INVOKANA® (canagliflozin) – Medicaid Testimony – P&T Committee Meeting

Submitted to Montana by Janssen Scientific Affairs, LLC

CURRENT INDICATIONS

INVOKANA (canagliflozin) is indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (T2DM), to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in adults with type 2 diabetes mellitus and established cardiovascular disease (CVD), to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria > 300 mg/day.[1]

BOXED WARNING: LOWER LIMB AMPUTATION: (*See full prescribing information for complete boxed warning)* In patients with type 2 diabetes who have established cardiovascular disease (CVD) or at risk for CVD, INVOKANA® has been associated with lower limb amputations, most frequently of the toe and midfoot; some also involved the leg. Before initiating, consider factors that may increase the risk of amputation. Monitor patients receiving INVOKANA® for infections or ulcers of the lower limbs, and discontinue if these occur.[1]

KEY PRESCRIBING INFORMATION UPDATES

The INVOKANA® Prescribing Information has been updated. The revision date is January 2020. Recent key updates include the following[1]:

- BOXED WARNING: the "approximately 2-fold" increase in amputation observed in the CANVAS program was changed to the annualized incidence rates for CANVAS and CANVAS-R for more precise presentation of the risk observed in the CANVAS program
- **New indication based on CREDENCE study**: to reduce the risk of end-stage kidney disease (ESKD), doubling of serum creatinine, cardiovascular (CV) death, and hospitalization for heart failure in adults with type 2 diabetes mellitus and diabetic nephropathy with albuminuria > 300 mg/day

CLINICAL DATA

CREDENCE (**C**anagliflozin and **R**enal **E**vents in **D**iabetes with **E**stablished **N**ephropathy **C**linical **E**valuation), was a randomized, double-blind, PBO-controlled, parallel group multicenter, event driven clinical trial to assess the effects of canagliflozin (100 mg) compared to PBO on clinically important renal outcomes in people with T2DM and established CKD (estimated glomerular filtration rate [eGFR] 30 to <90 mL/min/1.73m^2) and albuminuria (ratio of albumin to creatinine >300 to 5000 mg/g), who were receiving a stable, maximum tolerated labelled dose (for ≥4 weeks prior to randomization) of an angiotensin converting enzyme inhibitor (ACEi) or angiotensin II receptor blocker (ARB).[2, 3 4, 5]

Select Inclusion Criteria[2, 4]

- ≥30 years of age with CKD in the setting of T2DM (HbA1c ≥6.5% to ≤12.0%; participants in Germany required a HbA1c range of ≥6.5% to <10.5%).
- Estimated glomerular filtration rate (eGFR) ≥30 to <90 mL/min/1.73m^2
  - Prespecified to enroll ~60% with stage 3 CKD (eGFR 30 to <60 mL/min/1.73 m^2)
  - eGFR was calculated using the CKD-EPI formula
- Albuminuria (urine albumin:creatinine ratio [UACR] >300 mg/g and ≤5000 mg/g)
- On a stable, maximum tolerated labelled daily dose of an ACEi or ARB for ≥4 weeks prior to randomization.

Select Exclusion Criteria[2],[4]

- Type 1 diabetes, nondiabetic kidney disease, History (Hx) of kidney disease treated with immunosuppression, Hx of treatment with chronic dialysis or kidney transplantation, Hx of CV events within the previous 12 weeks or a history of New York Heart Association class IV heart failure at any time[4], Dual-agent treatment with an ACEi or an ARB, Use of a direct renin inhibitor or a mineralocorticoid receptor antagonist, Concomitant use of an sodium-glucose co-transporter 2 (SGLT2) inhibitor in the 12 weeks prior to randomization, current or past participation in another canagliflozin study, or known allergy, hypersensitivity, or intolerance to canagliflozin or excipients[4], Hx of atraumatic amputation within the 12 months prior to screening, or an active skin ulcer, osteomyelitis, gangrene, or critical ischemia of the lower extremity within 6 months of screening[4].

Outcomes[2, 4]

- The primary outcome was the composite of: ESKD (defined as chronic dialysis for ≥30 days, renal transplantation, or eGFR <15 mL/min/1.73m^2 sustained for ≥30 days), Doubling of serum creatinine from baseline average sustained for ≥30 days, Death due to renal or CV disease. Secondary outcomes were planned for sequential hierarchical testing. If canagliflozin was superior over PBO for reducing the risk of the primary efficacy endpoint, the treatment effects in the secondary endpoints would be tested subsequently. Statistical significance was required before testing the next hypothesis in the hierarchical test procedure.

