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 cardiovascular 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**
- **The CREDENCE study was halted early for positive efficacy findings and served as the basis for Janssen’s March 2019 filing of a supplemental New Drug Application to the U.S. Food and Drug Administration (FDA) for INVOKANA®**

**MELBOURNE, Australia, April 14, 2019** – The Janssen Pharmaceutical Companies of Johnson & Johnson announced today new results from the Phase 3 CREDENCE study, showing that INVOKANA® (canagliflozin) demonstrated a 30 percent 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 CV endpoints, including the risk of CV death.
and hospitalization for heart failure by 31 percent, major adverse CV events (MACE; composite of nonfatal myocardial infarction [MI], nonfatal stroke and CV death) by 20 percent, and the risk of hospitalization for heart failure alone by 39 percent. 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 today during a late-breaking clinical trials 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, 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 failure for millions of people worldwide, and this clear need for a new treatment option was the motivation for initiating the CREDENCE study. Today, we are pleased to share study results that potentially could establish INVOKANA® as the only medicine to safely reduce the risk of renal failure in this high-risk patient population when added to current standard of care,” said James List, M.D., Ph.D., Global Therapeutic Area Head, Cardiovascular & Metabolism, Janssen Research & Development, LLC. “We are working closely with the U.S. FDA and health authorities worldwide to bring this important medicine to those living with these life-threatening conditions.”

The Phase 3 CREDENCE (Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation, 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 m²), and macroalbuminuria (defined as urinary albumin-to-creatinine ratio (ACR) >300 to ≤5,000 mg/g), who were receiving
standard of care including a maximum tolerated labeled daily dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs).

“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.”

In March 2019, Janssen included the CREDENCE data in the submission of a supplemental New Drug Application to the U.S. FDA for INVOKANA® to reduce the risk of ESKD, the doubling of serum creatinine, and renal or CV death for adults with CKD and T2D. This followed an Independent Data Monitoring Committee meeting in July 2018, where the committee recommended that the CREDENCE trial stop early because it met the prespecified criteria for efficacy. If this new indication is approved, INVOKANA® would be the first diabetes medication to treat both T2D and CKD, and could be an important new treatment option for the millions of patients around the world who live with these illnesses.

**Study Results**

In the CREDENCE study, INVOKANA® showed a 30 percent 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 percent (HR: 0.68; 95% CI: 0.54 to 0.86; p=0.0015).

Furthermore, INVOKANA® showed a 20 percent 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 percent 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 percent 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 for the treatment of glycemia in patients with T2D and the reduction in MACE in patients with T2D and established CV disease, is contraindicated for patients with severe renal impairment (eGFR <30 mL/min/1.73 m²), ESKD, or patients on dialysis. In addition, INVOKANA® is not recommended when eGFR is persistently less than 45 mL/min/1.73 m². Please see the Important Safety Information below and the full Prescribing Information for additional details.

**WHAT IS INVOKANA®?**

INVOKANA® is a prescription medicine used:
- along with diet and exercise to lower blood sugar (glucose) in adults with type 2 diabetes
- to reduce the risk of major cardiovascular events such as heart attack, stroke, or death in adults with type 2 diabetes who have known cardiovascular disease.

INVOKANA® is not for people with type 1 diabetes or with diabetic ketoacidosis (increased ketones in blood or urine). It is not known if INVOKANA® is safe and effective in children under 18 years of age.

**IMPORTANT SAFETY INFORMATION**

INVOKANA® can cause important side effects, including:

- **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. You may be at a higher risk of lower-limb amputation if you: have a history of amputation, have heart disease or are at risk for heart disease, have had blocked or narrowed blood vessels (usually in leg), have damage to the nerves (neuropathy) in the leg, or have had diabetic foot ulcers or sores. **Call your doctor right away 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

- **Dehydration.** INVOKANA® can cause some people to become dehydrated (the loss of too much body water), which may cause you to feel dizzy, faint, lightheaded, or weak, especially when you stand up (orthostatic hypotension). You may be at higher risk of dehydration if you have low blood pressure, take medicines to lower your blood pressure (including diuretics [water
Vaginal yeast infection. Women who take INVOKANA® may get vaginal yeast infections. Symptoms include: vaginal odor, white or yellowish vaginal discharge (discharge may be lumpy or look like cottage cheese), 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.

