CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

204042Orig1s000

OFFICE DIRECTOR MEMO

Summary Basis for Regulatory Action

Date	March 29, 2013
From	Curtis J Rosebraugh, MD, MPH Director, Office of Drug Evaluation II
Subject	Summary Review
NDA/BLA # Supp #	204042
Applicant Name	Janssen Research & Development
Proprietary / Established (USAN) Names	Invokana (Canagliflozin)
Dosage Forms / Strength	Tablets 100 mg or 300 mg once daily
Proposed Indication(s)	As an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus
Action:	*Approval*

1. Introduction and Discussion

This review will be a brief summary of the basis for the regulatory action regarding canagliflozin and further detail is available in the action package. Canagliflozin is an orally active sodium glucose co-transporter 2 (SGLT2) inhibitor. The SGLT2 transporter is located mainly in the proximal tubule of the kidney and reabsorbs the majority of glucose filtered by the renal glomerulus. Thus, inhibition of this transporter results in increased urinary glucose excretion ultimately resulting in lower plasma glucose in patients with type 2 diabetes mellitus (T2DM). Therefore canagliflozin is proposed for the treatment of adults with type 2 diabetes (T2DM) as an adjunct to diet and exercise.

This is a different treatment paradigm than in years past, where the evaluation of good diabetic control included efforts to decrease glycosuria and the excess water loss associated with osmotic diuresis. The concept now is that SGLT2 inhibition holds promise for glycemic control because patients with T2DM may have upregulated glucose reabsorption and this type of therapy decreases glucotoxicity lowering plasma glucose levels by increasing urinary caloric wasting. Other theoretical benefits include the potential for weight loss as a result of glycemic wasting and decrease in blood pressure as a result of increased sodium excretion. SGLT2 inhibition for glucose control does not require beta-cell function or tissue insulin sensitivity. Nothing comes without a price however, and potential adverse effects could be dehydration, frequent urination, progressive loss of efficacy with reduced glomerular function[1], genitourinary infections and unknown renal effects due to chronic blockade of SGLT2 receptors.

[1] The efficacy of SGLT2 would theoretically be dependent upon the amount of glucose filtered through the glomerulus, which would decrease as glomerular filtration rate (GFR) declines in renal impairment.

Regarding safety, a cardiovascular (CV) meta-analysis safety review determined a potential risk signal of harm for those receiving therapy within the first 30 days with a neutral effect after 30 days. Also noted were potential decreases in GFR in those with compromised renal function, and effects on bone remodeling. These issues will be discussed further later in this review.

DMEP is recommending that this application receive an Approval action. I agree with this recommendation and will discuss reasoning and conclusions below.

Efficacy

Canagliflozin 300 mg and 100 mg was compared to placebo in HbA1c change from baseline for superiority in monotherapy and as add-on therapy to other anti-hyperglycemic agents (AHA) in a variety of patient populations. There also were non-inferiority comparisons with marketed anti-diabetic drugs. Below is a table from Dr. Liu's review summarizing the efficacy results (Page 6-7).

Table 1. 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	Canaglifozin minus control (95% CI)	p-value
Monotherapy						
DIA3005 (26) Main study	Cana 300 mg Cana 100 mg Placebo	193 191 189	8.01 ± 0.07 8.06 ± 0.07 7.97 ± 0.07	-1.03 ± 0.06 -0.77 ± 0.06 0.14 ± 0.06	-1.16 (-1.34, -0.99) -0.91 (-1.09, -0.73)	<.0001 <.0001
DIA3005 (26) High Glycemic	Cana 300 mg Cana 100 mg	43 46	10.62 ± 0.15 10.59 ± 0.13	-2.56±0.22 -2.13±0.22		
Add-on to AHA Monotherapy						
DIA3006 (26) Add-on to metformin	Cana 300 mg Cana 100 mg Placebo	360 365 181	7.95 ± 0.05 7.94 ± 0.05 7.96 ± 0.07	-0.94 ± 0.04 -0.79 ± 0.04 -0.17 ± 0.06	-0.77(-0.91,-0.64) -0.62 (-0.76,-0.48)	<.0001 <.0001
DIA3009 (52) Add-on to metform	Cana 300 mg Cana 100 mg Glimepiride ↑6/8 mg	474 478 473	7.79 ± 0.04 7.78 ± 0.04 7.83 ± 0.04	-0.93 ± 0.04 -0.82 ± 0.04 -0.82 ± 0.04	-0.12 (-0.22, -0.02) -0.01 (-0.11, 0.09)	0.0158 0.8074
Add-on to Dual Combination AHA Therapy						
DIA3002 (26) + metformin + sulfonylurea	Cana 300 mg Cana 100 mg Placebo	152 155 150	8.13 ± 0.08 8.13 ± 0.07 8.12 ± 0.07	-1.06 ± 0.08 -0.85 ± 0.08 -0.13 ± 0.08	-0.92 (-1.11, -0.73) -0.71 (-0.90, -0.52)	<.0001 <.0001
DIA3012 (26) + metformin	Cana 300 mg Cana 100 mg	112 113	7.84 ± 0.09 7.99 ± 0.09	-1.03 ± 0.07 -0.89 ± 0.07	-0.76 (-0.95, -0.57) -0.62 (-0.81, -0.44)	<.0001 <.0001

