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Real-World Study of More than 700,000 People with Type 2 Diabetes (T2D) Shows No Increased Risk of Below-Knee Lower Extremity Amputations with INVOKANA® (canagliflozin) Compared to Other Diabetes Medications

Results further characterize the safety and effectiveness of INVOKANA® in U.S. clinical practice

First head-to-head real-world study to evaluate safety data on amputation and hospitalization for heart failure among individual SGLT2i medicines

TITUSVILLE, NJ, and ORLANDO, FL, June 24, 2018 – The Janssen Pharmaceutical Companies of Johnson & Johnson today announced late-breaking results of a new real-world analysis of more than 700,000 U.S. T2D patients, which found no increased risk of below-knee lower extremity (BKLE) amputation with INVOKANA® (canagliflozin) compared to other sodium glucose cotransporter 2 inhibitors (SGLT2i) or non-SGLT2i anti-hyperglycemic medicines. In addition to the general T2D population, similar results were also seen in a sub-set of patients with T2D and established cardiovascular disease.

OBSERVE-4D is the largest, most comprehensive real-world observational study to evaluate the risk of BKLE amputation and hospitalization for heart failure (HHF) across anti-hyperglycemic therapies. Full findings from the late-breaking presentation were highlighted today in the American Diabetes Association's (ADA) 78th Official Press Program in Orlando, Florida and simultaneously published in *Diabetes, Obesity and*

Metabolism.

"We initiated OBSERVE-4D to better characterize the real-world use of INVOKANA® and the SGLT2i class, so physicians and their patients could make better informed treatment decisions," said Paul Burton, MD, PhD, FACC, Vice President, Medical Affairs, Janssen Scientific Affairs, LLC. "Prior to this analysis, no real-world study had evaluated head-to-head comparative evidence on amputation and hospitalization for heart failure across individual SGLT2i medicines."

Researchers observed no increased risks across the therapy comparisons for BKLE amputations in the general T2D population:

- INVOKANA® vs. all non-SGLT2i medicines: HR (95% CI): 0.75 (0.40, 1.41), p=0.30.
- INVOKANA® vs. other SGLT2i medicines: HR (95% CI): 1.14 (0.67, 1.93), p=0.53.
- Other SGLT2i medicines vs. all non-SGLT2i medicines: HR (95% CI): 0.84 (0.27, 2.55), p=0.68.

These amputation rates were also consistent in a sub-population with established cardiovascular disease:

- INVOKANA® vs. all non-SGLT2i medicines: HR (95% CI): 0.72 (0.34-1.51), p=0.29.
- INVOKANA® vs. other SGLT2i medicines: HR (95% CI): 1.08 (0.63-1.82), p=0.85.

"OBSERVE-4D depicts how INVOKANA® and other SGLT2is are being used by people with type 2 diabetes, including in those with established CV disease, in the real world," said John Buse, MD, PhD, Chief of the Division of Endocrinology and Director of the Diabetes Center, University of North Carolina School of Medicine, Chapel Hill, North Carolina. "The overall benefit-risk profile of SGLT2is is positive, and physicians should feel comfortable and confident in prescribing the class to their appropriate patients."

In addition to showing no significant imbalance of BKLE amputation, the study also identified a HHF reduction in the general T2D population that was consistent with rates seen in randomized clinical trials and other real-world evidence studies including the SGLT2i class. The HHF result is a positive confirmatory finding and supports the internal validity of the study results:

- INVOKANA® was associated with a 61 percent reduction in the risk of HHF compared to non-SGLT2i medicines: HR=0.39 (95% CI): 0.26, 0.60, p=0.01.
- Similar risk reductions were seen with INVOKANA® vs. other SGLT2i medicines: HR (CI) 0.90: 0.71, 1.13, p=0.28.

"The OBSERVE-4D findings are welcome news for patients and the physicians who treat them," said Ralph DeFronzo, MD, professor of medicine and chief of the Division of

Diabetes at UT Health. "These data reaffirm the confidence we've always had in the SGLT2i class."

