Boehringer Ingelheim and Lilly announce the CAROLINA® cardiovascular outcome trial of Tradjenta® met its primary endpoint of non-inferiority compared with glimepiride

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- Tradjenta (linagliptin) demonstrated no increased cardiovascular risk compared with glimepiride in adults with type 2 diabetes and cardiovascular risk

- With a median follow-up of more than 6 years, CAROLINA adds evidence to the long-term safety profile of Tradjenta

RIDGEFIELD, Conn. and INDIANAPOLIS, Feb. 14, 2019 /PRNewswire/ -- Boehringer Ingelheim and Eli Lilly and Company (NYSE: LLY) announced CAROLINA® (CARdiovascular Outcome study of LINAgliptin versus glimepiride in patients with type 2 diabetes) met its primary endpoint, defined as non-inferiority for Tradjenta® (linagliptin) versus glimepiride in time to first occurrence of cardiovascular death, non-fatal myocardial infarction or non-fatal stroke (3P-MACE).

CAROLINA is the only active-comparator cardiovascular outcome trial for a dipeptidyl peptidase-4 (DPP-4) inhibitor. The trial evaluated the cardiovascular safety of Tradjenta (5 mg once daily) compared with the sulfonylurea glimepiride, on top of standard of care, in 6,033 adults with type 2 diabetes and increased cardiovascular risk or established cardiovascular disease. The study assessed Tradjenta safety over the longest period ever studied in a DPP-4 inhibitor cardiovascular outcome trial, with a median follow-up of more than 6 years. The overall safety profile of Tradjenta in CAROLINA was consistent with previous data, and no new safety signals were observed.

People with type 2 diabetes have an increased risk of cardiovascular disease, and despite recent advancements in treatment options, cardiovascular disease remains the leading cause of death for this population. Together with CARMELINA®, which demonstrated similar long-term cardiovascular safety compared with placebo in adults with type 2 diabetes at high risk for cardiovascular and/or kidney disease, CAROLINA confirms the long-term overall safety profile of Tradjenta in a broad range of adults with type 2 diabetes.

"Guidelines from the American College of Cardiology and American Diabetes Association recommend type 2 diabetes treatments with proven cardiovascular benefits for patients with established cardiovascular disease," said Thomas Seck, M.D., senior vice president, Medicine and Regulatory Affairs, Boehringer Ingelheim Pharmaceuticals, Inc. "But physicians considering additional therapies to lower glucose values for their patients need a DPP-4 inhibitor with an established long-term safety profile. Along with CARMELINA, CAROLINA provides Tradjenta with one of the most comprehensive datasets on the safety of a DPP-4."

"These data provide further confidence in the well-established safety and tolerability profile of Tradjenta for the treatment of adults with type 2 diabetes," added Jeff Emmick, M.D., Ph.D., vice president, Product Development, Lilly Diabetes. "Tradjenta is an important option for physicians considering a DPP-4 inhibitor for their patients with type 2 diabetes. Boehringer Ingelheim and Lilly look forward to sharing the full results later this year.

The full results of CAROLINA will be presented on June 10 at the American Diabetes Association's 79th Scientific Sessions in San Francisco.

ABOUT CAROLINA (NCT01243424)

CAROLINA (CARdiovascular Outcome study of LINAgliptin versus glimepiride in patients with type 2 diabetes) is a multi-national, randomized, double-blind, active-controlled clinical trial that involved 6,033 adults with type 2 diabetes from 43 countries at more than 600 sites observed for a median duration of more than 6 years. The trial included adults with early type 2 diabetes: adults with a median disease duration of 6.2 years who either received no treatment or received one or two glucose-lowering agents (e.g., metformin). The study was designed to assess the effect of Tradjenta (5 mg once daily) compared with the sulfonylurea glimepiride (both added to stable background glucose-lowering medication and cardiovascular standard of care) on cardiovascular safety in adults with type 2 diabetes and increased cardiovascular risk or established cardiovascular disease. These patients reflect people that doctors typically see in their daily clinical practice.

CAROLINA was led by an academic trial steering committee and Boehringer Ingelheim and Eli Lilly and Company. CAROLINA is the first DPP-4 inhibitor active-comparator cardiovascular outcome trial.

About our cardiovascular outcome trials

Cardiovascular outcome trials are highly relevant, as cardiovascular disease is a major complication and the leading cause of death in people with type 2 diabetes. Worldwide, most people with type 2 diabetes die of a cardiovascular event. In 2015, Boehringer Ingelheim and Eli Lilly and Company announced results from the landmark cardiovascular outcome trial EMPA-REG OUTCOME® with the SGLT2 inhibitor empagliflozin, which reduced the relative risk of cardiovascular death by 38 percent in adults with type 2 diabetes and established cardiovascular disease, on top of standard of care.[*][†] As a result, empagliflozin was the first type 2 diabetes medicine approved by the FDA to reduce the risk of cardiovascular death.

CAROLINA is one of two cardiovascular outcome trials with the DPP-4 inhibitor Tradjenta. CAROLINA and CARMELINA (CArdiovascular safety and Renal Microvascular outcomE with LINAgliptin in patients with type 2 diabetes at high vascular risk) provide one of the most comprehensive datasets on the long-term safety of a DPP-4-inhibitor across a broad range of patients with type 2 diabetes.