+ pioglitazone	Placebo	114	8.00 ± 0.09	-0.26 ± 0.07		
DIA3015 (52) + metformin + sulfonylurea	Cana 300 mg Sitagliptin 100mg	365 374	8.13 ± 0.05 8.12 ± 0.05	-0.66 ± 0.05 -1.03 ± 0.05	-0.37 (-0.50, -0.25)	<.0001
Special Population						
DIA3010 (26)[1] older adults	Cana 300 mg Cana 100 mg Placebo	229 239 232	7.69 ± 0.05 7.77 ± 0.05 7.76 ± 0.05	-0.73 ± 0.06 -0.60 ± 0.06 -0.03 ± 0.06	-0.70 (-0.84, -0.57) -0.57 (-0.71, -0.44)	<.0001 <.0001
DIA3004 (26)[2] Moderate renal impairment	Cana 300 mg Cana 100 mg Placebo	89 88 87	7.97 ± 0.09 7.89 ± 0.10 8.02 ± 0.10	-0.44 ± 0.09 -0.32 ± 0.09 -0.03 ± 0.09	-0.42 (-0.65, -0.19) -0.29 (-0.53, -0.06)	0.0004 0.0131
DIA3008 (18) Sulphonylurea substudy[3]	Cana 300 mg Cana 100 mg Placebo	39 40 40	8.28 ± 0.16 8.29 ± 0.13 8.49 ± 0.18	-0.79 ± 0.15 -0.70 ± 0.15 0.04 ± 0.15	-0.83 (-1.24, -0.42) -0.74 (-1.14, -0.33)	0.0001 0.0005
DIA3008 (18) Insulin substudy[2]	Cana 300 mg Cana 100 mg Placebo	572 551 545	8.27 ± 0.04 8.34 ± 0.04 8.24 ± 0.04	-0.72 ± 0.03 -0.63 ± 0.03 0.02 ± 0.03	-0.74 (-0.82, -0.65) -0.65 (-0.74, -0.56)	<.0001 <.0001

[1] ≥55 to ≤80 years of age [2] eGFR ≥ 30 to <50 mL/min/1.73 m^2
[3] population 1 [4] population 2

Canagliflozin 300 mg and 100 mg demonstrated significant efficacy in all placebo comparisons. Both doses of canagliflozin were non-inferior to glimepiride and sitagliptin when using a non-inferiority margin of 0.3%. Placebo-subtracted change from baseline in HbA1c was -0.91 and -1.16 for the 100 and 300 mg doses, respectively, when used as monotherapy. When added to other anti-diabetic medications the treatment difference ranged from -0.62 to -0.92. Canagliflozin 300 mg demonstrated superiority to glimepiride (Study 3009) and to sitagliptin 100 mg (Study 3015) at 52 weeks.

Canagliflozin 300 mg demonstrated numerically greater point estimate changes than canagliflozin 100 mg on HbA1c (0.1% to 0.25% depending on population studied) in all studies.

Canagliflozin demonstrated modest efficacy in subjects with moderate renal impairment (Study 3004[2]-Dr. Liu's review, page 34-35).

