Studies Dataset (DS1), the occurrence of osmotic diuresis-related adverse events was higher in the canagliflozin treatment groups when compared to placebo (canagliflozin 100 mg = 6.7%, canagliflozin 300 mg = 5.6%, and placebo = 0.8%) and did not appear to be dose-dependent.

DIA3008 Sulphonylurea Substudy: Total canagliflozin = 0.59, placebo = 0.37;
DIA3015 (active-comparator [sitagliptin] controlled add-on to metformin/ sulphonylurea): Canagliflozin 300 mg = 4.14, Sitagliptin = 3.81.

[13] Testicular cancer was diagnosed in a 48-year old man two months after starting canagliflozin therapy (100 mg). 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.

In the 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%). Pollakiuria and thirst were the most frequently reported preferred terms.

In the Broad Dataset (DS3), the incidence of osmotic diuresis-related adverse events was higher in the canagliflozin groups compared to placebo (canagliflozin 100 mg = 6.8%, canagliflozin 300 mg = 7.1%, placebo = 1.9%). Pollakiuria, thirst, and polyuria were the most frequently reported preferred terms. Most of the osmotic diuresis-related adverse events occurred during the first 6 weeks of study and appear to plateau after that.

Volume Depletion Events Related to Decreased Intravascular Volume. In the DS1 dataset, volume depletion-related adverse events occurred at a slightly higher rate per 100 subject-years of exposure in the canagliflozin treatment groups compared to the placebo group (canagliflozin 100 mg = 2.6, canagliflozin 300 mg = 2.8, placebo = 2.4). The most commonly reported terms were hypotension (0.5% canagliflozin vs. 0.6% placebo), dizziness postural (0.4% canagliflozin vs. 0.3% placebo), and orthostatic hypotension (0.5% canagliflozin 300 mg vs. 0.2% placebo). The incidence of volume depletion adverse events was higher in the DS2 dataset compared to DS1 (canagliflozin 100 mg = 7.0, canagliflozin 300 mg = 11.9, placebo = 3.8). DS2 also showed an increase in frequency in the reporting of the terms dizziness postural, hypotension, and orthostatic hypotension in the canagliflozin group.

The DS3 dataset, including an older population with longer duration of diabetes, showed a dose-relationship and a higher incidence rate per 100 subject-years exposure of volume depletion-related adverse events (canagliflozin 100 mg = 3.1, canagliflozin 300 mg = 4.8, non-canagliflozin group = 2.2). Study subjects at high risk of experiencing volume depletion adverse events included those with low baseline eGFR (<60 mL/min/1.73m$_2$), age ≥65 years, 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).

Changes in Estimated Glomerular Filtration Rate. A modest, dose-dependent decrease in estimated glomerular filtration rate (eGFR) was documented in clinical trials; however, some subjects experienced larger decreases in eGFR (>30% reduction). Increases in BUN and serum creatinine in the canagliflozin treated groups were commensurate to intravascular volume changes. In the DS1 dataset, changes in eGFR, serum creatinine, and BUN were relatively small but higher in the canagliflozin groups.[14] Study DIA3004, which included subjects with moderately impaired renal function, showed larger mean percent increases from baseline in serum creatinine and BUN.[15] The increases in serum creatinine and decreases in eGFR remained stable over time. The occurrence of potentially clinical relevant decreases in renal function (eGFR reduction of >30% from baseline) was higher in the DS2 dataset (including subjects with moderate renal impairment) (canagliflozin 100 mg = 9.3%, canagliflozin 300 mg = 12.2%, placebo = 4.9%) compared to the DS1 dataset (canagliflozin 100 mg = 2%, canagliflozin 300 mg = 4.1%, placebo = 2.1).

[14] DS1: Changes from baseline **eGFR** – canagliflozin 100 mg = -1.8, canagliflozin 300 mg = -3.0%, placebo = -0.5%; Changes from baseline **serum creatinine** – canagliflozin 100 mg =-2.8%, canagliflozin 300 mg = 4.0% %, placebo = 1.5%; Changes in **BUN** – canagliflozin 100 mg = 17.1%, canagliflozin 300 mg = 18%, placebo = 2.7%.

[15] Increases from baseline in serum creatinine (canagliflozin 100 mg= 5.6%, canagliflozin 300 mg = 8.3%) and BUN (canagliflozin 100 mg= 11.8%, canagliflozin 300 mg = 13.2%).