Baseline Characteristics[2, 4, 5]

- A total of 4401 participants were randomized from 690 sites across 34 countries between March 2014 and May 2017 in the intention-to-treat (ITT) analysis set.
- Baseline characteristics were similar between the canagliflozin and PBO groups. These included a mean age of 63 years, 33.9% female participants, mean duration of T2DM of 15.8 years; mean HbA1c of 8.3%, mean eGFR of 56.2 mL/min/1.73m^2, median UACR of 927 mg/g[4].
  - In the total population, 50.4% had prior CV disease, 14.8% had a history of heart failure, and 5.3% had a history of amputation.
- Across both treatment groups, the mean exposure to study drug was 115 weeks.

Results

By July 2018, the number of confirmed primary endpoints to trigger the planned interim analysis had been accrued and the prespecified efficacy criteria for early cessation had been achieved. The independent data monitoring committee advised the Steering Committee to end the CREDENCE study early after a median follow-up duration of 2.62 years (range 0.02-4.53 years).[2] A total of 4361 (99.1%) of participants were followed until the study completion for clinical and safety endpoints. Final vital status was collected in 99.9% of participants.[2] The most frequent reason for study discontinuation was an AE (12% and 13% of canagliflozin and PBO groups, respectively). [2]

Primary Composite Outcome

- In the CREDENCE study, canagliflozin significantly reduced the rates of the composite outcome of ESKD, dSCr, or renal or CV death (43.2 and 61.2 per 1000 PY in the canagliflozin and PBO arms, respectively), resulting in a 30% relative risk reduction (RRR) (hazard ratio [HR], 0.70; 95% confidence interval (CI), 0.59–0.82; P=0.00001; NNT=22 over 2.5 years for the primary composite endpoint). [2]
  - The effects were consistent across regions and all prespecified subgroups. [2]
  - For additional information, see Table: Summary of Efficacy Results.

Summary of Efficacy Results[2]

	EVRT/1000 PY (n/N)		HR (95% CI)	P value
	CANA (N=2202)	PBO (N=2199)		
Primary composite outcome (ESKD, dSCr, or renal or CV death	43.2 (245)	61.2 (340)	0.70 (0.59-0.82)	0.00001
dSCr	20.7 (118)	33.8 (188)	0.60 (0.48-0.76)	<0.001
ESKD	20.4 (116)	29.4 (165)	0.68 (0.54-0.86)	0.002
eGFR <15 mL/min/1.73 m^2	13.6 (78)	22.2 (125)	0.60 (0.45-0.80)	–
Dialysis initiated or kidney transplantation	13.3 (76)	17.7 (100)	0.74 (0.55-1.00)	–
Renal death	0.3 (2)	0.9 (5)	–†	–†
CV death	19.0 (110)	24.4 (140)	0.78 (0.61-1.00)	0.0502
Prespecified secondary outcomes				
HHF or CV death	31.5 (179)	45.4 (253)	0.69 (0.57-0.83)	<0.001
CV death, nonfatal MI, or nonfatal stroke	38.7 (217)	48.7 (269)	0.80 (0.67-0.95)	0.01
HHF	15.7 (89)	25.3 (141)	0.61 (0.47-0.81)	<0.001
ESKD, dSCr, or renal death	27.0 (153)	40.4 (224)	0.66 (0.53-0.81)	<0.001
CV death	19.0 (110)	24.4 (140)	0.78 (0.61-1.00)	0.0502
All-cause mortality	29.0 (168)	35.0 (201)	0.83 (0.68-1.02)	–*
CV composite (CV death, nonfatal MI, nonfatal stroke, HHF, and hospitalized UA)	49.4 (273)	67.0 (361)	0.74 (0.63-0.86)	–*
Exploratory outcomes				
ESKD, renal death, or CV death *(prespecified)*	37.6 (214)	51.2 (287)	0.73 (0.61-0.87)	–*
Dialysis, kidney transplantation or renal death *(post hoc)*	13.6 (78)	18.6 (105)	0.72 (0.54-0.97)	–*

CANA, canagliflozin; CV, cardiovascular; dSCr, doubling of serum creatinine; ESKD, end-stage kidney disease; EVRT, event rate; HR, hazard ratio; HHF, hospitalized heart failure; MI, myocardial infarction; PBO, placebo; PY, patient years; UA, unstable angina

*These outcomes were not formally tested.

†Hazard ratios and 95% CIs were calculated for outcomes with >10 events.