Table 7.2 Primary Efficacy Results in DIA3004

Endpoint	**Placebo**		**Canagliflozin** 100 mg		**Canagliflozin** 300 mg	
HbA1c (%)	n		n		n	
Baseline mean ± SE	87	8.02 ± 0.10	88	7.89 ± 0.10	89	7.97 ± 0.09
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	87	-0.03 ± 0.09	88	-0.33 ± 0.09	89	-0.44 ± 0.09
MMRM	85	-0.10 ± 0.08	84	-0.33 ± 0.08	85	-0.48 ± 0.08

[2] GFR ≥30 and <50 mL/min/1.73m^2

PP* (by sponsor)	63	-0.16 ± 0.10	67	-0.32 ± 0.10	77	-0.48 ± 0.09
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-0.30 (-0.53, -0.07)		-0.40 (-0.63, -0.17)
MMRM				-0.23 (-0.44, -0.02)		-0.38 0.58, -0.17)
PP* (by sponsor)				-0.17 (-0.42, 0.09)		-0.33 (-0.57, -0.08)
Patients (%) achieving HbA1c <7[1,2]		8 (11%)		15 (20%)		21 (25%)
LOCF[1]		10 (13%)		18 (24%)		23 (28%)
sponsor's results (LOCF) [3]		15 (17%)		24 (27%)		29 (33%)

Integrated analysis of efficacy results from subjects with moderate renal impairment was performed across several trials to allow for a larger database and further stratification of efficacy based on GFR (Dr. Parks' review, page 9).

Table 7.3. Integrated Analysis of HbA1c Reduction in Patients with Moderated Renal Impairment

HbA1c (%)	**Placebo**		**Canagliflozin** 100 mg		**Canagliflozin** 300 mg	
eGFR ≥30 to 60 mL/min/1.73 m^2	n		n		n	
Baseline mean ± SE	356	7.98 ± 0.05	326	8.09 ± 0.05	354	8.07 ± 0.05
Adj. Mean Change from baseline±SE						
LOCF *(by sponsor)	356	-0.14 ± 0.06	326	-0.52 ± 0.06	354	-0.62 ± 0.06
PP	289	-0.32 ± 0.06	285	-0.63 ± 0.06	309	-0.72 ± 0.06
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-0.38 (-0.50, -0.26)		-0.47 (-0.60, -0.35)
PP				-0.31 (-0.44, -0.18)		-0.40 (-0.53, -0.28)
eGFR < 45 mL/min/1.73 m^2	n		n		n	
Baseline mean ± SE	108	8.10 ± 0.09	118	8.08 ± 0.09	122	8.10 ± 0.08
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	108	0.05 ± 0.19	118	-0.18 ± 0.19	122	-0.34 ± 0.19
PP	85	-0.48 ± 0.25	92	-0.76 ± 0.26	106	-0.84 ± 0.26
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-0.23 (-0.45, -0.01)		-0.39 (-0.61, -0.17)
PP				-0.28 (-0.53, -0.03)		-0.36 (-0.61, -0.12)
eGFR ≥ 45 mL/min/1.73 m^2	n		n		n	
Baseline mean ± SE	248	7.98 ± 0.06	208	8.11 ± 0.06	232	8.10 ± 0.06
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	248	-0.10 ± 0.07	208	-0.57 ± 0.07	232	-0.62 ± 0.07
PP ok	204	-0.28 ± 0.07	193	-0.61 ± 0.07	203	-0.72 ± 0.07
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-0.47 (-0.61, -0.32)		-0.52 (-0.66, -0.38)
PP				-0.34 (-0.49, -0.18)		-0.44 (-0.59, -0.29)

This analysis demonstrates that as GFR decreases, so to do reductions in HbA1c with placebo-subtracted reductions in HbA1c of approximately 0.5% for subjects with GFR ≥ 45 to < 60

mL/min/1.73m^2 and placebo-subtracted mean reduction of 0.2 to 0.4% for subjects with eGFR ≥30 to < 45 mL/min/1.73m^2. These results will need to be viewed in the context of any potential safety issues in these populations.

To provide information on the efficacy of canagliflozin in a larger group of T2DM subjects with moderate renal impairment, a population of subjects with a baseline eGFR of ≥30 to <60 mL/min/1.73m^2 were examined (Dr. Liu's review, page 41-42).

