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INVOKANA® (canagliflozin) Significantly Reduces the Risk of Renal Failure in Patients with Type 2 Diabetes and Chronic Kidney Disease in the Landmark Phase 3 CREDENCE Study

- *INVOKANA® is the only medicine in nearly 20 years and the first diabetes medicine to demonstrate significant reduction in risk of renal failure, dialysis or kidney transplantation, and renal or CV death in this high-risk patient population*
- *In the study, INVOKANA® significantly reduced the combined risk of cardiovascular death, myocardial infarction, and stroke, and demonstrated no imbalance in amputation or bone fracture*

MELBOURNE, Australia, April 15, 2019 – The Janssen Pharmaceutical Companies of Johnson & Johnson announced new results from the Phase 3 CREDENCE study, showing that INVOKANA® (canagliflozin) demonstrated a 30 per cent reduction in the risk of the primary composite endpoint, comprised of progression to end-stage kidney disease (ESKD), defined as the need for renal replacement therapy (RRT) such as chronic dialysis or renal transplant; doubling of serum creatinine, a key predictor of ESKD; and renal or cardiovascular (CV) death. The landmark study evaluated the efficacy and safety of INVOKANA® versus placebo in patients with chronic kidney disease (CKD) and type 2 diabetes (T2D) when used in addition to standard of care. Study results also showed INVOKANA® reduced the risk of the secondary cardiovascular endpoints, including the risk of CV death and hospitalization for heart failure by 31 per cent, major adverse CV events (MACE; composite of nonfatal myocardial infarction (MI), nonfatal stroke and CV death) by 20 per cent, and the risk of hospitalization for heart failure alone by 39 per cent. Importantly, the study showed no imbalance in amputation or bone fracture. Additionally, no new safety concerns were identified in this study of high-risk patients.

The data were presented during a late-breaking clinical trial session at the International Society of Nephrology (ISN) 2019 World Congress of Nephrology (WCN) in Melbourne, Australia, and simultaneously published in *The New England Journal of Medicine.*

"Canagliflozin is the first medical breakthrough in nearly twenty years proven to slow the progression of chronic kidney disease in patients with diabetes at high risk of developing kidney failure," said Vlado Perkovic[i], M.B.B.S, Ph.D., F.A.S.N., F.R.A.C.P., CREDENCE Steering Committee co-chair, Executive Director, The George Institute for Global Health, Australia and Professor of Medicine, UNSW Sydney. "These impressive results from the CREDENCE study have significant clinical implications for preventing kidney failure and improving health for millions of people living with chronic kidney disease and type 2 diabetes."

"Diabetes is the leading cause of kidney disease in Canada with up to 50 per cent of people with diabetes experiencing signs of kidney impairment. If left untreated, it will progress and lead to kidney failure where dialysis or transplant may be necessary," said Adeera Levin[ii], M.D., F.R.C.P.C., F.A.C.P., C.M., CREDENCE National Lead Investigator for Canada, Head, Division of Nephrology, Professor of Medicine, University of British Columbia and Executive Director, BC Provincial Renal Agency. "CREDENCE is the first dedicated renal outcomes study of any SGLT2 inhibitor in patients with chronic kidney disease and type 2 diabetes. The results acknowledge the significant protection that canagliflozin provides in preventing kidney failure in this high-risk patient population."

The Phase 3 CREDENCE (**C**anagliflozin and **R**enal **E**vents in **D**iabetes with **E**stablished **N**ephropathy **C**linical **E**valuation, NCT02065791) clinical trial was a randomized, double-blind, event-driven, placebo-controlled, parallel-group, 2-arm, multicenter study. It evaluated 4,401 patients with T2D, Stage 2 or 3 CKD (defined as an estimated glomerular filtration rate (eGFR) of ≥30 to <90 mL/min/1.73 m^2), and macroalbuminuria (defined as urinary albumin-to-creatinine ratio (ACR) >300 to ≤5,000 mg/g), who were receiving standard of care including the maximum labeled or tolerated daily dose of an angiotensin-converting enzyme inhibitor (ACEi) or angiotensin receptor blocker (ARB). There were 24 clinical sites in Canada.

"At Janssen, we tackle some of the world's most challenging and burdensome diseases, both by exploring the ability of our established medicines to meet unmet patient needs and by

leveraging the cutting edge of science to develop entirely new medicines," said Mathai Mammen, M.D., Ph.D., Global Head, Janssen Research & Development, Johnson & Johnson. "The CREDENCE clinical trial results demonstrate our commitment to helping patients, and bring us one step closer to treating the comorbidities associated with type 2 diabetes and meeting the unmet needs of the millions of people living with chronic kidney disease."

Study Results

In the CREDENCE study, INVOKANA® showed a 30 per cent reduction in the risk of the primary composite endpoint – comprised of progression to doubling of serum creatinine, ESKD, and renal or CV death (HR: 0.70; 95% CI: 0.59 to 0.82; p<0.0001). These findings were consistent across the individual components of the primary composite endpoint, as well as across all 15 prespecified subgroups tested. INVOKANA® reduced the risk of end-stage kidney disease by 32 per cent (HR: 0.68; 95% CI: 0.54 to 0.86; p=0.0015).