Hyperkalemia. The DS1 dataset episodes of elevated serum potassium values greater than 5.4 mEq/L and 15% above baseline were more frequent in the canagliflozin groups (canagliflozin 100 mg = 4.4%, canagliflozin 300 mg = 7.0%, placebo = 4.8%). In the DS2 dataset (moderate renal impairment), the episodes of elevated potassium were even more frequent in the canagliflozin group (canagliflozin 100 mg = 7.2%, canagliflozin 300 mg = 12.0%, placebo = 7.9%).

Decrease serum urate. There were moderate decreases in the mean percent change from baseline in serum urate in the canagliflozin groups compared with placebo (canagliflozin 100 mg = -10.1%, canagliflozin 300 mg = -10.6%, placebo = 1.9%). However, the DIA3005 study (canagliflozin monotherapy) showed that at week 26 there was no discernible change from baseline in urinary urate/creatinine ratio in the canagliflozin groups, suggesting that the initial increase in urate excretion is not associated with an increase in nephrolithiasis.

Renal safety data was evaluated by Dr. Aliza Thompson, a medical officer in the Division of Cardiovascular and Renal Products, who concluded that the long-term renal consequences of canagliflozin are unknown and that subjects with moderate renal function will be at an increased risk for adverse renal events with moderate efficacy.[16] Monitoring of renal function taking canagliflozin is necessary to assure both safety and efficacy.

3.2.2.3 Bone Safety

Animal studies conducted in rats exposed to canagliflozin showed the development of hyperostosis (increase in trabecular bone volume) and decreased bone turnover. In Phase 1 and Phase 2 trials, there was no clinically significant change in phosphate or calcium levels. Also, the DS1 dataset showed no clinically significant changes in serum calcium levels but a small to moderate, dose-related increase in serum phosphate was observed with canagliflozin (canagliflozin 100 mg = 3.6%, canagliflozin 300 mg = 5.1%) compared to placebo (1.5%). Changes in serum phosphate levels were also seen in other Phase 3 trials (DIA3004 and DIA3010). In addition, in DIA3010, canagliflozin showed a statistically significant, dose-dependent increase in a serum marker of bone resorption (beta-CTx) and a non-statistically significant increase in a bone formation marker (P1NP). Changes in bone mineral density (BMD) measured in DIA3010 by dual energy x-ray absorptiometry (DXA) were not clinically significant. The ongoing controlled extension of DIA3010 will provide bone density measurements at Week 52 and Week 104.

Data from DIA3004 showed a moderate decrease in the median percent change from baseline of parathyroid hormone (PTH) (canagliflozin 100 mg = -3.6%, canagliflozin 300 mg = -8.2%, placebo = 2.4%) and a moderate increase in percent change from baseline of 25-hydroxyvitamin D (canagliflozin 100 mg =18.6%, canagliflozin 300 mg = 22%, and placebo = 10.8%).

Regarding bone fractures, the DS4 dataset showed a higher incidence of low trauma fractures (upper limb, females >males) in the canagliflozin group compared to the non-canagliflozin group and a higher incidence of fractures (imbalance also related to upper limb fractures) among subjects with moderate renal impairment (eGFR 30 to <60).

[16] Aliza Thompson, MD, Medical Officer, Division of Cardiovascular and Renal Products: Review to evaluate and comment on the renal safety findings associated with canagliflozin use in NDA 204042. Dated December 2, 2012.

3.2.2.4 Hepatic Safety

In DS1, ALT levels decreased from baseline over time with canagliflozin compared to placebo (canagliflozin 100 mg =-7.5%, canagliflozin 300 mg = -11.1%, placebo = 2.7%). AST and alkaline phosphatase also decreased over time with canagliflozin therapy. To the contrary, the percent change of serum bilirubin was higher for the canagliflozin groups compared to placebo (canagliflozin 100 mg = 8%, canagliflozin 300 mg = 9.5%, placebo = 2.2%).

In the DS1and DS2 datasets, the proportion of subjects that met predefined limits of change (PDLC) criteria for ALT, AST, and bilirubin elevations was low with no significant difference between treatment groups. Data in DS3 showed that: (1) the proportion of subjects meeting the PDLC criteria for ALT and/or AST >3x and >5x upper limit of normal (ULN) in any post-baseline value was higher with canagliflozin 100 mg compared to canagliflozin 300 mg and non-canagliflozin, (2) the incidence rate per 1000 person-years exposure of ALT and/or AST elevation was higher for the canagliflozin 100 mg group than the 300 mg or non-canagliflozin groups, and that (3) 0.2% in the combined canagliflozin and 0.1% in non-canagliflozin group experienced any post-baseline value meeting PDLC criteria for bilirubin elevation (>2x ULN).

