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INVOKANA® (canagliflozin) Significantly Improved Renal Outcomes and Demonstrated Potential Renal Protective Effects in Patients with Type 2 Diabetes Who Have or Are at Risk for Cardiovascular Disease

Late-breaking renal data from the integrated CANVAS Program presented at the American Society of Nephrology Kidney Week 2017 Annual Meeting

Raritan, N.J., and New Orleans, November 3, 2017 – Janssen Research & Development, LLC today announced additional analyses from the landmark CANVAS clinical trial program showing INVOKANA® (canagliflozin) improved renal outcomes and demonstrated potential renal protective effects in patients with type 2 diabetes mellitus (T2DM), who either have, or are at risk for, cardiovascular (CV) disease. These data were presented at the American Society of Nephrology (ASN) Kidney Week 2017 Annual Meeting on November 3, 2017 in New Orleans.

The renal analyses showed that compared to placebo, canagliflozin reduced the risk of kidney disease progression, including significantly reducing urinary albumin excretion and stabilizing estimated glomerular filtration rate (eGFR) over a study duration of more than six years:

- Canagliflozin reduced the rates of several pre-specified major renal composite endpoints by up to 47 percent, such as end-stage kidney disease (ESKD), doubled serum creatinine (dSCr) or renal death (95% CI: 33% to 84%).
- Urinary albumin excretion was 18 percent lower in all participants treated with canagliflozin compared with placebo (95% CI: 16% to 20%). It was 34 percent lower (95% CI: 29% to 38%) in participants with baseline microalbuminuria and 36 percent lower (95% CI: 28% to 43%) in those participants with baseline macroalbuminuria. Median urinary albumin to creatinine ratio (UACR) was 12.3 mg/g.
- Participants treated with canagliflozin experienced an initial fall in mean eGFR; thereafter, that rate gradually increased over the study duration (6.5 years). In

contrast, participants treated with placebo experienced a progressive decline in eGFR. Mean baseline eGFR was 76.5 mL/min/1.73 m².

- There was no increase in renal adverse events (serious or non-serious) compared to placebo, including acute kidney injury and hyperkalemia.

INVOKANA® demonstrated consistent improvement of renal outcomes across multiple composite endpoints that were independently confirmed by an Endpoints Adjudication Committee.

“Millions of people around the world suffer from diabetic kidney disease, which will affect nearly one-third of all type 2 diabetes patients and is the most common cause of kidney failure in most countries.¹ This underscores the need to identify new treatment options for these people who have not seen an innovation in the space in the last 20 years,” said Vlado Perkovic, M.B.B.S, Ph.D., F.A.S.N., F.R.A.C.P., Professor of Medicine, University of New South Wales Sydney, and Executive Director, The George Institute for Global Health. “New data from the CANVAS Program clearly indicate better renal outcomes for people treated with canagliflozin, and suggest that this agent protects kidney function, in addition to providing previously presented cardiovascular benefits.”

The CANVAS Program is the longest, largest and broadest completed CV outcomes program of any sodium glucose cotransporter 2 (SGLT2) inhibitor, to date, and was the first program to assess the efficacy, safety, and durability of canagliflozin in more than 10,000 patients with T2DM who had either a prior history of CV disease or at least two CV risk factors. The data from the integrated analysis of the CANVAS and CANVAS-R trials were presented earlier this year in a special symposium at the [American Diabetes Association 77th Scientific Sessions](#) on June 12 in San Diego, CA, and simultaneously published in the [New England Journal of Medicine](#). The results from the integrated analysis showed canagliflozin significantly reduced the combined risk of CV death, myocardial infarction (MI), and nonfatal stroke versus placebo in patients with T2DM at risk for, or with a history of, CV disease. Additional analysis revealed canagliflozin treatment was associated with a reduced risk for hospitalization for heart failure and demonstrated potential renal protective effects.

The ongoing, fully enrolled [CREDESCENCE](#) trial, the first dedicated SGLT2 inhibitor Phase 3 renal outcomes trial, is evaluating the effects of canagliflozin on renal outcomes in patients with T2DM and kidney disease.

No new adverse events were observed during this additional analysis than were previously reported from the CANVAS Program.

About the CANVAS Program

The CANVAS Program is composed of two nearly-identical large outcomes studies: CANVAS (CANagliflozin CardioVascular Assessment Study ([NCT01032629](#))) and CANVAS-R (Study of the Effects of Canagliflozin on Renal Endpoints in Adult Subjects with T2DM, ([NCT01989754](#))).