Further, INVOKANA® showed a 20 per cent reduction in the risk of the secondary endpoints of MACE, which is composed of nonfatal MI, nonfatal stroke, and CV death (HR: 0.80; 95% CI: 0.67 to 0.95; p=0.0121), a 31 per cent reduction in the risk of the composite of CV death and hospitalization for heart failure (HR: 0.69; 95% CI: 0.57 to 0.83; p=0.0001), and a 39 per cent reduction in the risk of hospitalization for heart failure alone (HR: 0.61; 95% CI: 0.47 to 0.80; p=0.0003).

The incidence rates of adverse events and serious adverse events were numerically lower for patients treated with INVOKANA® as compared to placebo. There were no observed differences in the incidence of amputations (HR: 1.11; 95% CI: 0.79 to 1.56) or adjudicated fractures (HR: 0.98; 95% CI: 0.70 to 1.37).

At this time, INVOKANA®, which is currently indicated in Canada to improve glycemic control in adult patients with T2D and to reduce the risk of major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction and nonfatal stroke) in patients with T2D and established CV disease, is contraindicated in renally impaired patients with eGFR less than 45 mL/min/1.73 m2, end stage renal disease or patients on dialysis. In addition, INVOKANA® should not be initiated in patients with an eGFR <60 mL/min/1.73 m2, and should be discontinued when eGFR is below 45 mL/min/1.73 m2. Please see the Important Safety Information below and the full Product Monograph for additional details.

WHAT IS INVOKANA®?

INVOKANA® is a prescription medicine used along with diet and exercise:

- to improve blood sugar levels in adults with type 2 diabetes
- to lower the risk of major cardiovascular events such as nonfatal heart attack, nonfatal stroke, or risk of dying from events related to the heart or blood vessels (CV death) in adults with type 2 diabetes and an increased cardiovascular risk (health problems due to the heart or blood vessels).

IMPORTANT SAFETY INFORMATION

INVOKANA® can cause serious side effects, including:

- **Diabetic Ketoacidosis (DKA). DKA is a serious and life-threatening condition that requires urgent hospitalization. DKA has been reported in patients with type 2 diabetes mellitus (T2DM), with normal or high blood sugar levels, who are treated with INVOKANA® and other sodium-glucose co-transporter 2 (SGLT2) inhibitors. Some cases of DKA have led to death.** Seek medical attention right away and stop taking INVOKANA® immediately if you have any of the following symptoms (even if your blood sugar levels are normal): difficulty breathing, nausea, vomiting, stomach pain, loss of appetite, confusion, feeling very thirsty, feeling unusually tired, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat.
- **Lower Limb Amputations. INVOKANA® may increase your risk of lower-limb amputations. Amputations mainly involve removal of the toe or part of the foot; however, amputations involving the leg, below and above the knee, have also occurred. Some people had more than one amputation, some on both sides of the body.** Seek medical attention if you have new pain or tenderness, any sores, ulcers, or infections in your leg or foot. Your doctor may decide to stop your INVOKANA® for a while if you have any of these signs or symptoms. Talk to your doctor about proper foot care and keeping hydrated.

Do not take INVOKANA® if you:

- are allergic (hypersensitive) to canagliflozin or any of the nonmedicinal ingredients.
- have type 1 diabetes (a disease in which your body does not produce any insulin).
- have diabetic ketoacidosis (DKA, a complication of diabetes) or a history of DKA.
- have severe kidney problems or you are on dialysis.
- are under 18 years of age

Talk to your doctor if you experience these common side effects when taking INVOKANA®, including:

- **Low blood sugar (hypoglycemia)** when used with sulfonylurea (such as glimepiride, gliclazide, and glyburide) or insulin. The symptoms of low blood sugar include blurred vision, tingling lips, trembling, sweating, pale looking, a change in mood or feeling anxious or confused.
- **Vaginal yeast infection.** Women who take INVOKANA® may get vaginal yeast infections. Symptoms include: vaginal odor, white or yellowish vaginal discharge and/or vaginal itching
- **Yeast infection of the penis (balanitis or balanoposthitis).** Men who take INVOKANA® may get a yeast infection of the skin around the penis. Symptoms include: redness, itching, or swelling of the penis; rash of the penis; foul-smelling discharge from the penis; or pain in the skin around penis

- **Urinary Tract Infection.** Symptoms include burning sensation when urinating, cloudy urine, strong odor.
- Additional side effects include changes in urination such as urinating more often or in larger amounts, an urgent need to urinate, and a need to urinate at night, constipation, nausea and feeling thirsty.

Before you take INVOKANA®, tell your doctor if you have an increased chance of developing DKA, including if you are dehydrated or suffer from excessive vomiting, diarrhea, or sweating; are on a very low carbohydrate diet; drink a lot of alcohol; have/have had problems with your pancreas, including pancreatitis or surgery on your pancreas; are hospitalized for major surgery, serious infection or serious medical illnesses; have a history of diabetic ketoacidosis (DKA).