Assessment of eight cases meeting laboratory criteria for Hy's Law (ALT or AST ≥3x ULN with TB ≥2x ULN) did not establish a causal association to canagliflozin treatment since an alternative etiology for observed liver function changes were present in each of these cases. Eighteen cases that did not fulfill Hy's Law criteria were reviewed by Dr. Leonard Seeff, Office of Surveillance and Epidemiology, given these had significant elevation in aminotransferase and narratives lacking the necessary clinical information to completely exclude a role of canagliflozin in causing hepatic-related adverse events. Dr. Seeff considered two of these as 'possible' cases of drug-induced liver injury (DILI).

3.2.2.5 Cardiovascular Safety

Increased LDL-Cholesterol. Canagliflozin demonstrated a dose-dependent increase in LDL-C. In DS1, the placebo-subtracted LS mean percent change from baseline was 4.5% and 8.0% for canagliflozin 100 mg and 300 mg respectively. Use of statins at baseline had no meaningful impact on the magnitude of the LDL-C increase.

Hemoconcentration and Thromboembolic Events. The DS1 dataset, demonstrated a modest increase in hemoglobin concentration ≥20 g/L from baseline in the canagliflozin groups compared to placebo (canagliflozin 100 mg = 6.0%, canagliflozin 300 mg = 5.4%, placebo = 1.0%). Comparable findings were also observed in subjects with moderate renal impairment (DIA3004), older subjects (DIA3008), and in subjects receiving treatment with canagliflozin for a longer period of time (DIA3009).

There were 18 venous thromboembolic events (VTE) identified in Phase 3 trials; 16 were serious, and one event led to study drug discontinuation. In DS4, the incidence of VTE per 100 subject-years was higher for the canagliflozin 300 mg group (canagliflozin 100 mg = 0.15, canagliflozin 300 mg = 0.24, placebo = 0.15). Canagliflozin-induced volume depletion could be related to VTE events, however, the data indicate that only one subject with VTE had a blood volume-related event (hypotension).

Cardiovascular risk trial and meta-analysis. To assess the cardiovascular safety of canagliflozin, the sponsor conducted a dedicated cardiovascular study (DIA3008 - CANVAS) and a cardiovascular meta-analysis.

CANVAS is a placebo-controlled, parallel-group, multicenter study of canagliflozin plus standard of care compared with placebo plus standard of care in subjects with T2DM on a wide range of antihyperglycemic agents, who either have a history of or are at high risk for cardiovascular disease. The main goals of this study include evaluation of the effects of treatment with canagliflozin on major adverse cardiovascular events (MACE = cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke) plus hospitalized unstable angina (MACE plus) and to the assess safety and tolerability of canagliflozin. The pre-specified analysis was based on Cox proportional hazard model. The cardiovascular meta-analysis, including CANVAS and other canagliflozin Phase 2 and 3 studies, examined the hazard ratio of MACE-plus.

The meta-analysis showed an estimated hazard ratio of 0.91 (95% CI: 0.68, 1.22) for the risk of MACE-plus comparing canagliflozin to all comparators and a hazard ratio of 0.65 (95% CI: 0.35, 1.21) in studies other than CANVAS. Both estimates of the upper bound of the 95% CI were below 1.8, consistent with the FDA guidance of 2008.[17] Stroke was the only individual component of MACE-plus that showed a hazard ratio above one for the canagliflozin group compared to the non-canagliflozin group (HR=1.47, 95% CI: 0.83, 2.59).

The interpretation of the results from the meta-analysis is complicated by evidence suggesting that the assumption of proportional hazards was not met. Further analysis of the CANVAS dataset revealed a numerical imbalance in the number of early cardiovascular events. During the first 30 days after randomization, there were reports of cardiovascular events for 13 subjects (0.45%) in the canagliflozin group and for 1 subject in the placebo group (0.07%). The estimated hazard ratio during the first 30 days for CANVAS was 6.50 (95% CI: 0.85, 49.66); however, it was not significant due to small number of events. There were no major differences between subjects receiving canagliflozin who had early cardiovascular events compared to those receiving canagliflozin who had cardiovascular event after 30 days (HR = 0.89, 95% CI: 0.64, 1.25), or compared to subjects who received placebo and had a cardiovascular event in CANVAS.