Table 3.2.5.1. Results for Canagliflozin (300 mg and 100 mg) in Patients with Type 2 Diabetes with Moderate Renal Impairment (eGFR ≥30 to <60 mL/min) (mITT/LOCF)

HbA1c (%)	**Placebo**		**Canagliflozin** 100 mg		**Canagliflozin** 300 mg	
eGFR ≥30 to 60 mL/min/1.73 m^2	n		n		n	
Baseline mean ± SE	356	7.98 ± 0.05	326	8.09 ± 0.05	354	8.07 ± 0.05
Adj. Mean Change from baseline±SE						
LOCF *(by sponsor)	356	-0.14 ± 0.06	326	-0.52 ± 0.06	354	-0.62 ± 0.06
PP	289	-0.32 ± 0.06	285	-0.63 ± 0.06	309	-0.72 ± 0.06
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-0.38 (-0.50, -0.26)		-0.47 (-0.60, -0.35)
PP				-0.31 (-0.44, -0.18)		-0.40 (-0.53, -0.28)
eGFR < 45 mL/min/1.73 m^2	n		n		n	
Baseline mean ± SE	108	8.10 ± 0.09	118	8.08 ± 0.09	122	8.10 ± 0.08
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	108	0.05 ± 0.19	118	-0.18 ± 0.19	122	-0.34 ± 0.19
PP	85	-0.48 ± 0.25	92	-0.76 ± 0.26	106	-0.84 ± 0.26
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-0.23 (-0.45, -0.01)		-0.39 (-0.61, -0.17)
PP				-0.28 (-0.53, -0.03)		-0.36 (-0.61, -0.12)
eGFR ≥ 45 mL/min/1.73 m^2	n		n		n	
Baseline mean ± SE	248	7.98 ± 0.06	208	8.11 ± 0.06	232	8.10 ± 0.06
Adj. Mean Change from baseline±SE						
LOCF* (by sponsor)	248	-0.10 ± 0.07	208	-0.57 ± 0.07	232	-0.62 ± 0.07
PP ok	204	-0.28 ± 0.07	193	-0.61 ± 0.07	203	-0.72 ± 0.07
Cana−P, adjusted LS Mean (95% CI)						
LOCF* (by sponsor)				-0.47 (-0.61, -0.32)		-0.52 (-0.66, -0.38)
PP				-0.34 (-0.49, -0.18)		-0.44 (-0.59, -0.29)

* This reviewer obtained the same results as the sponsor

These findings, which include data from Studies DIA3004, DIA3005, DIA3008 and DIA3010, were similar to the findings of DIA3004 alone.

A variety of secondary endpoints were also evaluated as documented in other reviews. Some of interest includes end of study body weight, systolic blood pressure (SBP) and change in fasting serum lipid parameters. There are numerical changes in body weight and SBP favoring canagliflozin, usually dose related, in the studies.

Dr. Kwon has a nice summary of the efficacy results (Page 62-63):

The largest HbA1c reduction associated with canagliflozin was seen 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)*

As discussed above, canagliflozin 300 mg and 100 mg demonstrated statistically significant changes in HbA1c from placebo in a variety of different patient populations. There was a dose-response mean reduction in HbA1c of 0.1% to 0.25% depending upon the population studied. Canagliflozin 300 mg demonstrated non-inferiority and statistical superiority to sitagliptin and glimepiride in the populations studied. Efficacy decreased with decreasing renal function. Important secondary endpoints supported the findings in the primary endpoint. There were dose-related numerical decreases in weight[3] and blood pressure[4] in all studies favoring canagliflozin therapy.

Safety

The main safety issues to consider are CV safety[5], renal safety, bone effects, osmotic diuresis and potential for resultant dehydration. Canagliflozin also increases urinary glucose excretion

[3] 0.4-3.3% placebo adjusted percent reduction depending upon the trial with some dose response. Dual X-ray absortiometry and computed tomography suggest weight loss was predominantly due to fat mass loss both from visceral and subcutaneous compartments.
[4] 0.1-8 mm Hg depending on trial and dose. There was some dose response.
[5] While Canagloflozin use is associated with decreased weight and BP, it is also associated with increase in LDL of -2 to +8.5% for the 100 mg dose and +2.8 to +12% for the 300 mg dose.

with resultant increases in urinary tract infections, a known effect that I will not discuss further.

