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First dedicated outcome trials of empagliflozin in chronic heart failure initiated

- EMPEROR HF clinical trial program will evaluate the efficacy and safety of empagliflozin in patients with chronic heart failure, including those with and without type 2 diabetes
- Heart failure affects 26 million people worldwide, and 5.7 million people in the U.S., and is associated with high morbidity and mortality
- EMPEROR HF will include approximately 7,000 patients with chronic heart failure across two trials

RIDGEFIELD, Conn. and INDIANAPOLIS, March 17, 2017 /PRNewswire/ -- Boehringer Ingelheim and Eli Lilly and Company (NYSE: LLY) today announced that the EMPEROR HF clinical trial program was initiated. EMPEROR HF comprises two phase III outcome studies that will investigate empagliflozin for the treatment of adults with chronic heart failure. The trials will involve not only adults with type 2 diabetes who have heart failure, but also heart failure patients who do not have diabetes.

Heart failure is a condition where the heart cannot pump enough blood around the body, and is associated with high morbidity and mortality. Approximately 26 million people worldwide, and 5.7 million people in the U.S. suffer from heart failure. It is the leading cause of hospitalizations in the United States and Europe, with more than 1 million admissions annually for heart failure as the primary diagnosis. Readmission rates after a hospital stay for heart failure are as high as 30 percent within 60 to 90 days, and approximately 50 percent of patients diagnosed with heart failure will die within five years.

"Heart failure is a global health burden. We need to explore new treatment options, especially for those types of heart failure where treatments are currently limited," said Professor Milton Packer, MD, Baylor Heart and Vascular Institute, Baylor University Medical Center, USA, lead investigator of both trials. "The EMPA-REG OUTCOME® trial demonstrated a significant reduction in the risk of cardiovascular death with empagliflozin in adults with type 2 diabetes and cardiovascular disease. And now these new EMPEROR HF clinical trials will take a dedicated look at the effects of empagliflozin in heart failure patients."

Jardiance® (empagliflozin) is the first type 2 diabetes medicine approved by the U.S. Food and Drug Administration (FDA) to reduce the risk of cardiovascular death in adults with type 2 diabetes and established cardiovascular disease. EMPA-REG OUTCOME demonstrated that JARDIANCE reduced the risk of cardiovascular death by 38 percent versus placebo in patients with type 2 diabetes and established cardiovascular disease when added to standard of care (including glucose-lowering agents and cardiovascular drugs). As one of the secondary endpoints, the trial also showed a reduction in the risk of hospitalization for heart failure by 35 percent with JARDIANCE in this patient population. These data are not included in the current JARDIANCE label.

Heart failure can be categorized by ejection fraction, a measurement used to determine how well the heart pumps blood around the body. The EMPEROR HF program consists of two event-driven phase III clinical trials that will investigate empagliflozin for the treatment of adults with chronic heart failure with either preserved ejection fraction or reduced ejection fraction. Both trials will assess the impact of treatment with empagliflozin on cardiovascular death and hospitalization for heart failure as primary endpoints. The two trials will involve approximately 7,000 patients in total and are anticipated to complete in 2020.

"Despite currently available therapies, about half of people who develop heart failure die within 5 years of diagnosis. This highlights a real need for progress in the treatment of this condition," said Prof. Hans-Juergen Woerle, Global Vice President Medicine, Therapeutic Area Metabolism, Boehringer Ingelheim. "Our new studies aim to explore the potential of empagliflozin for patients affected by heart failure. At the same time, these studies mark the first time empagliflozin will be evaluated in people without type 2 diabetes. So we are very excited about the initiation of these two new studies."

JARDIANCE is not for people with type 1 diabetes or people with diabetic ketoacidosis (increased ketones in the blood or urine).