The statistical reviewer, Dr. Eugenio Andraca-Carrera, noted in his review "… *due to the small number of events in this analysis, the estimated hazard ratio is highly sensitive to any additional events. … Due to the small number of events within this time window, and as represented by the wide confidence interval of the hazard ratio, these findings cannot definitely conclude a significant increase in risk within 30 days associated with canagliflozin. It is possible that the observed imbalance of MACE-plus in the first 30 days of CANVAS might be attributable to chance*."[18]

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[17] Guidance for Industry, Diabetes Mellitus: Developing Drugs and Therapeutic Biologics for Treatment and Prevention; http://www fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm071627.pdf, page 7, accessed January 23, 2013. The guidance estates, "For completed studies, before submission of the new drug application (NDA)/biologics license application (BLA): Sponsors should compare the incidence of important cardiovascular events occurring with the investigational agent to the incidence of the same types of events occurring with the control group to show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.8. …".

[18] Eugenio Andraca-Carrrera, PhD., Canagliflozin, Advisory Committee Meeting FDA Briefing Document and slide presentation, January 10, 2013, page 123-124.

The FDA Guidance also indicated that if the premarketing application contains clinical data that show that the upper bound of the two-sided 95 percent confidence interval for the estimated increased risk is between 1.3 and 1.8, and the overall risk-benefit analysis supports approval, a postmarketing trial generally will be necessary to definitively show that the upper bound of the two-sided 95 percent confidence interval for the estimated risk ratio is less than 1.3.[17] The sponsor in planning to use the final results of the CANVAS study (expected in year 2015) to demonstrate the estimated risk is <1.3.

4 ADVISORY COMMITTEE DISCUSSION AND RECOMMENDATIONS

The Endocrinologic and Metabolic Drugs Advisory Committee (EMDAC) convened on January 10, 2013 to discuss the efficacy and safety of canagliflozin. The committee voted 10-5 in favor of approval. The focus of the panel's discussion was on renal, bone, and cardiovascular safety.

Regarding renal safety, the committee expressed concerns about the use of canagliflozin by patients with renal impairment because of the demonstrated decreased efficacy in this group, the increased risk of adverse events, including the risk of acute renal injury, and the relatively small amount of data available to support its use in this population. Some members considered that a minimum eGFR allowed to take canagliflozin should be 45mL/min/1.73 m^2; the sponsor's proposed label recommends against the use of canagliflozin in patients with a eGFR < 30 mL/min/1.73m^2.

The committee agreed that additional data is necessary to assess the potential long-term clinical impact of canagliflozin on bone safety. Specific concerns raised by members of the committee were the potential of canagliflozin for exacerbating bone loss in patients with renal impairment and the potential for off-label use in the younger, non-type 2 diabetes population where changes in bone density early in life could result in detrimental long-term consequences.

When asked if they had concerns about the conclusion that a cardiovascular risk margin of 1.8 had been excluded, the committee vote was split (Yes = 8, No = 7). However, several panel members who voted "yes" also expressed a degree of uncertainty about the cardiovascular safety of this drug, particularly, the imbalance in cardiovascular events identified in the first 30 days of CANVAS. The committee did agree that long-term follow up would be necessary to evaluate the clinical relevance of changes in blood pressure, weight, and LDL-C levels. The company plans to use final results from CANVAS (available year 2015), to meet the 1.3 upper bound requirement post-approval.

5 DISCUSSION

Canagliflozin clinical development program demonstrated this drug is effective in the management of T2DM in patients with normal or mildly impaired renal function. In addition to improvement of glycemic control, canagliflozin demonstrated favorable effects on several cardiovascular risk markers including decrease in blood pressure, decrease in body weight, and consistent trend towards reduction in triglycerides and increase of HDL-C. Due to its mechanism of action, the efficacy of canagliflozin in the presence of moderate renal impairment is diminished. Similar efficacy findings in subjects with renal impairment were observed in the clinical development program of dapagliflozin, another SGLT2 inhibitor recently evaluated by FDA for marketing approval.