Cardiovascular Safety

All non-insulin diabetic drugs seeking approval for use in T2DM are required to undergo evaluation to demonstrate that they do not increase CV risks. Canagliflozin use is associated with decreases in weight and blood pressure which if there are not other off-target effects could be viewed, at the very least, as effects that would not increase the risk for cardiovascular events. However, canagliflozin use is associated with increases in pooled placebo-adjusted LS mean LDL of 5.7% and 9.3% with the 100 mg and 300 mg doses, respectively.

The sponsor evaluated CV safety through a meta-analysis of 9 randomized, controlled trials. These trials included an interim analysis from a dedicated cardiovascular outcomes trial (CVOT) known as CANVAS. The data from CANVAS was unblinded by the sponsor and presented at the Advisory Committee Meeting and as I will discuss below brings up issues of whether CANVAS can continue and be relied upon for further evaluation of CV risk. Canvas had a total sample size of 4330 subjects, with 1442, 1445 and 1443 subjects assigned to placebo, canagliflozin 100 mg and canagliflozin 300 mg, respectively.[6] The primary safety endpoint was major adverse cardiovascular events plus (MACE plus; CV death, non-fatal MI, non-fatal stroke and hospitalizations due to unstable angina =201 events). There were 130 MACE-plus events in the canagliflozin treatment group and 71 MACE-plus events in the comparator group. CANVAS contributed 108 and 53 (≈80%) of these events in the canagliflozin and comparator groups, respectively. Below are the results in tables taken from Dr. Andraca-Carrera's review (Page 3, 4-5).

Table 1. Primary and Secondary Analyses of MACE-plus

	Canagliflozin (events / N)	Comparators (events / N)	Hazard Ratio (95% CI)
Primary Analysis (including all 9 trials)	**130 / 6396**	**71 / 3327**	**0.91 (0.68, 1.21)**[7]
Secondary Analyses			
First 30 Days in CANVAS	13 / 2886	1 / 1441	6.49 (0.85, 49.64)
After first 30 Days in CANVAS	95 / 2867	52 / 1435	0.89 (0.64, 1.25)
Non-CANVAS trials	22 / 3510	18 / 1886	0.64 (0.34, 1.19)

Source: Created by reviewer. Dataset: adttecv.xpt

[6] Inclusion criteria: men or women with a diagnosis of T2DM, HbA1c levels ≥7% and ≤10.5% at screening, either (1) not on antihyperglycemic agent (AHA) therapy or (2) on AHA monotherapy or combination therapy with any approved agent, history or high risk of CV disease defined as either (1) age ≥ 30 with documented symptomatic atherosclerotic CV disease or (2) age ≥ 50 with 2 or more risk factors for CV disease

[7] The 99.9% confidence interval to rule out 1.3 for the interim analysis is 0.56, 1.48).

Table 2. Components of MACE-plus in All Trials in the Meta-analysis

	Canagliflozin N= 6396	Comparators N = 3327	Hazard Ratio (95% CI)
MACE	104	53	0.98 (0.70, 1.36)
CV Death	21	16	0.65 (0.34, 1.24)
MI	45	27	0.83 (0.51, 1.34)
Stroke	47	16	1.46 (0.83, 2.58)
Hospitalized unstable angina	26	18	0.71 (0.39, 1.30)

Source: Created by reviewer. Dataset: adttecv.xpt

As the first table above demonstrates, the upper bound of the 95% confidence interval is below the risk margin of 1.8 necessary for adequate CV safety to allow marketing (for this specific issue). As noted above, there was an imbalance of MACE-plus events in the first 30 days not favoring canagliflozin in the total database and in CANVAS itself, but not in the meta-analysis when excluding CANVAS. Although at the Advisory Committee (AC) meeting, some panel members proposed possible biologically explanations as to why this may be a real finding, others felt this likely due to chance. The 30 day results are based on 14 events (canagliflozin 100 mg-7 events, canagliflozin 300 mg-6 events), recognizing the approximate 2:1 randomization[8] so there are essentially 7 events to 1. The small number of events, lack of dose-response, sensitivity of hazard ratio to small changes in the number of events in the comparator arm[9], and fewer events in the comparator arm than would be anticipated based on the overall rate make interpretation of the validity of this result (real vs. chance) difficult if not impossible. This certainly was not a sustained finding as results from further exposure did not demonstrate CV harm, and we have not found a specific population based on the 14 events that seems at greater risk of harm.[10]