CARMELINA is a multi-national, randomized, double-blind, placebo-controlled clinical trial that involved 6,979 adults with type 2 diabetes from 27 countries at more than 600 sites observed for a median duration of 2.2 years. CARMELINA studied the impact of Tradjenta on cardiovascular and kidney safety in adults with type 2 diabetes at high risk for cardiovascular and/or kidney disease. The study met its primary endpoint,[‡] with Tradjenta demonstrating a similar cardiovascular safety profile compared with placebo when added to standard of care. CARMELINA also included a key secondary composite endpoint,[§] showing a similar kidney safety profile compared with placebo. The overall safety profile of Tradjenta in CARMELINA was consistent with previous data, and no new safety signals were observed. CARMELINA also showed a similar rate of hospitalization for heart failure for Tradjenta compared with placebo.

To learn more about CARMELINA, please visit: https://www.carmelinatrial.com/

What is TRADJENTA?
TRADJENTA is a prescription medicine that is used along with diet and exercise to lower blood sugar in adults with type 2 diabetes.

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

If you have had inflammation of the pancreas (pancreatitis) in the past, it is not known if you have a higher chance of getting pancreatitis while you take TRADJENTA.

IMPORTANT SAFETY INFORMATION

What is the most important information I should know about TRADJENTA?
Serious side effects can happen to people taking TRADJENTA, including inflammation of the pancreas (pancreatitis), which may be severe and lead to death. Before you start taking TRADJENTA, tell your doctor if you have ever had pancreatitis, gallstones, a history of alcoholism, or high triglyceride levels.

Stop taking TRADJENTA and call your doctor right away if you have pain in your stomach area (abdomen) that is severe and will not go away. The pain may be felt going from your abdomen through to your back. The pain may happen with or without vomiting. These may be symptoms of pancreatitis.

Heart failure. Heart failure means your heart does not pump blood well enough. Before you start taking TRADJENTA, tell your doctor if you have ever had heart failure or have problems with your kidneys. Contact your doctor right away if you have any of the following symptoms: increasing shortness of breath or trouble breathing, especially when you lie down; swelling or fluid retention, especially in the feet, ankles, or legs; an unusually fast increase in weight or unusual tiredness. These may be symptoms of heart failure.

Who should not take TRADJENTA?
Do not take TRADJENTA if you are allergic to linagliptin or any of the ingredients in TRADJENTA.

Symptoms of a serious allergic reaction to TRADJENTA may include rash, itching, flaking or peeling; raised red patches on your skin (hives); swelling of your face, lips, tongue, and throat that may cause difficulty breathing or swallowing. If you have any of these symptoms, stop taking TRADJENTA and call your doctor or go to the emergency room right away.

What should I tell my doctor before using TRADJENTA?
Tell your doctor about all your medical conditions, including if you have or have had inflammation of your pancreas (pancreatitis). Tell your doctor about all the medicines you take, including prescription and non-prescription medicines, vitamins, and herbal supplements. TRADJENTA may affect the way other medicines work, and other medicines may affect how TRADJENTA works. Especially tell your doctor if you take

- other medicines that can lower your blood sugar. If you take TRADJENTA with another medicine that can cause low blood sugar, such as sulfonylurea or insulin, your risk of getting low blood sugar is higher. The dose of your sulfonylurea or insulin may need to be lowered while you take TRADJENTA.
- rifampin (Rifadin®, Rimactane®, Rifater®, Rifamate®),* an antibiotic that is used to treat tuberculosis.

*These trademarks are owned by third parties not affiliated with TRADJENTA.

Tell your doctor if you are pregnant or planning to become pregnant or are breastfeeding or plan to breastfeed.

What are the possible side effects of TRADJENTA?
TRADJENTA may cause serious side effects, including

- Inflammation of the pancreas (pancreatitis).
- Low blood sugar (hypoglycemia), especially if you take TRADJENTA with another medicine that can cause low blood sugar. Signs and symptoms of low blood sugar may include headache, drowsiness, weakness, dizziness, confusion, irritability, hunger, fast heartbeat, sweating, or feeling jittery.
- Allergic (hypersensitivity) reactions can happen after your first dose or up to 3 months after starting TRADJENTA. Symptoms may include swelling of your face, lips, throat, and other areas on your skin; difficulty with swallowing or breathing; raised, red areas on your skin (hives); skin rash, itching, flaking, or peeling.
- Joint pain. Some people who take medicines called dipeptidyl peptidase-4 (DPP-4) inhibitors like TRADJENTA, may develop joint pain that can be severe. Call your doctor if you have severe joint pain.
- Skin Reaction. Some people who take medicines called DPP-4 inhibitors like TRADJENTA, may develop a skin reaction called bullous pemphigoid which can be serious and may need to be treated in a hospital. Tell your doctor right away if you develop blisters.

The most common side effects of TRADJENTA include stuffy or runny nose, sore throat, cough, and diarrhea.

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

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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. The alliance leverages the strengths of two of the world's leading pharmaceutical companies. By joining forces, the companies demonstrate commitment in the care of people 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, 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 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 www.boehringer-ingelheim.us/csr to learn more about how we make more health through our Corporate Social Responsibility initiatives.

In 2017, Boehringer Ingelheim achieved net sales of about $20.4 billion (18.1 billion euros). R&D expenditure corresponds to approximately $3.4 billion (three billion euros), or 17.0 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 Tradjenta and its safety profile, 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 Tradjenta 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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[*] Adults with type 2 diabetes and coronary artery disease, peripheral artery disease, or a history of MI or stroke

[†] Standard of care included cardiovascular medications and blood sugar lowering agents given at the discretion of physicians

[‡] Primary endpoint defined as time to first occurrence of the 3P-MACE (cardiovascular death, non-fatal myocardial infarction or non-fatal stroke)

[§] Key secondary endpoint defined as time to first occurrence of sustained end stage kidney disease (ESKD), death due to kidney disease, or a

sustained decrease in eGFR from baseline of ≥40 percent compared to placebo

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SOURCE Eli Lilly and Company