New analysis shows cardiorenal risk reductions of Jardiance® are consistent in adults with type 2 diabetes, cardiovascular disease and kidney disease without overt proteinuria

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- Findings from an EMPA-REG OUTCOME® post-hoc analysis of adults with chronic kidney disease without overt proteinuria presented at American Diabetes Association's 79th Scientific Sessions®

RIDGEFIELD, Conn. and INDIANAPOLIS, June 10, 2019 /PRNewswire/ -- A new post-hoc analysis of data from the EMPA-REG OUTCOME® trial indicates a consistent effect of Jardiance® (empagliflozin) on reducing cardiovascular and renal risk in adults with type 2 diabetes and known cardiovascular disease, who also have a form of chronic kidney disease without overt proteinuria (high levels of protein in the urine), as well as others in the trial. The results were shared as an oral presentation on behalf of Boehringer Ingelheim and Eli Lilly and Company (NYSE: LLY) at the American Diabetes Association (ADA)'s 79th Scientific Sessions® on June 10 in San Francisco.

"We are pleased to share new research data from the landmark EMPA-REG OUTCOME trial, examining the effects of Jardiance in adults with type 2 diabetes who have an increasingly common, yet infrequently studied, form of chronic kidney disease," said Mohamed Eid, M.D., M.P.H., M.H.A., vice president, Clinical Development & Medical Affairs, Boehringer Ingelheim Pharmaceuticals, Inc. "The results support the need for additional studies aimed at addressing important unmet medical needs for people with various forms of kidney disease. To that end, we have initiated an outcomes trial, EMPA-KIDNEY, to investigate the effects of empagliflozin on cardiovascular death and the progression of kidney disease in a broad population of adults with chronic kidney disease."

Globally, more than 500 million people are affected by chronic kidney disease, up to 40 percent of whom have diabetes. Chronic kidney disease is typically accompanied by the presence of varying amounts of protein in the urine, known as proteinuria. The majority of people with chronic kidney disease, however, have normal to moderately increased urinary protein levels, rather than overt proteinuria. Kidney disease without overt proteinuria is becoming more common yet is rarely studied in clinical trials, despite the known increased risk for adverse outcomes.

In this new post-hoc analysis, the effect of Jardiance on reducing risk for cardiovascular and kidney outcomes was consistent between people in the EMPA-REG OUTCOME trial who had chronic kidney disease without overt proteinuria and all others in the trial. Outcomes examined included cardiovascular death, hospitalization for heart failure, new or worsening kidney disease, and the combination of cardiovascular death or hospitalization for heart failure, as well as safety outcomes of interest.

Furthermore, results from a separate post-hoc analysis recently presented at the ISN World Congress of Nephrology 2019, indicated that the effect of empagliflozin on the cardiorenal outcome* was consistent between people in the EMPA-REG OUTCOME trial who had proteinuric kidney disease and all others in the trial. Together, these post-hoc analyses suggest that the effect of empagliflozin on cardiorenal outcomes is consistent regardless of whether patients have proteinuric kidney disease or not.

"These new findings are just one part of a broad and comprehensive clinical development program that explores how Jardiance can improve patient health outcomes and fill therapeutic gaps to serve as a broad cardiometabolic treatment option," said Sherry Martin, M.D., vice president, Medical Affairs, Lilly. "We look forward to gathering additional information through results from EMPA-KIDNEY, which will examine the potential for empagliflozin to improve outcomes for people with chronic kidney disease, including those with and without proteinuria."

EMPA-KIDNEY (NCT03594110) will enroll approximately 5,000 adults with chronic kidney disease both with and without diabetes as well as with and without proteinuria. The trial is an academic collaboration that will be independently conducted, analyzed and reported by the Medical Research Council Population Health Research Unit at the University of Oxford (MRC PHRU), which is based in the Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU). Boehringer Ingelheim and Lilly will provide the funding for the study as part of their commitment to advancing treatments and pioneering research to address the public health challenges of cardiovascular, metabolic and kidney diseases beyond type 2 diabetes.

**Defined as end-stage kidney disease (initiation of maintenance renal replacement therapy or sustained eGFR <15 ml/min/1.73m^2), sustained doubling or creatinine, or renal/cardiovascular death.*

About EMPA-REG OUTCOME® (NCT01131676)
EMPA-REG OUTCOME was a long-term, multicenter, randomized, double-blind, placebo-controlled trial of more than 7,000 patients from 42 countries with type 2 diabetes and established cardiovascular disease over a median observation period of 3.1 years.