The risk:benefit assessment of canagliflozin by DMEP and DRISK did not identify any confirmed or potential risks that would require the implementation of a REMS to assure

the benefits of its use outweigh its risks. The main safety concerns identified with canagliflozin were related to renal, bone, and cardiovascular safety. It is important to note that dapagliflozin presented with a potential risk for malignancy, specifically, breast and bladder cancers. However, the data available for canagliflozin at the time when this review was completed, do not suggest an increased risk of malignancies associated with treatment with canagliflozin. In general, canagliflozin shares similar safety concerns with dapagliflozin, which are based on their common mechanism of action. These risks include osmotic diuresis, decreased intravascular volume, increase in genitourinary infections, and the risk of hypoglycemia when used in combination with other antihyperglycemic agents. It is important to communicate these risks to prescribers and patients since knowledge of their potential occurrence can prevent them or minimize their severity. If approved, patients treated with canagliflozin would likely benefit from the distribution of a medication guide highlighting the risk of use by patients with impaired renal function and the risks for genitourinary infections, volume depletion-related events, and hypoglycemia when used in combination with other antihyperglycemic agents.

The potential risk of hepatotoxicity could not be excluded for canagliflozin or dapagliflozin. There were 2 cases considered as "possible" drug-induced liver injury in the canagliflozin development program and a potentially serious case of drug-induced liver injury (meeting the biochemical threshold for "Hy's Law") reported in the dapagliflozin development program. Additional safety data collected postmarketing is required to characterize further the potential risk of hepatotoxicity.

As recommended by the advisory committee panel, additional long-term safety data is required to characterize the impact of therapy with canagliflozin on cardiovascular, bone, and renal safety, in particular among patients with moderate renal impairment. Additional bone safety data will be available from the extension of study DIA3010. Canagliflozin increases LDL-C which may increase the risk of cardiovascular adverse events despite the favorable changes demonstrated in blood pressure, body weight, and reduction of HDL-C. Additional cardiovascular safety data will be available once CANVAS is completed.

REMS implemented for managing the risks of other antidiabetic agents include: rosiglitazone (risk of serious cardiovascular events) and liraglutide (risk of medullary thyroid carcinoma and of acute pancreatitis, including necrotizing pancreatitis).[19, 20]

6 CONCLUSION AND RECOMMENDATIONS

DRISK recommends managing identified safety risks through labeling, including a Medication Guide. The need for a REMS can be re-evaluated if new safety data becomes available that warrants more extensive risk mitigation.

[19] Rosiglitazone REMS (Avandia, Avandamet, Avandaryl): includes a medication guide, elements to assure safe use, and implementation system. Elements to assure safe use include prescriber and pharmacy certification and patient enrollment in the program.

[20] Liraglutide REMS (Victoza): includes a communication plan.

