Boehringer Ingelheim and Lilly provide update on Jardiance® phase III exercise ability studies in chronic heart failure

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RIDGEFIELD, Conn. and INDIANAPOLIS, Dec. 13, 2019 /PRNewswire/ -- Boehringer Ingelheim and Eli Lilly and Company (NYSE: LLY) announced today results from the EMPERIAL-Reduced and EMPERIAL-Preserved trials related to functional endpoints with Jardiance® (empagliflozin) in adults with chronic heart failure with reduced and preserved ejection fraction, respectively. In both trials, there was no significant 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. The safety profile seen in the EMPERIAL trials was similar to the currently known safety profile of Jardiance and no new safety risks were identified.

The EMPERIAL trials, which included people with and without diabetes, deliver novel safety data for Jardiance in non-diabetic patients with heart failure. In addition, EMPERIAL-Preserved is the first trial to deliver safety data for Jardiance in heart failure with preserved ejection fraction.

"Our large heart failure clinical program underscores our dedication to researching new options for people living with this condition," 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 EMPERIAL trials set a high bar for Jardiance to demonstrate an improvement in exercise ability in people with chronic heart failure, and we continue to believe in its potential to improve clinical outcomes. The ongoing EMPEROR trials—which are investigating outcomes including cardiovascular death, hospitalization for heart failure and quality of life—remain the cornerstone of our heart failure program, and we look forward to sharing initial results in 2020."

The EMPERIAL trials used the six-minute walk test, which measures the distance a person can walk in six minutes, to evaluate changes in exercise ability over 12 weeks. For other heart failure guideline-recommended therapies, there have been 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.

The ongoing empagliflozin heart failure program also includes the EMPEROR-Preserved, EMPEROR-Reduced, EMPULSE and EMPA-VISION studies. The program, which will include more than 10,000 adults, investigates the effects of empagliflozin on heart failure-related outcomes and patient-related outcomes in people with heart failure. The EMPERIAL studies were initiated based on data obtained from the EMPA-REG OUTCOME® trial, in which Jardiance showed a 38% relative risk reduction in cardiovascular death and a 35% relative risk reduction in hospitalization for heart failure in adults with type 2 diabetes and established cardiovascular disease, compared to placebo.

"The EMPERIAL trials highlight our commitment to listening to patients' needs and studying the impact of our treatments on important measures such as quality of life," said Jeff Emmick, M.D., Ph.D., vice president, Product Development, Lilly. "Boehringer Ingelheim and Lilly will continue to explore how Jardiance can potentially improve health outcomes and fill treatment gaps for people with cardiorenal metabolic conditions, including adults with chronic heart failure."

Full results from the EMPERIAL trials will be shared in 2020.

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 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. Heart failure contributes to one in nine deaths and is a leading cause of hospitalization in the U.S.

There is a high unmet need in the treatment of heart failure, as approximately 50 percent of people diagnosed with heart failure will die within five years. Additionally, heart failure represents the most common cause of hospitalization among individuals aged 65 years and over in the U.S. and Europe.

About Cardiorenal Metabolic Conditions
Cardiorenal 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. A team approach to optimize patient care by coordinating treatment of related comorbidities, including the use of emerging therapies with broad cardiorenal metabolic effects, may 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. **Stop taking JARDIANCE and call your doctor right away if you get any of the following symptoms,** and if possible, check for ketones in your urine:

- nausea
- vomiting
- stomach-area (abdominal) pain
- tiredness
- trouble breathing

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

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

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

- **Necrotizing fasciitis. A rare but serious bacterial infection that causes damage to the tissue under the skin in the area between and around your anus and genitals (perineum).** This bacterial infection has happened in women and men who take JARDIANCE, and may lead to hospitalization, multiple surgeries, and death. **Seek medical attention immediately if you have fever or are feeling very weak, tired or uncomfortable (malaise), and you develop any of the following symptoms in the area between and around your anus and genitals: pain or tenderness, swelling, and redness of skin (erythema).**

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

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

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

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

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

Before taking JARDIANCE, tell your doctor if you:

- have kidney problems. Your doctor may do blood tests to check your kidneys before and during your treatment with JARDIANCE
- have liver problems
- have a history of urinary tract infections or problems with urination
- are going to have surgery
- are eating less due to illness, surgery, or a change in your diet
- have or have had problems with your pancreas, including pancreatitis or surgery on your pancreas
- drink alcohol very often, or drink a lot of alcohol in the short term ("binge" drinking)
- have any other medical conditions
- are pregnant or plan to become pregnant. JARDIANCE may harm your unborn baby. Tell your doctor right away if you become pregnant during treatment with JARDIANCE.

- are breastfeeding or are planning to breastfeed. JARDIANCE may pass into your breast milk and may harm your baby. Do not breastfeed while taking JARDIANCE.

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

You are encouraged to report negative side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch (link is external) 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 to help those living with heart failure or chronic kidney disease.

Currently, no Boehringer Ingelheim and Lilly products are approved for the treatment of heart failure or chronic kidney disease.

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

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

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

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

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

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

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

About Eli Lilly and Company
Lilly is a global 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 development and commercialization. Among other things, there can be no guarantee that future study results will be consistent with the results to date or that Jardiance will receive additional regulatory approvals. For further discussion of these and other risks and uncertainties, see Lilly's most recent Form 10-K and Form 10-Q filings with the United States Securities and Exchange Commission. Except as required by law, Lilly undertakes no duty to update forward-looking statements to reflect events after the date of this release.

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