Jardiance® provided a significant clinical benefit in adults stabilized in hospital following acute heart failure in EMPULSE phase III trial

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- Adults hospitalized for acute heart failure were 36% more likely to experience a clinical benefit over 90 days if initiated on Jardiance after stabilization and before discharge compared with placebo

- The benefit was consistent in adults with new or existing heart failure and in those with either preserved or reduced ejection fraction

RIDGEFIELD, Conn. and INDIANAPOLIS, March 1, 2022 /PRNewswire/ -- Adults hospitalized for acute heart failure were 36% more likely to experience a clinical benefit over 90 days if initiated on Jardiance® (empagliflozin) following stabilization and prior to discharge compared with placebo in the phase III EMPULSE trial, Boehringer Ingelheim and Eli Lilly and Company (NYSE: LLY) announced today. Clinical benefit reflected a composite primary endpoint that included all-cause mortality, frequency of heart failure events, time to first heart failure event and symptoms as measured by the Kansas City Cardiomyopathy Questionnaire total symptom score (KCCQ-TSS). The findings were published in *Nature Medicine* and presented at the American Heart Association's Late-Breaking Scientific Sessions 2021.

"The first months following hospitalization for heart failure are a particularly vulnerable time for patients," said Adriaan Voors, Professor of Cardiology, University Medical Center, Groningen, Netherlands, and EMPULSE principal investigator. "Current outcomes are poor, underscoring the urgent need for improved in-patient clinical management to prevent further hospitalizations or death. This significant clinical benefit with empagliflozin compared with placebo will advance our understanding of the treatment of heart failure during the early discharge phase."

Heart failure is a leading cause of hospitalizations, accounting for more than 1 million per year in the U.S. Outcomes for those who have been admitted to the hospital for heart failure are poor, with over 30% of patients readmitted within 90 days between 2010 and 2017, according to the National Readmission Database.

The overall clinical benefit with Jardiance was consistent for those with either new or pre-existing heart failure, for those with or without diabetes and for those with either preserved or reduced ejection fraction. In an exploratory secondary endpoint, Jardiance significantly improved KCCQ-TSS from baseline to day 90 by 4.5 points versus placebo.

The EMPULSE safety results were consistent with the well-established safety profile of Jardiance. Investigator-reported acute renal failure rates were 7.7% for Jardiance versus 12.1% for placebo, and there was a similar low incidence of hypoglycemia in both groups (1.9% for Jardiance vs. 1.5% for placebo). Volume depletion rates were 12.7% versus 10.2%, respectively.

"We are encouraged by the early and significant clinical benefit seen in EMPULSE with Jardiance when initiated in adults with heart failure with either preserved or reduced ejection fraction prior to hospital discharge, including improvements in an endpoint combining mortality, hospitalizations and quality of life," 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 remain committed to trials such as this that help us better understand how this therapy may benefit people with a range of cardio-renal-metabolic conditions for whom additional treatment options are greatly needed."

"The EMPULSE results add to the growing weight of evidence from our EMPOWER program supporting the potential role of Jardiance in a range of conditions affecting the heart, kidneys and metabolic system," said Jeff Emmick, M.D., Ph.D., vice president, Product Development, Lilly. "The clinical benefit and consistent safety results demonstrated in the vulnerable phase following hospital discharge suggest that in-hospital initiation with Jardiance for appropriate patients can improve outcomes during these critical months."

Recently, the U.S. Food and Drug Administration (FDA) approved Jardiance to reduce the risk of cardiovascular death and hospitalization for heart failure in adults with heart failure based on data from the EMPEROR-Preserved® trial. This decision marks the third U.S. FDA approval for Jardiance stemming from the EMPOWER program.

About EMPULSE

The EMPULSE trial is a multicenter, randomized, double-blind, 90-day superiority trial to evaluate the effect on clinical benefit, safety and tolerability of once daily Jardiance 10 mg compared with placebo, initiated in 530 patients hospitalized for acute heart failure (de novo or decompensated chronic heart failure) who have been stabilized. The primary endpoint was based on clinical benefit, a hierarchical composite endpoint of all-cause mortality, frequency of heart failure events, time to first heart failure event, and symptoms as measured by the KCCQ-TSS after 90 days of treatment, assessed by the win ratio.

The win ratio estimates the odds that a participant in the Jardiance arm will have a better clinical benefit than a participant in the placebo group; higher win ratios suggest a greater clinical benefit with Jardiance. For EMPULSE, patients were stratified by de novo versus decompensated chronic heart failure. Within each stratum, every individual in the Jardiance group was compared with every individual in the placebo group. The win ratio was determined by the total number of wins for Jardiance divided by the total number of losses. The components of the primary endpoint were evaluated in order of clinical importance, so that deaths are prioritized over heart failure events and symptoms.

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

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.

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 that can protect the organs of the cardio-renal-metabolic systems. 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?

JARDIANCE is a prescription medicine used to:

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

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 as a treatment for adults with type 2 diabetes, to reduce the risk of cardiovascular death in adults with type 2 diabetes and known cardiovascular disease, and to reduce the risk of cardiovascular death plus hospitalization for heart failure in adults with heart failure with reduced ejection fraction, and as a potential treatment for adults with cardio-renal-metabolic conditions and reflects Lilly's current beliefs and expectations. However, as with any pharmaceutical product, there are substantial risks and uncertainties in the process of drug research, development and commercialization. Among other things, there can be no guarantee that planned or ongoing studies will be completed as planned, 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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