Landmark trial demonstrates Jardiance® (empagliflozin) is the first therapy to show statistically significant improvement in heart failure outcomes in adults with preserved ejection fraction

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- In this clinical first for adults with heart failure with preserved ejection fraction, Jardiance demonstrated an impressive 21% relative risk reduction in the composite primary endpoint of cardiovascular death or hospitalization for heart failure

- The benefit in the primary endpoint was independent of ejection fraction or diabetes status

- Jardiance also reduced the relative risk of first and recurrent hospitalizations for heart failure by 27% and significantly slowed kidney function decline

- Results from the EMPEROR-Preserved phase III trial were presented today at the European Society of Cardiology Congress 2021 and published in The New England Journal of Medicine

RIDGEFIELD, Conn. and INDIANAPOLIS, Aug. 27, 2021 /PRNewswire/ -- Full results from the landmark EMPEROR-Preserved phase III trial demonstrated that Jardiance® (empagliflozin) showed an impressive 21% relative risk reduction for the composite primary endpoint of cardiovascular death or hospitalization for heart failure in adults with heart failure with preserved ejection fraction (HFpEF) compared with placebo. The benefit was independent of ejection fraction or diabetes status, establishing Jardiance as the first and only treatment to significantly improve outcomes for the full spectrum of heart failure patients. The results were presented today at the European Society of Cardiology (ESC) Congress 2021 and published in *The New England Journal of Medicine*, Boehringer Ingelheim and Eli Lilly and Company (NYSE: LLY) announced.

Key secondary endpoint analyses from the trial showed that Jardiance also reduced the relative risk of first and recurrent hospitalizations for heart failure by 27% and significantly slowed kidney function decline.

"For people with heart failure with preserved ejection fraction, the reality is that so far there are no clinically proven treatments we can offer that would make a significant impact on their condition," said Professor Stefan Anker, EMPEROR-Preserved principal investigator and heart failure cardiologist at Charité Berlin, Germany. "This data brings hope for millions of patients suffering from heart failure with a preserved ejection fraction. The primary endpoint was similarly improved in all subgroups of patients, in men and women, with and without diabetes, and regardless of their ejection fraction and kidney function level. This underlines the breadth of empagliflozin's efficacy and its potential overall impact."

More than 6 million people in the U.S. have heart failure, and approximately half of them have HFpEF, which is also known as diastolic heart failure. HFpEF has been described as the single largest unmet need in cardiovascular medicine based on prevalence, poor outcomes and the absence of clinically proven therapies to date.[1],[2]

EMPEROR-Preserved included 5,988 people with heart failure. Of these, 4,005 had a left ventricular ejection fraction (LVEF) of 50% or above and 1,983 had a LVEF below 50%. Trial participants were randomly assigned to Jardiance 10 mg (n=2,997) or placebo (n=2,991) once daily. The overall safety data was consistent with previous findings, confirming the well-established safety profile of Jardiance.

"In the first successful trial in this difficult-to-treat form of heart failure, Jardiance demonstrated a statistically significant improvement in outcomes for adults with heart failure across the spectrum of left ventricular ejection fraction in the trial. This is the kind of news that has the potential to change treatment paradigms, and it's thrilling to see this level of benefit in both hospitalizations and kidney function," 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. "We are moving quickly to share this impressive data with regulators and are looking forward to potentially bringing this breakthrough treatment option to a growing and underserved population."

"These impressive results will bring hope for the millions of people who currently have limited therapeutic options for a very serious, life-threatening condition," said Jeff Emmick, M.D., Ph.D., vice president, Product Development, Lilly. "Now there is a light at the end of the tunnel. If approved, Jardiance would become the first clinically proven therapy across the full heart failure spectrum. The results of EMPEROR-Preserved offer an opportunity to fundamentally change the future for people with heart failure."

The benefits demonstrated in the EMPEROR-Preserved trial are similar to those in the EMPEROR-Reduced trial, in which Jardiance significantly reduced the relative risk of the composite endpoint of cardiovascular death or hospitalization for heart failure by 25%, compared with placebo, in adults with heart failure with reduced ejection fraction (HFrEF). Together, these studies demonstrate the benefits of Jardiance for patients across the full heart failure spectrum.

Earlier this month, the U.S. Food and Drug Administration approved Jardiance to reduce the risk of cardiovascular death plus hospitalization for heart failure in adults with HFrEF. Jardiance was the first type 2 diabetes treatment approved to reduce the risk of cardiovascular death in adults with type 2 diabetes and known cardiovascular disease. The Boehringer Ingelheim-Lilly Alliance plans for global regulatory submissions in HFpEF in 2021. Research is ongoing regarding the effects of Jardiance on hospitalization for heart failure and mortality in post-myocardial infarction (heart attack) patients with high risk of heart failure. Jardiance is also currently being investigated in chronic kidney disease.

