Jardiance® reduced the combined relative risk of cardiovascular death and hospitalization for heart failure by 25% in adults with and without diabetes who had heart failure with reduced ejection fraction

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- Jardiance (empagliflozin) also significantly reduced the relative risk of first and recurrent hospitalization for heart failure by 30% and significantly slowed kidney function decline

- Results were consistent in subgroups with and without type 2 diabetes

- Heart failure is the leading cause of hospitalization in the U.S.

- Results from the phase III EMPEROR-Reduced trial were published today in The New England Journal of Medicine

RIDGEFIELD, Conn. and INDIANAPOLIS, Aug. 29, 2020 /PRNewswire/ -- Full results from the EMPEROR-Reduced phase III trial in adults with heart failure with reduced ejection fraction, with and without diabetes, showed that Jardiance® (empagliflozin) was associated with a significant 25% relative risk reduction in the primary endpoint of time to cardiovascular death or hospitalization due to heart failure. The trial evaluated the effect of adding Jardiance (10 mg) versus placebo to standard of care. The results will be presented today at the ESC Congress 2020, the annual meeting of the European Society of Cardiology, and published in *The New England Journal of Medicine*, Boehringer Ingelheim and Eli Lilly and Company (NYSE: LLY) announced.

The findings from the primary endpoint were consistent in subgroups with and without type 2 diabetes. Key secondary endpoint analyses from the trial demonstrated that Jardiance reduced the relative risk of first and recurrent hospitalization for heart failure by 30%. Additionally, the rate of decline in eGFR, a measure of kidney function decline, was slower with Jardiance than with placebo.

"Heart failure is a devastating and debilitating cardiovascular condition. Not only does it limit quality of life, but it is also a progressive disease that requires repeated hospitalizations and is accompanied by a loss in kidney function," said Milton Packer, M.D., Chair of the Executive Committee for the EMPEROR Program and Distinguished Scholar in Cardiovascular Science at Baylor University Medical Center in Dallas. "Results from the EMPEROR-Reduced trial show that, when given to adults with heart failure with reduced ejection fraction, empagliflozin reduces the number of heart failure hospitalizations while slowing the decline of kidney function. These results are highly statistically significant and clinically important."

In an exploratory analysis, the absolute risk reduction observed in the primary endpoint of EMPEROR-Reduced corresponded to a number needed to treat of 19 patients over 16 months to prevent one cardiovascular death or hospitalization for heart failure. An additional exploratory analysis showed that Jardiance decreased the relative risk of a composite kidney endpoint*, including end stage kidney disease and a profound loss of kidney function, by 50%.

In EMPEROR-Reduced, the efficacy results were achieved with a simple dosing regimen, with once daily dosing and no need for titration. The safety profile was similar to the well-established safety profile of Jardiance. There were no clinically meaningful differences in adverse events, including hypovolemia (decreased blood volume), hypotension (low blood pressure), volume depletion (loss of fluids), renal insufficiency (poor kidney function), hyperkalemia (high potassium levels) or hypoglycemic events (low blood sugar) compared with placebo.

Heart failure affects over 60 million people worldwide, with more than one million people being hospitalized due to the condition every year in the U.S. Heart failure occurs when the heart cannot pump sufficient blood to the rest of the body and is the most common and severe complication of a heart attack. People with heart failure often experience breathlessness and fatigue, which can severely impact their quality of life. Individuals with heart failure often also have impaired kidney function, which can have a significant negative impact on prognosis.

"Jardiance transformed the treatment paradigm as the first and only oral diabetes medicine proven to significantly reduce the risk of cardiovascular death in adults with type 2 diabetes and established cardiovascular disease, based on the EMPA-REG OUTCOME® trial," said Mohamed Eid, M.D., M.P.H, M.H.A, vice president, Clinical Development & Medical Affairs, Cardio-Metabolism & Respiratory Medicine, Boehringer Ingelheim Pharmaceuticals, Inc. "The positive results from EMPEROR-Reduced build on this legacy and demonstrate the potential of Jardiance to improve cardiovascular outcomes and slow kidney function decline in adults with heart failure, with and without diabetes. We look forward to submitting these data to regulatory authorities later this year."

"Tens of millions of people live with heart failure and kidney disease," said Jeff Emmick, M.D., Ph.D., Vice President, Product Development, Lilly. "Results from EMPEROR-Reduced show that Jardiance can help improve heart failure outcomes while also slowing kidney function decline. We are excited to share these data and, through our ongoing EMPOWER program, hope to redefine how people living with these conditions are treated."

The U.S. Food and Drug Administration (FDA) has granted Fast Track designation to Jardiance for the reduction of the risk of cardiovascular death and hospitalization for heart failure in people with heart failure. This designation is for the EMPEROR program, which consists of the EMPEROR-Reduced and EMPEROR-Preserved trials. EMPEROR-Preserved is exploring the effect of Jardiance on cardiovascular death or hospitalization for heart failure in adults with heart failure with preserved ejection fraction, an area that currently has no approved treatment options. EMPEROR-Preserved results are expected in 2021.