APPENDIX

APPENDIX 1: Phase 3 Clinical Studies of Canagliflozin

Study ID/Type (No. Centers)	Study Design, Duration (Duration to primary endpoint/ Duration of extension phase)	HbA_{1c} Inclusion Criterion	Study Treatment Daily Dosing (qd)	No. Subjects per Treatment Arm (mITT)	Primary Efficacy Endpoint
MONOTHERAPY					
DIA3005 Main Study[a] Monotherapy (90 centers)	R, DB, PC, PG 52 weeks double-blind (26 wks / 26 wks)	≥7.0% to ≤10.0%	Placebo CANA 100 mg CANA 300 mg	192 195 197	Δ BL to Wk 26 in HbA_{1c}
High Glycemic substudy Monotherapy (40 centers)	R, DB, PG 26 weeks double-blind (26 wks / no extension)	>10.0% to ≤12.0%	CANA 100 mg CANA 300 mg	47 44	Δ BL to Wk 26 in HbA_{1c}
ADD-ON TO AHA MONOTHERAPY					
DIA3006[a] Add-on to metformin monotherapy (169 centers)	R, DB, PC, AC, PG 52 weeks double-blind (26 wks / 26 wks)	≥7.0% to ≤10.5%	Placebo CANA 100 mg CANA 300 mg Sitagliptin 100 mg	183 368 367 366	Δ BL to Wk 26 in HbA_{1c}
DIA3009 Add-on to metformin monotherapy (157 centers)	R, DB, AC, PG 104 weeks double-blind (52 wks / 52 wks)	≥7.0% to ≤9.5%	CANA 100 mg CANA 300 mg Glimepiride (titrated from 1 to 6 or 8 mg)	483 485 482	Δ BL to Wk 52 in HbA_{1c}
ADD-ON TO DUAL COMBINATION AHA THERAPY					
DIA3002 Add-on to metformin + sulfonylurea (85 centers)	R, DB, PC, PG 52 weeks double-blind (26 wks / 26 wks)	≥7.0% to ≤10.5%	Placebo CANA 100 mg CANA 300 mg	156 157 156	Δ BL to Wk 26 in HbA_{1c}
DIA3012[a] Add-on to metformin + pioglitazone (74 centers)	R, DB, PC, PG 52 weeks double-blind (26 wks / 26 wks)	≥7.0% to ≤10.5%	Placebo CANA 100 mg CANA 300 mg	115 113 114	Δ BL to Wk 26 in HbA_{1c}
DIA3015 Add-on to metformin + sulfonylurea (140 centers)	R, DB, AC, PG 52 weeks double-blind (52 wks / no extension)	≥7.0% to ≤10.5%	CANA 300 mg Sitagliptin 100 mg	377 378	Δ BL to Wk 52 in HbA_{1c}
SPECIAL POPULATION STUDIES					
DIA3010 Older adults (≥55 to ≤80 years of age) (90 centers)	R, DB, PC, PG 104 weeks double-blind (26 wks / 78 wks)	≥7.0% to ≤10.0%	Placebo CANA 100 mg CANA 300 mg	237 241 236	Δ BL to Wk 26 in HbA_{1c}
SPECIAL POPULATION STUDIES					
DIA3004 Moderate renal impairment (eGFR ≥30 to <50 mL/min/1.73m^2) (89 centers)	R, DB, PC, PG 52 weeks double-blind (26 wks / 26 wks)	≥7.0% to ≤10.5%	Placebo CANA 100 mg CANA 300 mg	90 90 89	Δ BL to Wk 26 in HbA_{1c}
CARDIOVASCULAR ASSESSMENT STUDY WITH EFFICACY SUBSTUDIES					
DIA3008 Cardiovascular study (369 centers)	R, DB, PC, PG Duration is event driven based on number of MACE events	≥7.0% to ≤10.5% (with history or high risk of CV disease)	Placebo CANA 100 mg CANA 300 mg	1441[b] 1445[b] 1441[b]	Assessment of hazard ratio for MACE events
Glycemic Efficacy Substudies					
Insulin substudy (316 centers)	R, DB, PC, PG 18 weeks double-blind (18 wks / no extension)	≥7.0% to ≤10.5% while receiving insulin as monotherapy or in combination with other AHAs[c]	Placebo CANA 100 mg CANA 300 mg	565 566 587	Δ BL to Wk 18 in HbA_{1c}
Sulfonylurea substudy (80 centers)	R, DB, PC, PG 18 weeks double-blind (18 wks / no extension)	≥7.0% to ≤10.5% while SU monotherapy[d]	Placebo CANA 100 mg CANA 300 mg	45 42 40	Δ BL to Wk 18 in HbA_{1c}

[a] Subjects assigned to placebo were switched to sitagliptin during the double-blind extension period.

[b] Randomized and treated subjects (ie, safety analysis set).

[c] The primary analysis population discussed in this SCE for the DIA3008 Insulin substudy was defined as subjects randomized to any of the 3 insulin strata who were receiving insulin ≥30 IU/day at study entry (Population 2).

[d] The primary analysis population discussed in this SCE for the DIA3008 SU substudy was defined as subjects on protocol-specified doses of SU monotherapy regardless of the stratification used for randomization (Population 1).

Key: Δ = change from, AC = active-controlled, AHA = anti-hyperglycemic agent, BL = baseline, CANA = canagliflozin, CV = cardiovascular, DB = double-blind, eGFR = estimated glomerular filtration rate, MACE = major adverse cardiovascular events, mITT = modified intent-to-treat, No = number, PC = placebo-controlled, PG = parallel group, qd = once daily, R = randomized, SU = sulfonylurea; wks = weeks.

Source: Mod5.3.5.3\ISE\Table2.

Source: Summary of Clinical Efficacy, Table 2, page 16.

APPENDIX 2: 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/1.73m2	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

[1]High glycemic substudy is excluded. [2]Sitagliptin treatment group is excluded. [3]DIA3015 excluded.

Source: Hyon J. Kwon, PharmD, MPH, Clinical Reviewer, FDA Advisory Committee Briefing Document, Table 17.

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

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

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

Source: Hyon J. Kwon, PharmD, MPH, Clinical Review, Advisory Committee FDA Briefing Document, Table 2.

APPENDIX 4: Placebo-Subtracted LS Mean Change of Systolic Blood Pressure (SBP) and % Body Weight from Baseline (95% CI) to Primary Assessment Timepoint in Placebo-Controlled Phase 3 Trial - LOCF, mITT

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

Source: Hyon J. Kwon, PharmD, MPH, Clinical Review, Advisory Committee FDA Briefing Document, Table 15.

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/s/

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