Full results from EMPERIAL exercise ability trials presented

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RIDGEFIELD, Conn. and INDIANAPOLIS, June 19, 2020 /PRNewswire/ -- Boehringer Ingelheim and Eli Lilly and Company (NYSE:LLY) today announced full results from the EMPERIAL-Reduced and EMPERIAL-Preserved trials related to exercise ability and symptom improvement with Jardiance® (empagliflozin) in adults with chronic heart failure with reduced and preserved ejection fraction, respectively. The results were presented through the European Society of Cardiology's HFA Discoveries program.

"The EMPERIAL trials, which assessed exercise ability, are one piece of our clinical program evaluating the potential of Jardiance in treating heart failure, a condition affecting 60 million people worldwide," 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. "At the center of our heart failure program are the ongoing EMPEROR trials, which are investigating outcomes including cardiovascular death, hospitalization for heart failure and quality of life. We look forward to sharing results from the EMPEROR-Reduced trial this year for people with heart failure and reduced ejection fraction."

As previously reported, the EMPERIAL trials showed no significant difference in change from baseline to week 12 in exercise ability with Jardiance versus placebo, as measured by the six-minute walk test, which was the primary endpoint of the studies. In EMPERIAL-Reduced, the median six-minute walk test increased by 13.5 meters with Jardiance compared with 18.0 meters with placebo. In EMPERIAL-Preserved the increase was 10.0 meters with Jardiance versus 5.0 meters with placebo.

Exploratory analyses of EMPERIAL-Reduced suggest Jardiance was associated with improvements in quality of life. Researchers employed the Kansas City Cardiomyopathy Questionnaire (KCCQ), a widely used patient-reported measure of quality of life for heart failure. Mean improvement in total symptom score (TSS) of the KCCQ from baseline to week 12 was 4.55 points higher for Jardiance compared with placebo. Additionally, a greater proportion of those taking Jardiance had improvements compared with placebo in KCCQ-TSS of at least 5 and at least 8 points – two pre-specified thresholds that were identified to measure clinically meaningful response to treatment. Similar exploratory analyses of EMPERIAL-Preserved did not indicate improvements with Jardiance versus placebo in these same measures for adults with heart failure with preserved ejection fraction.

The EMPERIAL trials included people with and without diabetes. The safety profile in those with diabetes was similar to the known safety profile of Jardiance for adults with type 2 diabetes. In those without diabetes, no new safety events were identified, and the frequency of hypoglycemic events with Jardiance in this population was similar to that of placebo. Overall, in both trials, there was no notable difference between Jardiance and placebo in the frequency of adverse events, including those leading to discontinuation of study medication, and no new safety concerns were identified.

Other heart failure guideline-recommended therapies have shown divergent results between studies examining clinical outcomes and symptom improvement, with some showing improvements in outcomes such as mortality, but neutral or inconsistent results in exercise ability and patient-reported outcomes.

"Cardio-renal-metabolic conditions, a group of disorders affecting the heart, kidneys and endocrine systems, are becoming increasingly common," said Jeff Emmick, M.D., Ph.D., vice president, Product Development, Lilly. "Our EMPOWER clinical trial program, which is exploring the impact of Jardiance across the spectrum of cardio-renal-metabolic conditions, is one of the broadest and most comprehensive of any SGLT2 inhibitor. Through our research we aim to contribute new knowledge that can help improve outcomes for the millions of people affected by these conditions."

About EMPERIAL
EMPERIAL consisted of two Phase III randomized, double-blind trials in adults with or without diabetes. The trials evaluated the effect of 12 weeks' treatment of once-daily Jardiance 10 mg compared with placebo on exercise ability and heart failure symptoms in patients with chronic heart failure with preserved or reduced ejection fraction.* The primary endpoint was measured by the six-minute walk test, a common measure of exercise ability.

- **EMPERIAL-Preserved** [NCT03448406]: investigated Jardiance in patients with chronic heart failure with preserved ejection fraction (HFpEF). The study looked at a functional endpoint — how far patients can walk in six minutes — and at hear failure symptoms.
    - Primary endpoint: Change from baseline to week 12 in exercise ability as measured by the distance walked in six minutes
    - Number of patients enrolled: 315
    - Completed: October 9, 2019

- **EMPERIAL-Reduced** [NCT03448419]: investigated Jardiance in patients with chronic heart failure with reduced ejection fraction (HFrEF). The study looked at a functional endpoint — how far patients can walk in six minutes — and at hear failure symptoms.
    - Primary endpoint: Change from baseline to week 12 in exercise ability as measured by the distance walked in six minutes
    - Number of patients enrolled: 312
    - Completed: October 7, 2019

***Ejection fraction** is a measurement expressed as a percentage of the amount of blood that leaves the heart each time it contracts, related to the total

blood volume of the heart chambers. During each heartbeat pumping cycle, the heart contracts and relaxes. When the heart contracts, it ejects blood from the two pumping chambers (ventricles). When the heart relaxes, the ventricles refill with blood.

HFpEF occurs when the heart muscle contracts normally but the ventricle muscles are stiff. They do not relax as they should when the ventricle fills with blood, so less blood can enter the heart compared to a normally functioning heart.

HFrEF occurs when the heart muscle does not contract effectively and less blood is pumped out to the body compared to a normally functioning heart.

Both HFpEF and HFrEF lead to similar symptoms of heart failure, specifically difficulty breathing, swelling and fatigue.

About EMPOWER
The EMPOWER program reinforces the long-term commitment of Boehringer Ingelheim and Eli Lilly and Company to evaluate the potential of Jardiance to improve outcomes for adults living with cardio-renal-metabolic conditions. EMPOWER is one of the largest clinical trial programs for an SGLT2 inhibitor to date with more than 13,000 adults worldwide.

The development program encompasses:

- EMPEROR-Reduced, in adults with chronic heart failure with reduced ejection fraction to reduce the risk of cardiovascular death and hospitalization due to heart failure
- EMPEROR-Preserved, in adults with chronic heart failure with preserved ejection fraction to reduce the risk of cardiovascular death and hospitalization due to heart failure
- EMPULSE, in adults hospitalized for acute heart failure to improve clinical and patient reported outcomes
- EMPACT-MI, to improve outcomes and prevent heart failure in adults with and without diabetes who have had an acute myocardial infarction
- 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 improve exercise ability and patient reported outcomes
- EMPERIAL-Preserved, in adults with chronic heart failure with preserved ejection fraction to improve exercise 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, assessing comparative efficacy, safety, healthcare resource utilization and costs of care in routine clinical care in adult patients with diabetes

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 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 added to standard of care compared with placebo added to standard of care. EMPA-REG OUTCOME was the first SGLT2 inhibitor trial to show a relative risk reduction in cardiovascular death in adults with type 2 diabetes and established cardiovascular disease. This population was comprised of more than 45% of adults with a prior myocardial infarction.

About Cardio-Renal-Metabolic Conditions
Cardio-renal-metabolic conditions are a group of interconnected disorders affecting the heart, kidneys and endocrine system. In aggregate, these conditions are the leading cause of deaths worldwide, accounting for up to 20 million deaths annually. Conditions within this group include coronary artery disease, heart failure, chronic kidney disease and type 2 diabetes, among many others.

Emerging science on the link between the cardiorenal and metabolic systems supports taking a multidisciplinary approach toward diagnostic, preventive and therapeutic strategies for people living with these conditions. We remain committed to developing treatments with broad cardio-renal-metabolic effects, which may help improve outcomes for people with serious chronic conditions such as these.

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
- 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. 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 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 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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