Before you take INVOKANA®, tell your doctor if you have a history of amputation; heart disease or are at risk for heart disease; blocked or narrowed blood vessels (usually in leg); damage to the nerves (neuropathy) of your leg; diabetic foot ulcers or sores; lower limb infection, are dehydrated.

Before you take INVOKANA®, tell your doctor if you have kidney problems; liver problems; heart problems, have or have had low blood pressure (hypotension), often get urinary tract infections; are on a low sodium (salt) diet; are going to have surgery; are eating less due to illness, surgery, or change in diet; pancreas problems; drink alcohol very often (or drink a lot of alcohol in short-term)

Tell your doctor if you are or plan to become pregnant, are breastfeeding, or plan to breastfeed. INVOKANA® may harm your unborn baby. Do not breastfeed while taking INVOKANA®.

Tell your doctor about all the medicines you take, **including prescription and non-prescription medicines, vitamins, and herbal supplements**.

- Especially tell your doctor if you take diuretics (water pills), such as furosemide; or taking medicines to lower your blood pressure such as angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers (ARB) Taking INVOKANA® with any of these medicines may increase the risk of becoming dehydrated and/or low blood pressure (hypotension).
- Or are taking medicines to lower your blood sugar such as glyburide, gliclazide or glimepiride (sulfonylureas) or insulin. Taking INVOKANA® with any of these medicines can increase the risk of having low blood sugar (hypoglycemia).
- Or are taking medicines used to treat pain and reduce inflammation and fever knowns as NSAIDs (nonsteroidal anti-inflammatory drugs). Taking INVOKANA® with these medicines can increase the risk for kidney problems.
- Or if you are taking digoxin.

Broken Bones (fractures): Bone fractures have been seen in patients taking INVOKANA®. Talk to your doctor about factors that may increase your risk of bone fracture.

Please click here for the Product Monograph.

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About Janssen Cardiovascular & Metabolism

In Cardiovascular & Metabolism (CVM), we take on the most pervasive diseases that burden hundreds of millions of people and healthcare systems around the world. As part of this long-standing commitment and propelled by our successes in treating type 2 diabetes (T2D) and thrombosis, we advance highly differentiated therapies that prevent and treat life-threatening cardiovascular, metabolic and retinal diseases. Uncovering new therapies that can improve the quality of life for this large segment of the population is an important endeavor – one which Janssen CVM will continue to lead in the years to come. Our mission is global, and local and personal. Together, we can reshape the future of cardiovascular, metabolic and retinal disease prevention and treatment. Please visit www.janssen.com/cardiovascular-and-metabolism.

About the Janssen Pharmaceutical Companies of Johnson & Johnson

At Janssen, we're creating a future where disease is a thing of the past. We're the Pharmaceutical Companies of Johnson & Johnson, working tirelessly to make that future a reality for patients everywhere by fighting sickness with science, improving access with ingenuity, and healing hopelessness with heart. We focus on areas of medicine where we can make the biggest difference: Cardiovascular & Metabolism, Immunology, Infectious Diseases & Vaccines, Neuroscience, Oncology, and Pulmonary Hypertension.

Learn more at www.janssen.com/Canada. Follow us at www.twitter.com/JanssenCanada. Janssen Inc. is one of the Janssen Pharmaceutical Companies of Johnson & Johnson.

Cautions Concerning Forward-Looking Statements

This press release contains "forward-looking statements" as defined in the Private Securities Litigation Reform Act of 1995 regarding potential benefits and further development of canagliflozin. The reader is cautioned not to rely on these forward-looking statements. These statements are based on current expectations of future events. If underlying assumptions prove inaccurate or known or unknown risks or uncertainties materialize, actual results could vary materially from the expectations and projections of Janssen Research & Development, LLC, any of the other Janssen Pharmaceutical companies, and/or Johnson & Johnson. Risks and uncertainties include, but are not limited to: challenges and uncertainties inherent in product research and development, including the uncertainty of clinical success and of obtaining regulatory approvals; uncertainty of commercial success; manufacturing difficulties and delays; competition, including technological advances, new products and patents attained by competitors; challenges to patents; product efficacy or

safety concerns resulting in product recalls or regulatory action; changes in behavior and spending patterns of purchasers of health care products and services; changes to applicable laws and regulations, including global health care reforms; and trends toward health care cost containment. A further list and descriptions of these risks, uncertainties and other factors can be found in Johnson & Johnson's Annual Report on Form 10-K for the fiscal year ended December 30, 2018, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in the company's most recently filed Quarterly Report on Form 10-Q, and the company's subsequent filings with the Securities and Exchange Commission. Copies of these filings are available online at www.sec.gov, www.jnj.com or on request from Johnson & Johnson. None of the Janssen Pharmaceutical Companies nor Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

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[i] Dr. Vlado Perkovic worked directly with Janssen R&D and was compensated for his work on the CREDENCE study.

[ii] Dr. Levin was not compensated for any media work. She is a member of the steering committee for CREDENCE. She also has an advisory role for which she received compensation.