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Type 2 Diabetes: Investigational Empagliflozin/Linagliptin Combination Tablet Showed Reduction in Blood Glucose in Two Phase III Trials

- For those taking metformin, empagliflozin/linagliptin combination tablet showed statistically significant reductions in blood glucose vs. empagliflozin or linagliptin alone after 24 weeks
- For treatment-naïve adults, empagliflozin 10 mg/linagliptin 5 mg combination tablet showed significant reductions in baseline blood glucose levels compared with empagliflozin 10 mg or linagliptin 5 mg; however, reductions seen with empagliflozin 25 mg/linagliptin 5 mg did not reach statistical significance compared with empagliflozin 25 mg
- Safety data of the combination tablet were similar to the known safety data of the individual components

RIDGEFIELD, Conn. and INDIANAPOLIS, June 15, 2014 /PRNewswire/ -- Two phase III clinical trials found the investigational combination tablet of empagliflozin and linagliptin reduced blood glucose levels in adults with type 2 diabetes (T2D), Boehringer Ingelheim Pharmaceuticals, Inc. (BIPI) and Eli Lilly and Company (NYSE: LLY) announced. The findings were presented as late breaking abstracts today at the American Diabetes Association 74th Scientific Sessions®. The 24-week primary findings of these two 52-week trials compared the combination of empagliflozin and linagliptin with empagliflozin or linagliptin alone in patients with T2D and moderately elevated blood glucose levels consistent with what is often seen in clinical practice.[1,2,3]

"We are encouraged by the reductions in blood glucose levels with the empagliflozin/linagliptin combination tablet and by the fact that more than half of the 494 adults with type 2 diabetes in these studies were able to achieve blood glucose goals below 7.0 percent with the combination," said Christophe Arbet-Engels, M.D., Ph.D., vice president, metabolic clinical development and medical affairs, BIPI. "People with type 2 diabetes must often take more than one medication to adequately control their blood sugar levels. If approved, this combination tablet with two mechanisms of action that lower A1C through different pathways in a single pill could be an important treatment option for physicians and patients."

If approved, this investigational combination would bring together the distinct mechanisms of action of a sodium glucose co-transporter-2 (SGLT2) inhibitor and a dipeptidyl peptidase-4 (DPP-4) inhibitor for the first time in one tablet. SGLT2 inhibitors remove excess glucose through the urine by blocking blood glucose re-absorption in the kidney. DPP-4 inhibitors work by increasing hormones that stimulate the pancreas to produce more insulin and stimulate the liver to produce less glucose.

Investigational empagliflozin/linagliptin combination in adults with T2D with moderate hyperglycemia at baseline (mean baseline of 8.0 percent) who were taking metformin

This 52-week study of 686 randomized adults with T2D examined the change from baseline of hemoglobin A1C (a measure of average blood glucose over the past two to three months) at 24 weeks. Adults in this study had a mean baseline A1C of 8.0 percent.

- Both empagliflozin/linagliptin combination doses showed statistically significant reductions in A1C vs. the empagliflozin component dose or linagliptin alone.
- Statistically significantly more adults who had A1C levels of 7.0 percent or more at baseline achieved A1C levels less than 7.0 percent after 24 weeks with both doses of the empagliflozin/linagliptin combination versus either empagliflozin or linagliptin alone.
    - Empagliflozin 25 mg/linagliptin 5 mg: 61.8 percent
    - Empagliflozin 10 mg/linagliptin 5 mg: 57.8 percent
    - Empagliflozin 25 mg: 32.6 percent
    - Empagliflozin 10 mg: 28.0 percent
    - Linagliptin 5 mg: 36.1 percent
- For adults who had A1C levels of 8.5 percent or greater at baseline, the following reductions in A1C were seen.
    - The empagliflozin 25 mg/linagliptin 5 mg combination reduced A1C by 1.8 percent, compared with 1.2 percent for empagliflozin 25 mg.
    - The empagliflozin 10 mg/linagliptin 5 mg combination reduced A1C by 1.6 percent, compared with 1.3 percent for empagliflozin 10 mg.
    - Linagliptin 5 mg alone reduced A1C by 1.0 percent.
- The empagliflozin/linagliptin combinations resulted in weight loss similar to that of empagliflozin monotherapy.

- Empagliflozin 25 mg/linagliptin 5 mg: body weight reduction of 3.0 kg from a mean baseline of 85.5 kg
- Empagliflozin 10 mg/linagliptin 5 mg: body weight reduction of 2.6 kg from a mean baseline of 86.6 kg
- Empagliflozin 25 mg: body weight reduction of 3.2 kg from a mean baseline of 87.7 kg
- Empagliflozin 10 mg: body weight reduction of 2.5 kg from a mean baseline of 86.1 kg

Adverse events (AEs) were reported in 54.7 percent of subjects on the empagliflozin 25 mg/linagliptin 5 mg combination, 54.4 percent of subjects on the empagliflozin 10 mg/linagliptin 5 mg combination, 63.1 percent of subjects on empagliflozin 25 mg, 57.1 percent of subjects on empagliflozin 10 mg and 54.5 percent of subjects on linagliptin 5 mg. Confirmed hypoglycemic AEs were reported in two subjects each on the empagliflozin 25 mg/linagliptin 5 mg combination (1.5 percent), the empagliflozin 10 mg/linagliptin 5 mg combination (1.5 percent), empagliflozin 10 mg (1.4 percent) and linagliptin 5 mg (1.5 percent), and four on empagliflozin 25 mg (2.8 percent); none required assistance.