SGLT2is, including INVOKANA®, are anti-hyperglycemic therapies prescribed for the treatment of T2D. Evidence was published last year from the CANVAS (CANagliflozin cardioVascular Assessment Study) Program, which was the first program to assess the efficacy, safety, and durability of INVOKANA® in more than 10,000 patients with T2D who had either a prior history of CV disease or at least two CV risk factors.

However, an increased risk of BKLE amputation was seen with INVOKANA® in the CANVAS Program and is reflected in its U.S. prescribing information.[1,2]

About OBSERVE-4D

The OBSERVE-4D analysis was based on data from four large U.S. medical claims databases, and included 714,582 adults with T2D across multiple categories: those who took INVOKANA® (142,800), other SGLT2i therapies (110,897, empagliflozin or dapagliflozin), or non-SGLT2i therapies (460,885), defined as any dipeptidyl peptidase-4 inhibitor (DPP-4i), glucagon-like peptide-1 (GLP-1) receptor agonist, or other anti-hyperglycemic agents (acarbose, bromocriptine, miglitol, nateglinide, and repaglinide).

Patients represented a diverse population covered by employer-sponsored plans, Medicare or Medicaid. The two primary outcomes were HHF and BKLE amputation. Patients in the different treatment groups were matched based on demographic and clinical characteristics, including the presence of other diseases and their associated mortality risks.

Investigators found similar results for HHF and BKLE amputation in a separate sub-group analysis of 215,633 patients who had established CV disease, representing 30 percent of the entire population from the four databases:

- Truven MarketScan® Commercial Claims and Encounters: Active employees, early retirees, and their dependents insured by employer-sponsored plans
- Truven MarketScan® Multi-state Medicaid: Medicaid enrollees from multiple states
- Truven MarketScan® Medicare Supplemental Beneficiaries: Medicare-eligible active and retired employees and their Medicare-eligible dependents from employer-sponsored supplemental plans
- OptumInsight's Clinformatics™ Datamart: Individuals fully insured in commercial plans or in administrative services only and commercial Medicare

To advance transparency and ensure open access for future research, the study protocol and all results are publicly available at: data.ohdsi.org/AhasHfBkleAmputation. Because of the volume and complexity of the analyses, the researchers created an

interactive matrix that allows other scientists to fully explore the data.

Real-World Study Limitations
Real-world data have the potential to supplement randomized controlled trial data by providing additional information about how a medicine performs in routine medical practice. However, they have limitations and cannot be used as stand-alone evidence to validate the efficacy or safety of a treatment.

OBSERVE-4D investigators also noted that although these results are derived from multiple large datasets reflecting current use in the United States, the number of patients with long-duration exposure (>6 months) and the study's power are limited. Further study will help to fully understand the issue.

WHAT IS INVOKANA®?
INVOKANA® (canagliflozin) 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. The recommended starting dose is 100 mg once daily, taken before the first meal of the day. The dose can be increased to 300 mg once daily in patients tolerating INVOKANA® 100 mg once daily who have an eGFR of 60 mL/min/1.73 m2 or greater and require additional glycemic control.

IMPORTANT SAFETY INFORMATION

INVOKANA® (canagliflozin) 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®
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 on Twitter at @JanssenUS. Janssen Pharmaceuticals, Inc. and Janssen Scientific Affairs, LLC are part 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 the potential benefits and further development of INVOKANA® (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 Scientific Affairs, 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 31, 2017, including in the sections captioned "Cautionary Note Regarding Forward-Looking Statements" and "Item 1A. Risk Factors," and in the company's subsequent Quarterly Reports on Form 10-Q, and other 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 or Johnson & Johnson undertakes to update any forward-looking statement as a result of new information or future events or developments.

[1] Neal B, Perkovic V, Mahaffey KW, et al. Canagliflozin and cardiovascular and renal events in type 2 diabetes. N Engl J Med. 2017;377(7):644-657.

[2] INVOKANA® (canagliflozin) U.S. Prescribing Information. Available at http://www.janssenlabels.com/package-insert/product-monograph/prescribing-information/INVOKANA-pi.pdf.

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