Media contacts:
Sarah Freeman
Mobile: (215) 510-4758
sfreem21@its.jnj.com

Jessica Castles Smith
Mobile: (732) 501-8181
jcastlsm@its.jnj.com

Investor contacts:
Johnson & Johnson
Christopher DelOrefice
Office: (732) 524-2955

Lesley Fishman
Office: (732) 524-3922

INVOKANA® (canagliflozin) Significantly Reduced Major Cardiovascular Events and Kidney Failure in Patients with Type 2 Diabetes and Chronic Kidney Disease in New CREDENCE Analysis

Protective effect observed in patients with and without known cardiovascular disease

Analysis builds on primary CREDENCE results, which were recently added to the American Diabetes Association's Standards of Medical Care in Diabetes

Primary results also served as the basis for a recent supplemental New Drug Application for INVOKANA®

SAN FRANCISCO, June 11, 2019 – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced results of a new subgroup analysis from the landmark phase 3 CREDENCE study, showing INVOKANA® (canagliflozin) significantly reduced the risk of major cardiovascular (CV) events and kidney failure in patients with type 2 diabetes (T2D) and chronic kidney disease (CKD). These positive results were observed in patients taking INVOKANA®, including those with CV risk factors but no history of CV disease (primary prevention group) and

patients with history of CV disease, defined as a history of coronary, cerebrovascular or peripheral vascular disease (secondary prevention group). Results were presented today at the American Diabetes Association's 79th Scientific Sessions.

"The CREDENCE study demonstrates canagliflozin's ability to manage some of the most common yet serious complications from T2D, including CV and kidney diseases," said study investigator Kenneth W. Mahaffey, M.D., Professor and Vice Chair of Clinical Research, Department of Medicine, Stanford University School of Medicine, and Director, Stanford Center for Clinical Research (SCCR), Stanford, Calif.[1] "We're particularly excited about this new analysis because it's the first time a type 2 diabetes medicine has shown a cardiovascular benefit in patients who did not have preexisting CV disease. This is an important, clinically meaningful finding as it uncovers the potential of canagliflozin to offer a protective effect in this patient population."

Published in *The New England Journal of Medicine* this past April, the Phase 3 CREDENCE study evaluated CV and renal outcomes in patients with T2D and CKD taking either INVOKANA® or placebo, in addition to standard of care. Results from the CREDENCE study were also recently added to the American Diabetes Association's *Standards of Medical Care in Diabetes*, which gives healthcare professionals the latest evidence-based recommendations to treat people with type 2 diabetes and chronic kidney disease.

For the new subgroup analysis being presented at ADA, CREDENCE researchers specifically examined CV and renal outcomes in the primary prevention group (n=2,181; 49.6%) and secondary prevention group (n=2,220; 50.4%). Compared to secondary prevention participants, primary prevention participants were younger (61.4 vs. 64.6 years) and more often female (36.6% vs. 31.3%), but with similar T2D duration (15.2 vs. 16.4 years).

[1] Dr. Kenneth Mahaffey worked directly with Janssen R&D and was compensated for his work on the CREDENCE study.

***Click to Tweet:* New #CREDENCE analysis shows significant reduction in #CV events and kidney failure in patients with T2D and chronic #kidneydisease #ADA2019 https://ctt.ec/rye7a+**

"About one in three people with type 2 diabetes have chronic kidney disease, which puts them at increased risk of kidney failure and negative cardiovascular outcomes,[i] like cardiovascular death, heart attack, stroke, and heart failure," said James List, M.D., Ph.D., Global Therapeutic Area Head, Cardiovascular & Metabolism, Janssen Research & Development, LLC. "With the results from our CREDENCE study, INVOKANA® is now poised to become the first therapy in nearly two decades for treating chronic kidney disease in people with type 2 diabetes, providing both kidney and cardiovascular protection."