The estimated hazard ratio and 95% confidence interval for MACE is 0.98 (0.70, 1.36) also demonstrating no evidence of increased risk associated with canagliflozin. Noted above is that stroke has a point estimate of 1.46 and is the only component of MACE with a point estimate that is not less than one. The estimated hazard ratio and 95% confidence interval for the primary endpoint MACE-plus and MACE associated with canagliflozin in the 8 trials excluding CANVAS was 0.64 (0.34, 1.19) and 0.63 (0.32, 1.25), respectively. However, CANVAS was a dedicated study which may give more validity to the cardiovascular findings if they are in conflict with the meta-analysis. It is interesting to note that the imbalance for stroke noted above in the overall meta-analysis is not present in the analysis of CANVAS by itself as noted in the table below from Dr. Parks' review (Page 17).

[8] Canaglizozin N=6396 (6876 pt-yrs), comparator N=3327 (3470 pt-yrs).

[9] Expected number of comparator events was 3.76 during first 30 days. 1and 3 additional events in the comparator arm would result in hazard ratio and 95% CI of 3.25 (0.73, 14.38) and 1.62 (0.53, 4.97) respectively

[10] The first post-randomization visit was scheduled for 12-weeks and there was no systematic planned within trial assessment at one month . Those with the early events did not have distinguishing features to identify a subpopulation, or particular reaction to the medication (dehydration, hypoglycemia) that may lend credibility to this being a real finding. Mean age, sex HbA1c levels, baseline eGFR, LDL-C, BMI, previous history of CV disease, CV risk factors, Diabetes >/=10 years, SBP >140 mmHg and micro-albuminuria were all similar in those with events within and after 30 days.

Table 18. Number of Events (Rate per 1000 Patient-Years) in CANVAS after Day 30

	Canagliflozin N=2867 PY = 3175	Comparators N = 1435 PY = 1546	Hazard Ratio (95% CI)
MACE-plus	**95 (29.9)**	**52 (33.6)**	**0.89 (0.64, 1.25)**
MACE	75 (23.6)	37 (23.9)	0.99 (0.67, 1.47)
CV Death	18 (5.7)	14 (9.1)	0.63 (0.31, 1.26)
MI	33 (10.4)	13 (8.4)	1.24 (0.65, 2.35)
Stroke	31 (9.8)	15 (9.7)	1.01 (0.55, 1.87)
Hospitalized unstable angina	20 (6.3)	15 (9.7)	0.65 (0.33, 1.27)

Source: Created by reviewer. Dataset: adttecv.xpt

It is also interesting to note the contradiction between CV death and MI and MI between the meta-analysis and CANVAS. All of the various disparate results noted between meta-analysis and comparison to CANVAS illustrate the need for complete data from a dedicated trial.

The sponsor plans to exclude a risk margin of 1.3 after 500 and 700 MACE-plus events in the canagliflozin development program through a meta-analysis of several disparate trials. This will not be acceptable from the standpoint that the 1.3 risk margin should be evaluated from what would essentially be considered a stand-alone trial. Therefore, the events used in the final evaluation should come solely from CANVAS or something similar. Additionally, MACE-plus will not be an acceptable primary endpoint. While we have been willing to accept some discretion in the choice of endpoint for 1.8 in the interest of not unduly delaying access to effective drugs, for the 1.3 goalpost we want more certainty that 'truth' is being represented. We are concerned that the further evaluations stray from more objective criteria of strict MACE (CV death, non-fatal MI, non-fatal stroke), the more 'noise' is introduced into the evaluation which may bias results toward non-inferiority. Therefore, we have been requiring strict MACE as the endpoint in CVOT trials to demonstrate a risk margin less than 1.3 which would allow continued marketing.