The CANVAS Program is the largest completed CV outcomes program of any SGLT2 inhibitor to date, with a total of 10,142 patients – 4,330 patients in CANVAS and 5,812 patients in CANVAS-R. In the randomized, placebo-controlled Phase 3/4 studies, a vast

majority of patients were obese, with a history of hypertension, 66 percent of patients had a history of CV disease (14 percent had a history of heart failure), and 34 percent of patients had at least two CV risk factors. The study assessed the safety of canagliflozin relative to placebo in patients receiving specific commonly-used diabetes agents. The primary endpoint was defined as major adverse CV events (MACE), composed of nonfatal MI, nonfatal stroke, and CV death, and the secondary endpoint was defined as progression of albuminuria, beta-cell function, eGFR changes and UACR.

In the CANVAS study, patients were randomly assigned in a 1:1:1 ratio to placebo, canagliflozin 100mg and canagliflozin 300mg. The mean and median exposure to investigational product was approximately 4.3 and 5.8 years, respectively. The mean and median follow-up time was 5.7 and 6.1 years, respectively.

In the CANVAS-R study, patients were randomly assigned in a 1:1 ratio to placebo or canagliflozin 100mg (with an investigator option to up-titrate to 300mg if the patient required additional glycemic control, provided the 100mg dosage was well tolerated). The mean and median exposure to investigational product was approximately 1.8 and 1.9 years, respectively. The mean and median follow-up time was 2.1 years.

These CANVAS and CANVAS-R studies were designed to be highly similar in patient population, procedures and assessments, evaluating the effects of canagliflozin on CV events in a similar study population. This approach is demonstrated in three published studies: "Rationale, design, and baseline characteristics of the Canagliflozin Cardiovascular Assessment Study (CANVAS)—A randomized placebo-controlled trial," published online by [American Heart Journal](#); "Rationale, design and baseline characteristics of the CANagliflozin cardioVascular Assessment Study—Renal (CANVAS-R): A randomized, placebo-controlled trial," published online by [Diabetes, Obesity and Metabolism](#); and "Optimizing the analysis strategy for the CANVAS Program – a pre-specified plan for the integrated analyses of the CANVAS and CANVAS-R trials," published online by [Diabetes, Obesity and Metabolism](#).

About INVOKANA®

In [March 2013](#), the U.S. FDA approved canagliflozin – INVOKANA® – as a single agent. In two studies comparing INVOKANA® plus metformin to current standard treatments plus metformin – one studying sitagliptinⁱⁱ and the other studying glimepirideⁱⁱⁱ – INVOKANA® dosed at 300 mg provided greater reductions in A1C levels and body weight than either comparator. In the two studies, the overall incidence of adverse events was similar with INVOKANA® and the comparators. INVOKANA® continues to be the number-one prescribed SGLT2 inhibitor. Since its launch, more than 16 million prescriptions have been written for INVOKANA® in the U.S. *

WHAT IS INVOKANA®?

INVOKANA® is a prescription medicine used along with diet and exercise to lower blood sugar in adults with type 2 diabetes. 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®. 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[®]

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 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.

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 see full [Product Information, including Boxed Warning](#), and [Medication Guide](#) for INVOKANA[®].

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About the Janssen Pharmaceutical Companies

At the Janssen Pharmaceutical Companies of Johnson & Johnson, we are working to create a world without disease. Transforming lives by finding new and better ways to prevent, intercept, treat and cure disease inspires us. We bring together the best minds and pursue the most promising science. We are Janssen. We collaborate with the world for the health of everyone in it. Learn more at www.janssen.com. Follow us at [@JanssenUS](https://twitter.com/JanssenUS).

Cautions Concerning Forward-Looking Statements

This press release contains “forward-looking statements” as defined in the Private Securities Litigation Reform Act of 1995 regarding the 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 January 1, 2017, including under “Item 1A. Risk Factors,” its most recently filed Quarterly Report on Form 10-Q, including under the caption “Cautionary Note Regarding Forward-Looking Statements,” 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. The Janssen

Pharmaceutical Companies and Johnson & Johnson do not undertake to update any forward-looking statement as a result of new information or future events or developments.

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**YTD TRx Volumes in 2017. IMS NPA weekly data through 10/20/17.*

ⁱ Gheith, O., Farouk, N., Nampoory, N., Halim, M. A., & Al-Otaibi, T. (2016). Diabetic kidney disease: world wide difference of prevalence and risk factors. Accesed November, 2017, <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5297507/>

ⁱⁱ Lavallo-Gonzalez F, Januszewicz A, Davidson J, et al. Efficacy and safety of canagliflozin compared with placebo and sitagliptin in patients with type 2 diabetes on background metformin monotherapy: a randomised trial. *Diabetologia*. 2013 Dec;56(12):2582-92.

ⁱⁱⁱ Cefalu T, Leiter L, Yoon K-H, Arias P, Niskanen L, Xie J, Balis D, Canovatchel W, Meininger G. Efficacy and safety of canagliflozin versus glimepiride in patients with type 2 diabetes inadequately controlled with metformin (CANTATA-SU): 52 week results from a randomised, double-blind, phase 3 non-inferiority trial. *Lancet*. 2013 Sep 14;382(9896):941-50.