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New Real-World Analysis Shows INVOKANA® (canagliflozin) and Other SGLT2 Inhibitors Reduced the Risk of Death and Cardiovascular Events Compared to Other Diabetes Medicines

EASEL is the first real-world study to show adults with type 2 diabetes and established cardiovascular disease (CVD) have a lower risk of major adverse cardiovascular events (MACE) with SGLT2i therapy

TITUSVILLE, NJ, November 17, 2017 – A new real-world analysis of adults with type 2 diabetes and established cardiovascular disease (CVD) shows adult patients who initiated therapy with INVOKANA® (canagliflozin) or another sodium glucose cotransporter-2 inhibitor (SGLT2i) had a 43 percent reduced risk for all-cause mortality (ACM) and hospitalization for heart failure (HHF) after an average of 1.6 years, compared to similar patients who initiated treatment with a non-SGLT2i medication using an intent-to-treat (ITT) approach. Additionally, patients who initiated SGLT2i therapy had a 33 percent reduced risk of major adverse cardiovascular events (MACE), including ACM, non-fatal myocardial infarction (MI) and non-fatal stroke. This new retrospective analysis from the EASEL (Evidence for cArdiovascular outcomes with Sodium glucose co-transporter 2 inhibitors in the rEal worLd) study is based on data from the U.S. Department of Defense Military Health System and was published this week in *Circulation*.

"This is the first real-world study to demonstrate a lower risk of MACE in patients with type 2 diabetes and established CVD who were initiated on SGLT2i therapy," said Paul

Burton, MD, PhD, FACC, Vice President, Medical Affairs, Janssen. "These results further reinforce the positive effects of INVOKANA® and SGLT2is in cardiovascular risk reduction."

Study and Findings

The population-based EASEL study included two cohorts: 12,629 new users of a SGLT2i and 12,629 new users of a non-SGLT2i diabetes medication, both on top of standard-of-care therapy. The two cohorts were matched on propensity scores, with a model including various characteristics such as demographics, duration of diabetes, baseline comorbidities and medication use, diagnoses and procedures, and various health care resource utilization measures. In the SGLT2i cohort, canagliflozin, empagliflozin and dapagliflozin accounted for 58.1 percent, 26.4 percent and 15.5 percent of patients, respectively. The median follow-up for the two cohorts was 1.6 years based on the ITT approach.

The primary outcome was the composite of ACM and HHF. Several other CVD-related events were also assessed as secondary endpoints. The ITT analysis showed that the SGLT2i cohort had statistically significant reductions in the incidence of multiple endpoints compared to the non-SGLT2i cohort, respectively, including:

- 43 percent reduction in the composite outcome of ACM and HHF (primary endpoint): 1.73 vs. 3.01 events per 100-person-years; hazard ratio (HR) 0.57, 95 percent confidence interval (CI): 0.50-0.65; P < 0.0001.
- 43 percent reduction in ACM (secondary endpoint): 1.29 vs. 2.26 events per 100 person-years; HR 0.57, CI: 0.49-0.66; P <0.0001.
- 43 percent reduction in HHF (secondary endpoint): 0.51 vs. 0.90 events per 100 person-years; HR 0.57, CI: 0.45-0.73; P <0.0001.
- 33 percent reduction in MACE (secondary endpoint): 2.31 vs. 3.45 events per 100 person-years; HR 0.67, CI: 0.60-0.75; P <0.0001. The rate of the individual endpoints of nonfatal MI and nonfatal stroke were not significantly different between the two cohorts.
- 34 percent reduction in the composite of MACE and HHF (secondary endpoint): 2.72 vs. 4.11 events per 100 person-years; HR 0.66, CI: 0.60-0.74; P <0.0001.

The incidence rate of below-knee lower extremity amputation (BKA) in the SGLT2i cohort was relatively infrequent — approximately two-fold compared to the non-SGLT2i cohort: 35 vs. 18 events (0.17 vs. 0.09 events per 100 person-years, HR 1.99, CI: 1.12-3.51; P=0.018). It remains unclear whether the BKA risk extends across the SGLT2i class of medications as the study was not powered to make comparisons among individual treatments.

Of the approximately 30 million people living with diabetes in the United States, 90 to 95 percent have type 2 diabetes,[1] and are two to four times more likely to die from heart disease than those without diabetes.[2]

One of the largest public health insurance claims programs in the United States, the Department of Defense Military Health System (MHS) includes active or retired service members and their dependents, with close to 10 million patients actively receiving care. The database integrates all medical, clinical, pharmacy and administrative data for every eligible MHS beneficiary across the United States.

INVOKANA® (canagliflozin) is indicated as an adjunct to diet and exercise to lower blood sugar in adults with type 2 diabetes. It is not indicated to reduce the risk of ACM, HHF or MACE, which includes ACM, non-fatal MI and non-fatal stroke. The landmark CANVAS Program, the largest completed CV outcomes program to date, evaluated the cardiovascular safety and efficacy of canagliflozin relative to placebo in adults with type 2 diabetes who had either established CVD or were at risk for CVD. A supplemental new drug application (sNDA) based on data from the CANVAS Program was filed with the FDA on October 2, 2017.

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.

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 at @JanssenUS.

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[1] Centers for Disease Control and Prevention. National diabetes statistic report, 2017: estimates of diabetes in the United States. Atlanta, GA: U.S. Department of Health & Human Services, Centers for Disease Control and Prevention, 2017. Available at: https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. Accessed November 16, 2017.

[2] American Heart Association. Cardiovascular Disease & Diabetes. American Heart Association, 2017. Available at: http://www.heart.org/HEARTORG/Conditions/More/Diabetes/WhyDiabetesMatters/Cardiovascular-Disease-Diabetes_UCM_313865_Article.jsp#.WbawtvnyuUl. Accessed November 16, 2017.