Safety Outcomes

The overall rates of AEs, serious AEs, and events of osmotic diuresis, volume depletion, hypoglycemia, urinary tract infection, hypersensitivity/cutaneous reaction, hepatic injury photosensitivity, and venous thromboembolism were similar between the treatment groups.[2] In addition, there was no imbalance observed in the risk of lower limb amputation between the canagliflozin vs PBO arms (12.3 vs 11.2 per 1000 PY; HR 1.11; 95% CI: 0.79-1.56).[2] Rates of fracture were similar between the canagliflozin and PBO treatment arms (11.8 vs 12.1 per 1000 PY; HR 0.98; 95% CI: 0.70-1.37).[2] Diabetic ketoacidosis rates were low overall, but higher in participants treated with canagliflozin (2.2 vs 0.2 events per 1000 PY; HR 10.8; 95% CI 1.39-83.65).[2]

CHIEF-HF

The Janssen Pharmaceutical Companies of Johnson & Johnson announced, on November 16, 2019, the launch of the next evolution of digital clinical trial design with CHIEF-HF (**C**anagliflozin: Impact on **H**ealth Status, Quali**t**y of Life and **F**unctional Status in **H**eart **F**ailure), the first decentralized, mobile, indication-seeking clinical study. The trial is estimated to begin February 2020 with an estimated completion date of February 2021.[6, 7]

CHIEF-HF is a randomized, double-blind, placebo-controlled, parallel group, interventional, superiority study, which will examine the use of canagliflozin 100 mg compared to placebo on quality of life improvement scales, in participants with symptomatic heart failure with either preserved or reduced ejection fraction heart failure with or without type 2 diabetes (T2D).

CHIEF-HF will enroll an estimated 1900 adults aged 18 years or older who have clinically stable symptomatic HF with a baseline Kansas City Cardiomyopathy Questionnaire-Total Symptom Score (KCCQ-TSS) score of >40 and <80 who will be stratified based on their ejection fraction (HFrEF or HFpEF) as recorded at study entry. Clinically stable symptomatic HF with reduced ejection fraction [HFrEF] is defined as: (a) ejection fraction (EF) < 40%; or (b) a primary diagnosis of HF or 2 outpatient visits for HF in the past 1 year. Clinically stable HF with preserved ejection fraction [HFpEF]) is defined as: (a) EF > 40%; or (b) a primary diagnosis of HF or 2 outpatient visits for HF; or (c) on a loop diuretic in the past 1 year. Participants will be recruited by investigators at large integrated delivery networks (IDN) using data systems (such as electronic patient records), email and smartphone, to screen, identify, and onboard potential study participants. To be enrolled, participants must possess and have sole use of a smartphone compatible with a Fitbit® device and be willing to wear the device on a regular basis for the duration of the study.

The primary outcome for the study will be the change from baseline in KCCQ-TSS to week 12. Secondary outcomes include change in total daily step count from baseline to week 12 and change from baseline in eight individual KCCQ domain scores to week 12.

REFERENCES

1. INVOKANA (canagliflozin) [Prescribing Information]. Titusville, NJ: Janssen Pharmaceuticals, Inc; https://imedicalknowledge.veevavault.com/ui/approved_viewer?token=7994-7a0de53e-b334-4268-9c97-f34348dad65c.
2. Perkovic V, Jardine MJ, Neal B, et al. Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *NEJM*. 2019;380(24):2295-2306. doi:10.1056/NEJMoa1811744.
3. Wheeler DC, Bakris G, Jardine MJ, et al. CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation). Symposium presented at the ISN World Congress of Nephrology (WCN); 15 April 2019; Melbourne, Australia. Available at: http://www.georgeinstitute.org/sites/default/files/credence-trial-results.pptx. Webcast available at https://www.youtube.com/watch?v=gZC6PSN7Jt8. 2019.
4. Perkovic V, Jardine MJ, Neal B et al., et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy: Protocol and Statistical Analysis Plan. *NEJM* 2019;380:2295-2306.
5. Perkovic V, Jardine MJ, Neal B et al, et al. Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy: Supplementary Appendix. *NEJM*. 2019;380:2295-2306.
6. Janssen Leverages Wearable Technology to Reimagine Clinical Trial Design [press release]. https://www.janssen.com/us/sites/www_janssen_com_usa/files/janssen_leverages_wearable_technology_to_reimagine_clinical_trial_design_0.pdf2019.
7. Janssen Research & Development LLC. A study on the impact of canagliflozin on health status, quality of life, and functional status in heart failure (CHIEF-HF). In: ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2020- [cited 2020 February 12]. Available from: https://clinicaltrials.gov/ct2/show/study/NCT04252287?term=chief-hf&draw=2&rank=1.