Boehringer Ingelheim and Lilly announce an academic collaboration with University of Oxford to investigate the effects of Jardiance® in adults with chronic kidney disease

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- University of Oxford, in partnership with the Duke Clinical Research Institute, to assess effect of Jardiance (empagliflozin) on heart and kidney disease in adults with chronic kidney disease

- EMPA-KIDNEY will be part of the empagliflozin clinical development program which explores the efficacy and safety of Jardiance across a broad spectrum of patients and clinical conditions

RIDGEFIELD, Conn. and INDIANAPOLIS, April 16, 2018 /PRNewswire/ -- Boehringer Ingelheim and Eli Lilly and Company (NYSE: LLY) today announced an academic collaboration with the University of Oxford to investigate the effects of Jardiance® on the progression of kidney disease and the occurrence of cardiovascular death, in adults with established chronic kidney disease with and without diabetes. EMPA-KIDNEY will be independently conducted, analyzed and reported by the Medical Research Council Population Health Research Unit at the University of Oxford (MRC PHRU), which is based in the Clinical Trial Service Unit and Epidemiological Studies Unit (CTSU), in partnership with the Duke Clinical Research Institute. Boehringer Ingelheim and Lilly will provide the funding for the study.

The plan to conduct a dedicated outcomes study in adults with chronic kidney disease is based on insights previously obtained from the EMPA-REG OUTCOME® trial. This landmark trial investigated the effect of Jardiance, when added to the standard of care, on cardiovascular outcomes in adults with type 2 diabetes and established cardiovascular disease, compared with placebo. Approximately one third of patients in the EMPA-REG OUTCOME trial also had established chronic kidney disease at baseline. A secondary exploratory endpoint of the study provided promising data relating to the reduction in the relative risk of new onset or worsening kidney disease. EMPA-KIDNEY will help further our understanding of these data.

"We need to explore new treatment options that can help slow the progression of chronic kidney disease, given that 30 million adults in the United States are living with this condition," said Jennifer Green, M.D., endocrinologist and associate professor of medicine at the Duke Clinical Research Institute, which is responsible for U.S. trial operations. "The EMPA-REG OUTCOME trial findings prompted us to explore further the effects of empagliflozin on the risk of new or worsening kidney disease in adults with type 2 diabetes and established cardiovascular disease. Now, EMPA-KIDNEY will examine whether empagliflozin has the potential to be a new treatment option for people with chronic kidney disease."

EMPA-KIDNEY will include approximately 5,000 adults with established chronic kidney disease, with and without diabetes. The primary outcome of the study is to assess the effect of Jardiance on time to clinically relevant kidney disease progression or cardiovascular death. The study will be part of the empagliflozin clinical development program, the largest clinical development program of an SGLT2 inhibitor.

"Boehringer Ingelheim and Lilly are committed to exploring how Jardiance can potentially fill gaps where unmet treatment needs exist," said Thomas Seck, M.D., vice president of Clinical Development and Medical Affairs – Primary Care, Boehringer Ingelheim Pharmaceuticals, Inc. "Given the institution's knowledge and history of prestigious research in chronic kidney disease, we are excited to collaborate with the University of Oxford on this initiative to help address a pressing need for people with chronic kidney disease."

"The EMPA-KIDNEY study, which will build on results of the EMPA-REG OUTCOME trial, will continue to expand our understanding of how Jardiance can impact the lives of a broad range of people with and without diabetes," said Jeff Emmick, M.D., Ph.D., vice president, Product Development, Lilly Diabetes. "We look forward to this new partnership and the opportunity to follow the progress of the EMPA-KIDNEY study."

About the MRC PHRU at the University of Oxford

The focus of MRC PHRU at the University of Oxford (https://www.mrc-phru.ox.ac.uk/), which is led by Professor Colin Baigent, is to improve treatment and prevention of chronic diseases, particularly cardiovascular disease and metabolic disease (e.g. diabetes mellitus and chronic kidney disease), which collectively account for a large proportion of premature adult deaths and the burden of disability worldwide. MRC PHRU leads innovative clinical trials and meta-analyses to identify important advances that could have a major impact on health. Its worldwide approach, involving the study of large numbers of people, provides reliable information about the causes of disease and the effects of treatments, which can have a major impact on global health.

About EMPA-KIDNEY: The study of heart and kidney protection with empagliflozin

EMPA-KIDNEY is a multinational randomized, double-blind, placebo-controlled clinical trial. It is designed to evaluate the effect of empagliflozin on clinically relevant outcomes: kidney disease progression and cardiovascular mortality risk. The primary outcome is defined as time to a first event of either a cardiovascular death or kidney disease progression, defined as end stage kidney disease (the need for kidney replacement therapy such as, dialysis or kidney transplantation), a sustained decline in eGFR to <10mL/min/1.73m^2, renal death or a sustained decline of ≥40% in eGFR from randomization. EMPA-KIDNEY will include people with established chronic kidney disease both with and without diabetes receiving current standard of care.

The study will be conducted in selected countries representing a global footprint and aims to randomize approximately 5,000 participants to receive either empagliflozin 10 mg once daily or placebo, on top of standard of care.

About Chronic Kidney Disease

Chronic kidney disease is defined as a progressive decline of kidney function over time. About two thirds of chronic kidney disease cases are attributable to metabolic diseases such as diabetes, hypertension and obesity. Notably, chronic kidney disease is associated with increased morbidity and mortality. The majority of deaths among people with chronic kidney disease occur as a result of cardiovascular complications, often before reaching end stage renal disease. Chronic kidney disease affects approximately 15 percent of adults in the United States and treatment costs are estimated to exceed $48 billion annually. Since there are currently only few treatment options, the overarching unmet medical need for new treatment options in chronic kidney disease is evident.

About EMPA-REG OUTCOME® (NCT01131676)
EMPA-REG OUTCOME was a long-term, multicenter, randomized, double-blind, placebo-controlled trial of more than 7,000 patients from 42 countries with type 2 diabetes and established cardiovascular disease.

The study assessed the effect of Jardiance (10 mg or 25 mg once daily) added to standard of care compared with placebo added to standard of care. Standard of care was comprised of glucose-lowering agents and cardiovascular drugs (including for blood pressure and cholesterol). The primary endpoint was defined as time to first occurrence of cardiovascular death, non-fatal heart attack or non-fatal stroke.

Although the EMPA-REG OUTCOME trial was not designed to assess the potential mechanisms behind the effect of Jardiance on kidney outcomes, the kidney assessment was part of a pre-specified exploratory analysis plan of additional endpoints.

The overall safety profile of Jardiance was consistent with that of previous trials.

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.

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 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 plan 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.

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.
- **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.

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 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 creates value through innovation for three business areas including human pharmaceuticals, animal health and biopharmaceutical contract manufacturing.

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

In 2016, Boehringer Ingelheim achieved net sales of about $17.6 billion (15.9 billion euros). R&D expenditure corresponds to 19.6 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 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 the expansion of clinical trials to evaluate Jardiance as a treatment for adults with chronic kidney disease 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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