The study assessed the effect of Jardiance (10 mg or 25 mg once daily) added to standard of care compared with placebo added to standard of care. Standard of care was comprised of glucose-lowering agents and cardiovascular drugs (including for blood pressure and cholesterol). The primary endpoint was defined as time to first occurrence of cardiovascular death, non-fatal heart attack or non-fatal stroke.

Although the EMPA-REG OUTCOME trial was not designed to assess the potential mechanisms behind the effect of Jardiance on kidney outcomes, the kidney assessment was part of a pre-specified exploratory analysis plan of additional endpoints.

The overall safety profile of Jardiance was consistent with that of previous trials.

About Chronic Kidney Disease
Chronic kidney disease is defined as a progressive decline of kidney function over time. About two thirds of chronic kidney disease cases are attributable to metabolic diseases such as diabetes (known as diabetic kidney disease), hypertension and obesity. Notably, chronic kidney disease is associated with increased morbidity and mortality. The majority of deaths among people with chronic kidney disease occur as a result of cardiovascular complications, often before reaching end stage renal disease. Chronic kidney disease affects approximately 15 percent of adults in the United States and treatment costs are estimated to exceed $48 billion annually. Since there are currently only few treatment options, the overarching unmet medical need for new treatment options in chronic kidney disease is evident.

What is JARDIANCE? (www.jardiance.com)
JARDIANCE is a prescription medicine used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.

JARDIANCE is also used to reduce the risk of cardiovascular death in adults with type 2 diabetes who have known cardiovascular disease.

JARDIANCE is not for people with type 1 diabetes or for people with diabetic ketoacidosis (increased ketones in the blood or urine).

IMPORTANT SAFETY INFORMATION
Do not take JARDIANCE if you are allergic to empagliflozin or any of the ingredients in JARDIANCE.

Do not take JARDIANCE if you have severe kidney problems or are on dialysis.

JARDIANCE can cause serious side effects, including:

- **Dehydration. JARDIANCE** can cause some people to have dehydration (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, light-headed, or weak, especially when you stand up
  You may be at a higher risk of dehydration if you:
  - have low blood pressure
  - take medicines to lower your blood pressure, including water pills (diuretics)
  - are on a low salt diet
  - have kidney problems
  - are 65 years of age or older.

- **Vaginal yeast infection.** Women who take JARDIANCE may get vaginal yeast infections. Talk to your doctor if you experience vaginal odor, white or yellowish vaginal discharge (discharge may be lumpy or look like cottage cheese), and/or vaginal itching.

- **Yeast infection of the penis.** Men who take JARDIANCE may get a yeast infection of the skin around the penis, especially uncircumcised males and those with chronic infections. Talk to your doctor if you experience redness, itching or swelling of the penis, rash of the penis, foul smelling discharge from the penis, and/or pain in the skin around penis.

- **Ketoacidosis (increased ketones in your blood or urine).** Ketoacidosis is a serious condition and may need to be treated in the hospital. Ketoacidosis may lead to death. Ketoacidosis occurs in people with type 1 diabetes and can also occur in people with type 2 diabetes taking JARDIANCE, even if blood sugar is less than 250 mg/dL. **Stop taking JARDIANCE and call your doctor right away if you get any of the following symptoms,** and if possible, check for ketones in your urine:
  - nausea
  - vomiting
  - stomach-area (abdominal) pain
  - tiredness
  - trouble breathing

- **Kidney problems.** Sudden kidney injury has happened in people taking JARDIANCE. Talk to your doctor right away if you reduce the amount you eat or drink, or if you lose liquids; for example, from vomiting, diarrhea, or being in the sun too long.

- **Serious urinary tract infections.** Serious urinary tract infections can occur in people taking JARDIANCE and may lead to hospitalization. Tell your doctor if you have symptoms of a urinary tract infection, such as a burning feeling when passing urine, a need to urinate often or right away, pain in the lower part of your stomach or pelvis, or blood in the urine. Sometimes people also may have a fever, back pain, nausea or vomiting.

- **Low blood sugar** (hypoglycemia): If you take JARDIANCE with another medicine that can cause low blood sugar, such as sulfonylurea or insulin, your risk of low blood sugar is higher. The dose of your sulfonylurea or insulin may need to be lowered. Symptoms of low blood sugar may include:
  - headache
  - drowsiness
  - weakness

- dizziness
- confusion
- irritability
- hunger
- fast heartbeat
- sweating
- shaking or feeling jittery

- **Necrotizing fasciitis. A rare but serious bacterial infection that causes damage to the tissue under the skin in the area between and around your anus and genitals (perineum).** This bacterial infection has happened in women and men who take JARDIANCE, and may lead to hospitalization, multiple surgeries, and death. **Seek medical attention immediately if you have fever or 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, and redness of skin (erythema).**

- **Allergic (hypersensitivity) reactions**. Symptoms of serious allergic reactions to JARDIANCE may include:
  - swelling of your face, lips, throat and other areas of your skin
  - difficulty with swallowing or breathing
  - raised, red areas on your skin (hives)

  If you have any of these symptoms, stop taking JARDIANCE and contact your doctor or go to the nearest emergency room right away.