Additionally, the ongoing EMPA-KIDNEY study is evaluating the effect of Jardiance on the progression of kidney disease and occurrence of cardiovascular death in adults with established chronic kidney disease, with and without diabetes. The FDA has also granted Fast Track designation to

Jardiance for the treatment of chronic kidney disease, demonstrating the urgent need for new treatment options for people living with the condition worldwide. Results from EMPA-KIDNEY are expected in 2022.

The EMPEROR and EMPA-KIDNEY studies are part of the EMPOWER clinical program, the broadest and most comprehensive of any SGLT2 inhibitor, exploring the impact of Jardiance on the lives of people across the spectrum of cardio-renal-metabolic conditions. The program also includes the EMPACT-MI study, which will investigate the effect of Jardiance on all-cause mortality and hospitalization for heart failure in adults, with and without diabetes, who have had a heart attack, and the EMPULSE study, which is exploring Jardiance in adults, with and without diabetes, who are hospitalized for acute heart failure and have been stabilized.

**Composite exploratory endpoint included chronic dialysis or renal transplant or sustained reduction of ≥ 40% in eGFR (CKD-EPI) or a sustained eGFR < 15 mL/min/1.73m2 (for patients with baseline eGFR ≥ 30) or sustained eGFR < 10 mL/min/1.73m2 (for patients with baseline eGFR < 30 mL/min/1.73m2).*

About the EMPEROR Heart Failure Studies
The EMPEROR (EMPagliflozin outcomE tRial in patients with chrOnic heaRt failure) heart failure studies are two phase III, randomized, double-blind trials investigating once-daily Jardiance compared with placebo in adults with heart failure with preserved or reduced ejection fraction*, both with and without diabetes, who are receiving current standard of care:

- **EMPEROR-Reduced** [NCT03057977] investigated the safety and efficacy of Jardiance in patients with chronic heart failure with **reduced ejection fraction** (HFrEF).
    - Primary endpoint: time to first event of adjudicated cardiovascular death or adjudicated hospitalization for heart failure
    - Number of patients: 3,730
    - Completion: 2020
- **EMPEROR-Preserved** [NCT03057951] investigates the safety and efficacy of Jardiance in patients with chronic heart failure with **preserved ejection fraction** (HFpEF).
    - Primary endpoint: time to first event of adjudicated cardiovascular death or adjudicated hospitalization for heart failure [Time Frame: up to 38 months]
    - Anticipated number of patients: approx. 5,990
    - Estimated completion: 2021

***Ejection fraction** is a measurement of the percentage of blood the left ventricle pumps out with each contraction. When the heart relaxes, the ventricle refills with blood.

- **HFrEF** occurs when the heart muscle does not contract effectively, and less blood is pumped out to the body compared with a normally functioning heart.
- **HFpEF** occurs when the heart muscle contracts normally but the ventricle does not fill with enough blood, so less blood can enter the heart compared with a normally functioning heart.

About the EMPOWER program
The Alliance has developed the EMPOWER program to explore the impact of Jardiance on major clinical cardiovascular and renal outcomes in a spectrum of cardio-renal-metabolic conditions. Cardio-renal-metabolic conditions are the leading cause of mortality worldwide and account for up to 20 million deaths annually. Through the EMPOWER program, Boehringer Ingelheim and Lilly are working to advance knowledge of these interconnected systems and create care which offers integrated, multi-organ benefits. Comprised of eight clinical trials and two real-world evidence studies, EMPOWER reinforces the long-term commitment of the Alliance to improve outcomes for people living with cardio-renal-metabolic conditions. With more than 257,000 adults studied worldwide in clinical studies, it is the broadest and most comprehensive clinical program for an SGLT2 inhibitor to date.

The development program encompasses:

- EMPEROR-Reduced, in adults with chronic heart failure with reduced ejection fraction to reduce the risk of cardiovascular death or hospitalization due to heart failure
- EMPEROR-Preserved, in adults with chronic heart failure with preserved ejection fraction to reduce the risk of cardiovascular death or hospitalization due to heart failure
- EMPULSE, in adults hospitalized for acute heart failure and stabilized to improve clinical and patient reported outcomes
- EMPACT-MI, to evaluate all-cause mortality and hospitalization for heart failure in adults with and without type 2 diabetes who have had an acute myocardial infarction, with the aim to prevent heart failure and improve outcomes
- EMPA-KIDNEY, in adults with established chronic kidney disease to reduce the progression of kidney disease and the occurrence of cardiovascular death
- EMPERIAL-Reduced, in adults with chronic heart failure with reduced ejection fraction to evaluate functional ability and patient reported outcomes
- EMPERIAL-Preserved, in adults with chronic heart failure with preserved ejection fraction to evaluate functional ability and patient-reported outcomes
- EMPA-REG OUTCOME, in adults with type 2 diabetes and established cardiovascular disease to reduce the risk of major adverse cardiovascular events, including cardiovascular death
- EMPRISE, a non-interventional study of the effectiveness, safety, healthcare utilization and cost of care of empagliflozin in

routine clinical practice in adults with type 2 diabetes across the cardiovascular risk continuum