The CV information above is adequate to demonstrate safety that would allow marketing for this specific issue. However, unblinding of the CVOT and public disclosure of interim results brings up a number of issues that must be grappled with regarding whether the unblinding could affect the conduct of the trial so as to invalidate final results. While there is much concern that investigator or participant behaviors could be affected such that bias may be introduced (initial favorable results may drive those on study to seek off-study drug, unfavorable results may cause unbalanced withdrawal from study corrupting evaluation arms), there also are not many (or perhaps any) examples to validate these concerns. Things that may make unblinding less concerning are that the CVOT was fully enrolled at the time of public disclosure and the point estimate for MACE was essentially unity. In reality, it will not truly be known what, if any, impact the public disclosure had unless the trial is finalized and the database fully reviewed.

In order for the sponsor to fully comply with a completed CVOT analysis fulfilling the 1.3 upper bound margin that will allow continued marketing, they will need to have a stand-alone trial, not a meta-analysis of many disparate trials. The analysis showing an upper bound of 1.3 will also need to be based on strict MACE, and not MACE+. This may be accomplished by

performing a new trial[11], or perhaps by expanding enrollment of CANVAS[12] (although this may carry more risk than performing a new trial).

The sponsor has proposed, (b) (4)

Bone Safety

Nonclinical studies in rats with canagliflozin, as well as SGLT-2 inhibitors, have shown hypersostosis, increased urinary calcium excretion, decreased PTH and 1,25-OH Vit D, and increases in bone turnover markers thought to be due to carbohydrate malabsorption from the intestine of animals (effect of SGLT-1 inhibition). Nonclinical studies in which fructose was substituted for glucose did not show similar effects of drug on calcium absorption, bone accretion rates or turnover markers. Findings from the clinical evaluation of bone safety have not replicated the observations in the nonclinical program as there were no significant changes in calcium levels, PTH, or vitamin D levels. Fractures observed in clinical trials were evaluated in multiple ways with the only difference noted between canagliflozin and comparators being numerically higher fractures of low trauma in the upper limb between canagliflozin and comparators. The sponsor is conducting a 104-week trial (DIA3010) to further evaluate any potential risk.

Renal Safety

Canagliflozin has been associated with dose-dependent decrease in eGFR. Subjects with different baseline renal function have different patterns of decreased eGFR as those with normal to mild renal function (eGFR 30 to 60 mL/min/1.73m^2, median eGFR of 86 mL/min/1.73m^2) have a nadir in eGFR early that recovers towards baseline over time. Subjects with moderate renal function (median eGFR of 76 mL/min/1.73m^2) have an early decrease in eGFR that appears to persist over time, or at least never quite resolves during the duration of the trials. While the sponsor has put forth that these changes in GFR are the result of volume depletion as a result of the diuretic effect of canagliflozin, this has not been proven and, at least in those with greater renal compromise, GFR does not always return to baseline[13]

[11] Although it is not clear that if there is publicity surrounding an interim analysis such that it corrupts an ongoing trial, that a new trial would be successful as the publicity may also affect its enrollment. Additionally, there does seem to be wasted effort in stopping an ongoing trial that has ≈25%-30% of necessary events when it is unclear if the trial will be corrupted or not.

[12] Expanding enrollment allows for a timely answer to the question. With present enrollment, (b) (4) events will probably be after yea (b) (4) However, expanding enrollment will bring in the concern of whether the new subjects are different in some way from the existing trial subjects.

[13] At least for the length of the trials where this was evaluated which was usually 26 weeks.

as volume status stabilizes. These results have to be viewed under the context that as renal function declines, so does efficacy of canagliflozin.

Because of canagliflozin action as an osmotic diuretic, increases in urinary output may lead to volume contraction and volume-related events. The incidence of osmotic diuresis did not appear to be dose-dependent whereas the incidence of volume depletion appeared to be dose-dependent with elderly (≥75 years) subjects with low baseline renal function (<60 mL/min/1.73m^2) using loop diuretics at greatest risk.

To evaluate the effect of canagliflozin on GFR, baseline renal function in the impaired range was stratified according to two categories: GFR ≥45 to 60 mL/min/1.73m^2 and GFR ≥30 to 45 mL/min/1.73m^2. The mean reduction in GFR from baseline was between 1 and 5 ml/min/1.73 m^2 depending upon dose for the group whose GFR at baseline was 45-60 mL/min/1.73m^2.[14] An inconsistent pattern is demonstrated for the group whose baseline GFR was ≥30 to 45 mL/min/1.73m^2, likely due to a smaller sample size, but the absolute decrease appears to be approximately the same as that of the GFR > 45 to 60 mL/min/1.73m2 group , which based on a lower initial GFR represents a greater percentage of functional decrease.