Talk to your doctor about what to do if you get symptoms of a yeast infection of the vagina or penis.

Do not take INVOKANA® if you:
- are allergic to canagliflozin or any of the ingredients in INVOKANA®. Symptoms of allergic reaction may include: rash; raised red patches on your skin (hives); or swelling of the face, lips, tongue, and throat that may cause difficulty in breathing or swallowing
- have severe kidney problems or are on dialysis

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; kidney problems; liver problems; history of urinary tract infections or problems with urination; 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); ever had an allergic reaction to INVOKANA®; or have other medical conditions.

Tell your doctor if you are or plan to become pregnant, are breastfeeding, or plan to breastfeed. INVOKANA® may harm your unborn baby. If you become pregnant while taking INVOKANA®, tell your doctor right away. INVOKANA® may pass into your breast milk and may harm your 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), rifampin (used to treat or prevent tuberculosis), phenytoin or phenobarbital (used to control seizures), ritonavir (Norvir®, Kaletra® – used to treat HIV infection), or digoxin (Lanoxin®– used to treat heart problems).

Possible Side Effects of INVOKANA®

INVOKANA® may cause serious side effects, including:
- Ketoacidosis (increased ketones in your blood or urine). Ketoacidosis has happened in people who have type 1 or type 2 diabetes, during treatment with INVOKANA®. Ketoacidosis is a serious condition, which may need to be treated in a hospital. Ketoacidosis may lead to death. Ketoacidosis can happen with INVOKANA® even if your blood sugar is less than 250 mg/dL. Stop taking INVOKANA® and call your doctor right away if you get any of the following conditions.
**symptoms**: nausea, vomiting, stomach-area pain, tiredness, or trouble breathing

- **Kidney problems.** Sudden kidney injury has happened to people taking INVOKANA®. Talk to your doctor right away if you: 1) reduce the amount of food or liquid you drink, if you are sick, or cannot eat or 2) you start to lose liquids from your body from vomiting, diarrhea, or being in the sun too long

- **A high amount of potassium in your blood (hyperkalemia)**

- **Serious Urinary Tract Infections:** may lead to hospitalization and have happened in people taking INVOKANA®. Tell your doctor if you have signs or symptoms of a urinary tract infection such as: burning feeling while urinating, need to urinate often or right away, pain in the lower part of your stomach (pelvis), or blood in the urine. Some people may also have high fever, back pain, nausea, or vomiting

- **Low blood sugar (hypoglycemia).** If you take INVOKANA® with another medicine that can cause low blood sugar, such as a sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea medicine or insulin may need to be lowered while you take INVOKANA®

Signs and symptoms of low blood sugar may include: headache, drowsiness, weakness, dizziness, confusion, irritability, hunger, fast heartbeat, sweating, shaking, or feeling jittery.

- **A rare but serious bacterial infection that destroys the tissue under the skin (necrotizing fasciitis) in the area between and around the anus and genitals (perineum).** Necrotizing fasciitis of the perineum has happened in women and men who take INVOKANA®. Necrotizing fasciitis of the perineum may lead to hospitalization, may require multiple surgeries to remove affected tissues, and may lead to death. **Seek medical attention immediately if you have fever or you are feeling very weak, tired, or uncomfortable (malaise) and you develop any of the following symptoms in the area between and around your anus and genitals:** pain or tenderness, swelling, or redness of the skin (erythema).

**Serious allergic reaction.** If you have any symptoms of a serious allergic reaction, stop taking INVOKANA® and call your doctor right away or go to the nearest hospital emergency room.

**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.

The most common side effects of INVOKANA® include: vaginal yeast infections and yeast infections of the penis; changes in urination, including urgent need to urinate more often, in larger amounts, or at night.

Tell your doctor if you have any side effect that bothers you or that does not go away. Call your doctor for medical advice about side effects. You may report side effects to FDA at 1-800-FDA-1088. You may also report side effects to Janssen Scientific Affairs, LLC at 1-800-526-7736.

**Please click here for full Product Information, including Boxed Warning, and Medication Guide for INVOKANA®.**
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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, 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](http://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.


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