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] investigated 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]
    - Number of patients: 5,988
    - 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 nine 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 400,000 adults enrolled worldwide in clinical trials, it is one of the broadest and most comprehensive clinical programs 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, two non-interventional studies (U.S. and EU-Asia) 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

Prioritizing Cardio-Renal-Metabolic Care
Through research and educational initiatives, Boehringer Ingelheim and Lilly are driven to redefine 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 (kidney) and metabolic systems are closely intertwined and share many of the same disease-related pathways. Dysfunction in one system may accelerate the onset of dysfunction in others, resulting in the progression of comorbid diseases such as type 2 diabetes, heart failure and chronic kidney disease. Conversely, improving the health of one system can lead to positive effects across the others and can help reduce the risk for further complications.

Understanding their interconnected nature, we are working to advance treatments for people with cardio-renal-metabolic conditions. It is only through a holistic approach to care that we can truly transform outcomes and restore the harmony between these critical systems.

What is JARDIANCE? (www.jardiance.com)

JARDIANCE is a prescription medicine used to:

- lower blood sugar along with diet and exercise in adults with type 2 diabetes
- reduce the risk of cardiovascular death in adults with type 2 diabetes who also have known cardiovascular disease
- reduce the risk of cardiovascular death and hospitalization for heart failure (when the heart is weak and cannot pump enough blood to the rest of your body) in adults with heart failure

JARDIANCE is not for people with type 1 diabetes. It may increase their risk of diabetic ketoacidosis (increased ketones in the blood or urine).

JARDIANCE is not for use to lower blood sugar in adults with type 2 diabetes who have severe kidney problems, because it may not work.

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 are on dialysis.

JARDIANCE can cause serious side effects, including:

- **Ketoacidosis (increased ketones in your blood or urine).** Ketoacidosis is a serious condition which needs 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 healthcare provider right away or go to the nearest hospital emergency room 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

- **Dehydration. JARDIANCE** can cause some people to become dehydrated (the loss of body water and salt). Dehydration may cause you to feel dizzy, faint, light-headed, or weak, especially when you stand up. Sudden worsening of kidney function has happened in people who are taking JARDIANCE.

  You may be at a higher risk of dehydration if you:

    - 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

  Talk to your healthcare provider about what you can do to prevent dehydration, including how much fluid you should drink on a daily basis, and if you reduce the amount of food or liquid you drink, if you are sick or cannot eat, or start to lose liquids from your body 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 healthcare provider 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).**

- **Vaginal yeast infection.** Talk to your healthcare provider if you have 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.** Swelling of an uncircumcised penis may develop that makes it difficult to pull back the skin around the tip of the penis. Talk to your healthcare provider if you have redness, itching or swelling of the penis, rash of the penis, foul smelling discharge from the penis, and/or pain in the skin around the penis.

  Talk to your healthcare provider about what to do if you get symptoms of a yeast infection of the vagina or penis. Your healthcare provider may suggest you use an over-the-counter antifungal medicine. Talk to your healthcare provider right away if you use an over-the-counter antifungal medication and your symptoms do not go away.

- **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 healthcare provider or go to the nearest emergency room right away.

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 healthcare provider or pharmacist.

Before taking JARDIANCE, tell your healthcare provider about all of your medical conditions, including if you:

- have kidney problems
- have liver problems
- have a history of infection of the vagina or penis
- have a history of urinary tract infections or problems with urination
- are going to have surgery. Your healthcare provider may stop your JARDIANCE before you have surgery. Talk to your healthcare provider 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 type 1 diabetes. JARDIANCE should not be used to treat people with type 1 diabetes
- are pregnant or plan to become pregnant. JARDIANCE may harm your unborn baby. Tell your healthcare provider 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 healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements. **Especially tell your healthcare provider 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, with around 52,000 employees, we create value through innovation daily for our three business areas: Human Pharma, Animal Health, and Biopharmaceutical Contract Manufacturing. In 2020, Boehringer Ingelheim achieved net sales of around 22.33 billion USD (19.57 billion EUR). Our significant investment of over 4.2 billion USD (3.7 billion EUR) in 2020 (18.9% of net sales) 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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[1] Butler J, Fonarow G, Zile M, *et al*. Developing therapies for heart failure with preserved ejection fraction: Current State and Future Directions. *JACC Heart Fail*. 2014 Apr;2(2):97–112.
[2] Shah SJ, Borlaug B, Kitzman D, *et al*. Research priorities for heart failure with preserved ejection fraction. *Circulation*. 2020;141:1001–26.

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