- **Increased fats in your blood (cholesterol).**

The most common side effects of JARDIANCE include urinary tract infections and yeast infections in females.

These are not all the possible side effects of JARDIANCE. For more information, ask your doctor or pharmacist.

Before taking JARDIANCE, tell your doctor if you:

- have kidney problems. Your doctor may do blood tests to check your kidneys before and during your treatment with JARDIANCE
- have liver problems
- have a history of urinary tract infections or problems with urination
- are going to have surgery
- are eating less due to illness, surgery, or a change in your diet
- have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas
- drink alcohol very often, or drink a lot of alcohol in the short term ("binge" drinking)
- have any other medical conditions
- are pregnant or plan to become pregnant. JARDIANCE may harm your unborn baby. Tell your doctor right away if you become pregnant during treatment with JARDIANCE.
- are breastfeeding or are planning to breastfeed. JARDIANCE may pass into your breast milk and may harm your baby. Do not breastfeed while taking JARDIANCE.

Tell your doctor about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. Especially tell your doctor if you take water pills (diuretics) or medicines that can lower your blood sugar, such as insulin.

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088. For more information, please see Prescribing Information and Medication Guide.

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Boehringer Ingelheim and Eli Lilly and Company
In January 2011, Boehringer Ingelheim and Eli Lilly and Company announced an alliance in diabetes that centers on compounds representing several of the largest diabetes treatment classes. This alliance leverages the strengths of two of the world's leading pharmaceutical companies. By joining forces, the companies demonstrate commitment in the care of patients with diabetes and stand together to focus on patient needs. Find out more about the alliance at www.boehringer-ingelheim.com or www.lilly.com.

About Boehringer Ingelheim Pharmaceuticals, Inc.
Boehringer Ingelheim Pharmaceuticals, Inc., based in Ridgefield, Conn., is the largest U.S. subsidiary of Boehringer Ingelheim Corporation.

Boehringer Ingelheim is one of the world's top 20 pharmaceutical companies. Headquartered in Ingelheim, Germany, the company operates globally with approximately 50,000 employees. Since its founding in 1885, the company has remained family-owned, and today our goal is to improve the lives of humans and animals through its three business areas: human pharmaceuticals, animal health and biopharmaceutical contract manufacturing.

Boehringer Ingelheim concentrates on developing innovative therapies that can improve and extend patients' lives. As a research-driven pharmaceutical company, it plans in generations for long-term success. Its research efforts are focused on diseases with high, unmet medical need. In animal health, the company stands for advanced prevention.

In 2018, Boehringer Ingelheim achieved net sales of around $20.7 billion (17.5 billion euros). R&D expenditure of almost $3.7 billion (3.2 billion euros) corresponded to 18.1 per cent of net sales.

Boehringer Ingelheim is committed to improving lives and strengthening our communities. Please visit www.boehringer-ingelheim.us/csr to learn more about Corporate Social Responsibility initiatives.

For more information, please visit www.boehringer-ingelheim.us, or follow us on Twitter @BoehringerUS.

About Lilly Diabetes
Lilly has been a global leader in diabetes care since 1923, when we introduced the world's first commercial insulin. Today we are building upon this heritage by working to meet the diverse needs of people with diabetes and those who care for them. Through research and collaboration, a wide range of therapies and a continued determination to provide real solutions—from medicines to support programs and more—we strive to make life better for all those affected by diabetes around the world. For more information, visit www.lillydiabetes.com.

About Eli Lilly and Company
Lilly is a global healthcare leader that unites caring with discovery to make life better for people around the world. We were founded more than a century ago by a man committed to creating high-quality medicines that meet real needs, and today we remain true to that mission in all our work. Across the globe, Lilly employees work to discover and bring life-changing medicines to those who need them, improve the understanding and management of disease, and give back to communities through philanthropy and volunteerism. To learn more about Lilly, please visit us at www.lilly.com and newsroom.lilly.com/social-channels.

This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about Jardiance and reflects Lilly's current belief. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of development and commercialization. Among other things, there can be no guarantee that future study results will be consistent with the results to date or that Jardiance will receive additional regulatory approvals. For further discussion of these and other risks and uncertainties, see Lilly's most recent Form 10-K and Form 10-Q filings with the United States Securities and Exchange Commission. Except as required by law, Lilly undertakes no duty to update forward-looking statements to reflect events after the date of this release.

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