About the EMPEROR HF Clinical Trial Program

The EMPEROR (EMPagliflozin outcomE tRial in patients with chrOnic heaRt failure) HF clinical trial program will investigate

once daily empagliflozin compared with placebo in heart failure patients both with and without type 2 diabetes receiving current standard of care. The program comprises the following two phase III, randomized, double-blind trials which assess heart failure in patients with preserved ejection fraction or patients with reduced ejection fraction*:

- **EMPEROR HF-Preserved** [NCT03057951]**:** will investigate the safety and efficacy of empagliflozin 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 (HHF) [Time Frame: up to 38 months]
  - Anticipated number of patients: approx. 4,100
  - Estimated completion: 2020
- **EMPEROR HF-Reduced** [NCT03057977]: will investigate the safety and efficacy of empagliflozin in patients with chronic heart failure with **reduced ejection fraction** (HFrEF).
  - Primary endpoint: time to first event of adjudicated cardiovascular death or adjudicated HHF [Time Frame: up to 38 months]
  - Anticipated number of patients: approx. 2,800
  - Estimated completion: 2020

***Ejection fraction** is a measurement of the percentage of blood leaving the heart each time it contracts. 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 with a normally functioning heart.

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.

About Heart Failure
Heart failure is a debilitating and potentially fatal condition that occurs when the heart cannot pump enough blood around the body. Heart failure is a prevalent disease; 26 million people around the world, and 5.7 million people in the U.S. have chronic heart failure. There is a high unmet need in the treatment of heart failure as there remains a significant morbidity and mortality associated with the condition. Heart failure is the leading cause of hospitalization in the United States and Europe, with over 1 million admissions. Readmission rates after a hospital stay for heart failure are as high as 30 percent within 60 to 90 days, and approximately 50 percent of patients diagnosed with heart failure will die within five years. Heart failure is highly prevalent in patients with diabetes; however, approximately half of all heart failure patients do not have diabetes.

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

What is the most important information I should know about JARDIANCE?

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.

- **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

- **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.
- **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.

Who should not take JARDIANCE?

Do not take JARDIANCE if you are allergic to empagliflozin or any of the ingredients in JARDIANCE. Symptoms of serious allergic reactions to JARDIANCE may include:

- skin rash
- raised red patches on your skin (hives)
- swelling of the face, lips, tongue, and throat that may cause difficulty breathing or swallowing.

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

Do not take JARDIANCE if you have severe kidney problems or are on dialysis.

What should I tell my doctor before using 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 planning to become pregnant. It is unknown if JARDIANCE will harm your unborn baby
- are breastfeeding, or plan to breastfeed. It is unknown if JARDIANCE passes into your breast milk.

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.

What are other possible side effects of JARDIANCE?

- **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

- **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.

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

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

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 full Prescribing Information and Patient Information.

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Boehringer Ingelheim and Eli Lilly and Company
In January 2011, Boehringer Ingelheim and Eli Lilly and Company announced an alliance in diabetes that centers on compounds representing several of the largest diabetes treatment classes. This alliance leverages the strengths of two of the world's leading pharmaceutical companies. By joining forces, the companies demonstrate commitment in the care of patients with diabetes and stand together to focus on patient needs. Find out more about the alliance at www.boehringer-ingelheim.com or www.lilly.com.

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

Boehringer Ingelheim is one of the world's 20 leading pharmaceutical companies. Headquartered in Ingelheim, Germany, the company operates globally with 145 affiliates and about 50,000 employees. Since its founding in 1885, the family-owned company has been committed to researching, developing, manufacturing and marketing novel treatments for human and veterinary medicine.

Boehringer Ingelheim is committed to improving lives and providing valuable services and support to patients and families. Our employees create and engage in programs that strengthen our communities. To learn more about how we make more health for more people, visit our Corporate Social Responsibility Report.

In 2015, Boehringer Ingelheim achieved net sales of about $15.8 billion (14.8 billion euros). R&D expenditure corresponds to 20.3 percent of its net sales.

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 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 www.lilly.com/newsroom/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 as a treatment for adults with heart failure 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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