About Heart Failure
Heart failure is a progressive, debilitating and potentially fatal condition that occurs when the heart cannot supply adequate circulation to meet the body's demands for oxygenated blood or to do so requires increased blood volume leading to fluid accumulation (congestion) in the lungs and peripheral tissues. It is a widespread condition affecting over 60 million people worldwide and expected to increase as the population ages. Heart failure is highly prevalent in people with diabetes; however, approximately half of all people with heart failure do not have diabetes.

The Jardiance heart failure program was initiated based on data from the EMPA-REG OUTCOME trial, which assessed the effect of Jardiance (10 mg or 25 mg once daily) in adults with type 2 diabetes and established cardiovascular disease when added to standard of care, compared with placebo.

About Cardio-Renal-Metabolic Conditions
Boehringer Ingelheim and Lilly are driven to transform care for people with cardio-renal-metabolic conditions, a group of interconnected disorders that affect more than one billion people worldwide and are a leading cause of death.

The cardiovascular, renal and metabolic systems are interconnected, and share many of the same risk factors and pathological pathways along the disease continuum. Dysfunction in one system may accelerate the onset of others, resulting in progression of interconnected diseases such as type 2 diabetes, cardiovascular disease, heart failure, and kidney disease, which in turn leads to an increased risk of cardiovascular death. Conversely, improving the health of one system can lead to positive effects throughout the others.

Through our research and treatments, our goal is to support people's health, restoring the harmony between the interconnected cardio-renal-metabolic systems and reducing their risk of serious complications. As part of our commitment to those whose health is jeopardized by cardio-renal-metabolic conditions, we will continue embracing a multidisciplinary approach towards care and focusing our resources on filling treatment gaps.

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. Ketoacidosis has also happened in people with diabetes who were sick or who had surgery during treatment with JARDIANCE. **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
- confusion
- irritability
- hunger
- weakness
- dizziness
- 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. Your doctor may stop your JARDIANCE before you have surgery. Talk to your doctor if you are having surgery about when to stop taking JARDIANCE and when to start it again
- are eating less or there is 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 that centers on compounds representing several of the largest diabetes treatment classes. Depending on geographies, the companies either co-promote or separately promote the respective molecules each contributing to the alliance. The alliance leverages the strengths of two of the world's leading pharmaceutical companies to focus on patient needs. By joining forces, the companies demonstrate their commitment, not only to the care of people with diabetes, but also to investigating the potential to address areas of unmet medical need. Clinical trials have been initiated to evaluate the impact of Jardiance on people living with heart failure or chronic kidney disease.

About Boehringer Ingelheim
Making new and better medicines for humans and animals is at the heart of what we do. Our mission is to create breakthrough therapies that change lives. Since its founding in 1885, Boehringer Ingelheim is independent and family-owned. We have the freedom to pursue our long-term vision, looking ahead to identify the health challenges of the future and targeting those areas of need where we can do the most good.

As a world-leading, research-driven pharmaceutical company, more than 51,000 employees create value through innovation daily for our three business areas: Human Pharma, Animal Health, and Biopharmaceutical Contract Manufacturing. In 2019, Boehringer Ingelheim achieved net sales of around $21.3 billion (19 billion euros). Our significant investment of over $3.9 billion (3.5 billion euros) in R&D drives innovation, enabling the next generation of medicines that save lives and improve quality of life.

We realize more scientific opportunities by embracing the power of partnership and diversity of experts across the life-science community. By working together, we accelerate the delivery of the next medical breakthrough that will transform the lives of patients now, and in generations to come.

Boehringer Ingelheim Pharmaceuticals, Inc., based in Ridgefield, CT, is the largest U.S. subsidiary of Boehringer Ingelheim Corporation and is part of the Boehringer Ingelheim group of companies. In addition, there are Boehringer Ingelheim Animal Health in Duluth, GA and Boehringer Ingelheim Fremont, Inc. in Fremont, CA.

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, collaboration and quality manufacturing we strive to make life better for people affected by diabetes and related conditions. We work to deliver breakthrough outcomes through innovative solutions—from medicines and technologies to support programs and more. For the latest updates, visithttp://www.lillydiabetes.com/ or follow us on Twitter: @LillyDiabetes and Facebook: LillyDiabetesUS.

About Eli Lilly and Company
Lilly is a global health care leader that unites caring with discovery to create medicines that 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 lilly.com and lilly.com/newsroom.

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 drug 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 a further discussion of these and other risks and uncertainties that could cause actual results to differ from Lilly's expectations, please see Lilly's most recent Forms 10-K and 10-Q filed with the U.S. Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.

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