

Breakthrough results for Jardiance® (empagliflozin) confirm EMPEROR-Preserved as first and only successful trial for heart failure with preserved ejection fraction

- The EMPEROR-Preserved phase III trial met its primary endpoint and demonstrated significant risk reduction with Jardiance for the composite of cardiovascular death or hospitalization for heart failure in adults with heart failure with preserved ejection fraction

- Heart failure with preserved ejection fraction has been classified as "the single largest unmet need in cardiovascular medicine" based on prevalence, poor outcomes and absence of clinically proven therapies to date

- With approval, Jardiance would become the first and only clinically proven therapy to improve outcomes for the full spectrum of heart failure patients regardless of ejection fraction

RIDGEFIELD, Conn. and INDIANAPOLIS, July 6, 2021 /PRNewswire/ -- The EMPEROR-Preserved phase III trial met its primary endpoint, establishing Jardiance® (empagliflozin) as the first and only therapy to significantly reduce the risk of the composite of cardiovascular death or hospitalization for heart failure in adults, with or without diabetes, who live with heart failure with preserved ejection fraction (HFpEF). Boehringer Ingelheim and Eli Lilly and Company (NYSE: LLY) announced the topline results today. When added to the EMPEROR-Reduced trial results, these findings demonstrate Jardiance's efficacy in all forms of heart failure regardless of ejection fraction. The safety profile was generally consistent with the known safety profile of Jardiance.

"We look forward to presenting the EMPEROR-Preserved results at ESC 2021, which should offer a significant breakthrough in cardiovascular medicine and a new hope for people with HFpEF, which is an increasingly prevalent public health issue. HFpEF has long been the most challenging form of heart failure to treat," said Professor Stefan Anker, heart failure cardiologist at Charité Berlin, Germany, and EMPEROR-Preserved principal investigator. "Building on previous results from the EMPA-REG OUTCOME trial, and the EMPEROR-Reduced trial in heart failure with reduced ejection fraction, the EMPEROR-Preserved findings demonstrate that empagliflozin reduces cardiovascular death or hospitalization for heart failure and has the potential to transform the care of people living with heart failure."

Heart failure poses a significant global disease burden: more than 60 million patients worldwide have heart failure, and half of them have HFpEF. Heart failure is a leading cause of hospitalization and is becoming increasingly prevalent in Western countries due to aging populations. The risk of death in people with heart failure rises with each hospital admission. Heart failure with left ventricular preserved ejection fraction occurs when the left ventricle of the heart is unable to fill properly, resulting in less blood being pumped to the body.

"No approved therapies have been clinically proven to improve outcomes specifically for people with HFpEF, leaving a significant unmet medical need in this already prevalent and increasingly common form of heart failure," 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 totality of the data from the EMPEROR-Preserved trial marks a possible new chapter in heart failure, supporting the potential of Jardiance to become the first SGLT2 inhibitor to treat a defined population of adults with heart failure with either preserved or reduced ejection fraction."

"Jardiance was the first SGLT2 inhibitor to reduce cardiovascular death for people with type 2 diabetes and cardiovascular disease, and we have now reached another important milestone, this time in heart failure," added Jeff Emmick, M.D., Ph.D., vice president, Product Development, Lilly. "The EMPEROR-Preserved results offer promise in a type of heart failure that until now has traditionally been very challenging to treat effectively. The EMPEROR heart failure studies are part of our EMPOWER clinical trial program exploring the effect of Jardiance across a spectrum of cardio-renal-metabolic diseases, aiming to significantly improve outcomes in these highly prevalent conditions that impact many people's lives."

The EMPEROR-Preserved trial investigated Jardiance 10 mg compared with placebo. Full results from the EMPEROR-Preserved trial are scheduled for presentation at the European Society of Cardiology (ESC) Congress 2021 on August 27. Boehringer Ingelheim and Lilly plan for regulatory submissions in 2021.

These results add to previous findings from the EMPEROR-Reduced phase III trial, which showed that Jardiance significantly reduced the combined relative risk of cardiovascular death or hospitalization for heart failure by 25% compared to placebo in adults with heart failure with reduced ejection fraction (HFrEF). Together, these studies demonstrate the benefits of Jardiance for patients across the full heart failure spectrum (including HFrEF and HFpEF).

The EMPEROR-Reduced results formed the basis of the recent approval of a new indication for Jardiance for the treatment of adults with HFrEF by the European Commission. In the U.S., Jardiance is not approved for the treatment of heart failure. A supplemental New Drug Application (sNDA) for Jardiance to reduce the risk of cardiovascular death or hospitalization for heart failure in adults with HFrEF has been submitted to the U.S. Food and Drug Administration (FDA), with a decision expected later this year. Research is ongoing regarding Jardiance's effects on hospitalization for heart failure and mortality in post-myocardial infarction (heart attack) patients with high risk of heart failure. Jardiance is also currently being investigated in chronic kidney disease.

About the EMPEROR Heart Failure Studies

The EMPEROR (EMPAgliflozin outcomE tRial in patients with chrOnic heaRt failure) heart failure studies are two phase III, randomized, double-blind trials investigating once-daily Jardiance compared with placebo in adults with heart failure with preserved or reduced ejection fraction*, both with and without diabetes, who are receiving current standard of care:

- **EMPEROR-Reduced** [[NCT03057977](#)] investigated the safety and efficacy of Jardiance in patients with chronic heart failure with **reduced ejection fraction** (HFrEF).
 - Primary endpoint: time to first event of adjudicated cardiovascular death or adjudicated hospitalization for heart failure
 - Number of patients: 3,730
 - Completion: 2020
- **EMPEROR-Preserved** [[NCT03057951](#)] investigated the safety and efficacy of Jardiance 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 [Time Frame: up to 38 months]
 - Number of patients: 5,988
 - Completion: 2021

***Ejection fraction** is a measurement of the percentage of blood the left ventricle pumps out with each contraction. When the heart relaxes, the ventricle refills with blood.

- **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.
- **HFpEF** occurs when the heart muscle contracts normally but the ventricle does not fill with enough blood, so less blood can enter the heart compared with a normally functioning heart.

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

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? (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. 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 doctor 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 doctor 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 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).**
- **Vaginal yeast infection.** Talk to your doctor 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 doctor 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 penis.
- **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.

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 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 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 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 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, 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, visit <http://www.lillydiabetes.com/> or follow us on Twitter: [@LillyDiabetes](https://twitter.com/LillyDiabetes) and Facebook: [LillyDiabetesUS](https://www.facebook.com/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 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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¹ Butler J, Fonarow G, Zile M, *et al.* Developing therapies for heart failure with preserved ejection fraction: Current State and Future Directions. *JACC Heart Fail.* 2014 Apr;2(2):97–112.



SOURCE Eli Lilly and Company

<https://stage.mediaroom.com/lilly/2021-07-06-Breakthrough-results-for-Jardiance-R-empagliflozin-confirm-EMPEROR-Preserved-as-first-and-only-successful-trial-for-heart-failure-with-preserved-ejection-fraction>