Categorical changes based on GFR are presented in the table below from Dr. Parks' review (Page 24).

Table 8.2 Change in eGFR by Baseline Renal Status; n (%) from DS3

	Control	Cana 100	Cana 300
> 60 ml/kg/1.73 m2			
>30% decrease (any value)	162/2739 (5.9%)	146/2643 (5.5%)	225/2583 (8.7%)
>30% decrease (last value)	67 (2739 (2.4%)	57/2643 (2.2%)	84/2583 (3.3%)
>50% decrease (any value)	16/2739 (0.6%)	14/2643 (0.5%)	23/2583 (0.9%)
>50% decrease (last value)	6/2739 (0.2%)	1/2643 (<0.1%)	9/2583 (0.3%)
45-60 ml/kg/1.73 m2			
>30% decrease (any value)	21/300 (7%)	23/252 (9.1%)	34/255 (13.3%)
>30% decrease (last value)	6/300 (2.0%)	9/252 (3.6%)	13/255 (5.1%)
>50% decrease (any value)	0	4/252 (1.6%)	0
>50% decrease (last value)	0	1/252 (0.4%)	0
30-45 ml/kg/1.73 m2			
>30% decrease (any value)	12/114 (10.5%)	24/121 (19.8%)	27/123 (22%)

[14] Based on data from DIA3008.

>30% decrease (last value)	6/114 (5.3%)	9/121 (7.4%)	9/123 (7.3%)
>50% decrease (any value)	0	2/121 (1.7%)	4/123 (3.3%)
>50% decrease (last value)	0	1/121 (0.8%)	0

Source: Applicant's 3/15/13 response to FDA information request

The results above demonstrate again that as GFR decrease, categorical increases in >30% decreases occur.

As there is a lingering question regarding the effect of canagliflozin on renal function, and given the marginal meaningful benefit in those with renal function <45 ml/kg/1.73 m^2, it seems reasonable to exclude this group from therapy. In those with GFR ≥45 to 60 mL/min/1.73m^2 canagliflozin does have efficacy, but also seems to have dose related decreases in GFR. Therefore, given the small amount of efficacy between doses, it would be reasonable to limit the dose in this group to 100 mg a day.

Advisory Committee Meeting

An advisory committee meeting was held on January 10, 2013. Most of the discussion pertained to the assessment of CV safety, renal safety. As noted before, panel members discussed the potential for CV disadvantage for the first 30 days of use but there wasn't consensus with views ranging from chance finding to potential biologic plausibility. Concern was voiced whether the disclosure of the interim results of CANVAS would invalidate the final results.

Discussions regarding renal safety were focused on whether there should be limitations placed on use in those with moderate to severe renal function due to the safety findings and waning efficacy.

The panel members voted 10 to 5 on the question, "*Based on the information included in the briefing materials and presentations today, has the applicant provided sufficient efficacy and safety data to support marketing of canagliflozin for the treatment of Type 2 diabetes mellitus?*"

Conclusions and Recommendations

Canagliflozin has demonstrated efficacy for the 300 and 100 mg per day dose in the overall population with an indication of a small increase of mean effect with increased dose. As renal function decreases, so too does the efficacy such that the effect for those with GFR <45 mL/min/1.73m^2 is marginal. There also seems to be increasing adverse effect with increasing dose.

There are lingering questions regarding canagliflozin's effect on renal function, which seems the most pronounced in those with GFR <45 mL/min/1.73m^2 such that these patients should

not receive therapy until more is known. Because of the possible dose-effect on GFR, those patients with GFR 45-60 mL/min/1.73m2 should not exceed 100 mg per day. Also, since there seems to be dose-related adverse events and a marginal increased in mean efficacy with higher doses, the starting dose should be 100 mg per day in all subjects with dose escalation for those that require more intensive therapy (with the exceptions for those with renal compromise as discussed above).

The sponsor will have to complete the PMRs as noted in other reviews and with agreed upon labeling I recommend an approval action.

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

/s/

CURTIS J ROSEBRAUGH
03/29/2013