CV Outcomes

The CV results from CREDENCE found INVOKANA® significantly reduced major CV events in the overall study population, with consistent results across all composite endpoints and individual components of the composite endpoints. Specifically, INVOKANA® reduced the risk of CV death, heart attack or stroke by 20 percent compared to placebo (9.9% vs. 12.2%; hazard ratio [HR]: 0.80; 95% confidence interval [CI]: 0.67 to 0.95; P=0.01). INVOKANA® also reduced the risk of CV death or hospitalization for heart failure by 31 percent (8.1% vs. 11.5%; HR: 0.69; 95% CI: 0.57 to 0.83; P<0.001) and hospitalization for heart failure by 39 percent (4.0% vs. 6.4%; HR: 0.61; 95% CI: 0.47 to 0.80; P<0.001). For the subgroup analysis, researchers found:

- CV results observed in the overall study population were consistent across the primary and secondary prevention groups, including all clinical subgroups and across groups defined by renal function.
- For CV death, heart attack and stroke, there was no evidence of heterogeneity between the primary and secondary prevention groups (p-interaction=0.25). Specifically, INVOKANA® reduced the risk of the composite of CV death, heart attack and stroke by 32 percent in the primary prevention group (HR: 0.68; 95% CI, 0.49 to 0.94) and 15 percent in the secondary

prevention group (HR: 0.85; 95% CI, 0.69 to 1.06).

Renal and Safety Outcomes

The renal results from CREDENCE found INVOKANA® demonstrated a 30 percent reduction in the risk of the primary composite endpoint – comprised of progression to doubling of serum creatinine, end-stage renal disease (ESKD), and renal or CV death (HR: 0.70; 95% CI: 0.59 to 0.82; P<0.0001) – with consistent results across individual components of the primary composite endpoint, as well as across all 15 prespecified subgroups examined. For the subgroup analysis, researchers found:

- Renal results observed in the overall study population were consistent across the primary and secondary prevention groups.
- Specifically, INVOKANA® reduced the risk of ESKD by 31 percent (HR: 0.69; 95% CI: 0.51 to 0.95; P-interaction: 0.89) and 33 percent (HR: 0.67; 95% CI: 0.47 to 0.96; P-interaction: 0.89) in the primary and secondary prevention groups, respectively.

In addition, CREDENCE found the incidence rates of adverse events and serious adverse events were numerically lower for patients treated with INVOKANA® as compared to placebo. For the subgroup analysis, safety outcomes were similar in both primary and secondary prevention groups. Of note, there was no difference in fracture risk or incidence of amputations in the primary and secondary prevention groups.

About CREDENCE

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, two-arm, multicenter study. It evaluated 4,401 patients from 34 countries with T2D and established stage 2 or 3 CKD who were receiving standard of care, which included a maximum tolerated labeled daily dose of angiotensin-converting enzyme (ACE) inhibitors or angiotensin II receptor blockers (ARBs). Patients were randomized in a 1:1 ratio and received either INVOKANA® 100 mg daily or matching placebo, with a

mean follow-up of 2.62 years.

In March 2019, Janssen submitted a supplemental New Drug Application to the U.S. Food and Drug Administration (FDA) for INVOKANA® to reduce the risk of end-stage kidney disease, the doubling of serum creatinine, and renal or CV death for adults with CKD and T2D, based on data from the CREDENCE study. The application was given a Priority Review, which FDA assigns to medicines that may offer significant improvements in the treatment, diagnosis or prevention of a serious condition. If this new indication is approved, INVOKANA® would be the first T2D medication to treat CKD, one of the most common and potentially life-threatening comorbidities associated with T2D.[i]

The FDA most recently approved an indication for INVOKANA® in October 2018 to reduce the risk of major adverse CV events, including heart attack, stroke or death due to a CV cause in adults with T2D who have established CV disease. INVOKANA® is also indicated to lower blood sugar in adults with T2D. INVOKANA® is contraindicated for patients with severe renal impairment (eGFR <30 mL/min/1.73 m^2), ESKD, or those on dialysis. In addition, INVOKANA® is not recommended when eGFR is persistently less than 45 mL/min/1.73 m^2.

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 pills]), are on a low sodium (salt) diet, have kidney problems, or are 65 years of age or older

- **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®

I**NVOKANA® 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 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 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.

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. Follow us at www.twitter.com/JanssenGlobal. Janssen Research & Development, LLC, 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 Janssen research in type 2 diabetes. 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] Bailey RA, Wang Y, Zhu V, Rupnow MF. Chronic kidney disease in US adults with type 2 diabetes: an updated national estimate of prevalence based on Kidney Disease: Improving Global Outcomes (KDIGO) staging. *BMC Research Note*s. 2014;7:415. doi:10.1186/1756-0500-7-415.