Investigational empagliflozin/linagliptin combination in treatment-naïve adults with T2D with moderate hyperglycemia at baseline (mean baseline of 8.0 percent)

This 52-week study of 677 adults with T2D who were treatment-naïve examined the reduction in A1C from baseline at 24 weeks. As with the metformin study, adults in this study had moderate hyperglycemia (mean A1C of 8.0 percent) at baseline.

- A1C reduction with the empagliflozin 25 mg/linagliptin 5 mg combination was not statistically significantly greater than that of empagliflozin 25 mg.
- A1C reduction with the empagliflozin 10 mg/linagliptin 5 mg combination was significantly greater than that of empagliflozin 10 mg alone.
- Compared with linagliptin 5 mg, both combination doses significantly reduced A1C and body weight.
- Significantly more adults who had A1C levels of 7.0 percent or more at baseline achieved A1C levels less than 7.0 percent after 24 weeks with both doses of the empagliflozin/linagliptin combination versus the empagliflozin component dose or linagliptin alone.
    - Empagliflozin 25 mg/linagliptin 5 mg: 55.4 percent
    - Empagliflozin 10 mg/linagliptin 5 mg: 62.3 percent
    - Empagliflozin 25 mg: 41.5 percent
    - Empagliflozin 10 mg: 38.8 percent
    - Linagliptin 5 mg: 32.3 percent

AEs were reported in 58.8 percent of subjects on the empagliflozin 25 mg/linagliptin 5 mg combination, 63.2 percent of subjects on the empagliflozin 10 mg/linagliptin 5 mg combination, 57.8 percent of subjects on empagliflozin 25 mg, 62.2 percent of subjects on empagliflozin 10 mg and 64.4 percent of subjects on linagliptin 5 mg. Confirmed hypoglycemic AEs were reported in two subjects (1.5 percent) on empagliflozin 25 mg and one each (0.7 percent) on empagliflozin 10 mg and linagliptin 5 mg; none required assistance. No confirmed hypoglycemic events were reported for patients randomized to empagliflozin/linagliptin combinations.

About Empagliflozin
Empagliflozin is an investigational sodium glucose co-transporter-2 (SGLT2) inhibitor and is being studied for the reduction of blood glucose levels in adults with diabetes. The emerging SGLT2 inhibitor class removes excess glucose through the urine by blocking glucose re-absorption in the kidney. Empagliflozin is being studied in one of the largest clinical registration programs in its class, comprised of more than 10 multinational clinical trials and more than 13,000 adults with T2D.

About Linagliptin
Linagliptin, which is marketed as Tradjenta® (linagliptin) tablets in the U.S., is a once-daily, 5-mg tablet used along with diet and exercise to improve glycemic control in adults with T2D. TRADJENTA should not be used in patients with type 1 diabetes or for the treatment of diabetic ketoacidosis. TRADJENTA has not been studied in patients with a history of pancreatitis.

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.

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 symptoms of a serious allergic reaction, 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.

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.

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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To learn more about TRADJENTA visit: www.TRADJENTA.com. For full Prescribing Information and Medication Guide visit: http://bidocs.boehringer-ingelheim.com/BIWebAccess/ViewServlet.ser?docBase=renetnt&folderPath=/Prescribing+Information/PIs/Tradjenta/Tradjenta.pdf.

Please report any unexpected effects or product problems to the Boehringer Ingelheim Drug Information Unit by calling 1-800-

542-6257.

About Diabetes
Approximately 24.4 million Americans and an estimated 382 million people worldwide have type 1 or type 2 diabetes. T2D is the most common type, accounting for an estimated 85 to 95 percent of all diabetes cases. Diabetes is a chronic condition that occurs when the body either does not properly produce, or use, the hormone insulin.[4]

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 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 Pharmaceuticals, Inc.
Boehringer Ingelheim Pharmaceuticals, Inc., based in Ridgefield, CT, is the largest U.S. subsidiary of Boehringer Ingelheim Corporation (Ridgefield, CT) and a member of the Boehringer Ingelheim group of companies.

The Boehringer Ingelheim group is one of the world's 20 leading pharmaceutical companies. Headquartered in Ingelheim, Germany, it operates globally with 142 affiliates and more than 47,400 employees. Since it was founded in 1885, the family-owned company has been committed to researching, developing, manufacturing and marketing novel medications of high therapeutic value for human and veterinary medicine.

Social responsibility is a central element of Boehringer Ingelheim's culture. Involvement in social projects, caring for employees and their families, and providing equal opportunities for all employees form the foundation of the global operations. Mutual cooperation and respect, as well as environmental protection and sustainability are intrinsic factors in all of Boehringer Ingelheim's endeavors.

In 2013, Boehringer Ingelheim achieved net sales of about $18.7 billion (14.1 billion euro). R&D expenditure in the Prescription Medicines business corresponds to 19.5% of its net sales.

For more information please visit http://www.us.boehringer-ingelheim.com.

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 broad and growing product portfolio 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 http://newsroom.lilly.com/social-channels.

This press release contains forward looking statements about the investigational combination tablet of empagliflozin and linagliptin. Empagliflozin is an investigational SGLT2 inhibitor being studied for the treatment of type 2 diabetes, and linagliptin, a DPP-4 inhibitor, is approved for the treatment of type 2 diabetes along with diet and exercise. It reflects Lilly's current beliefs; however, as with any such undertaking, there are substantial risks and uncertainties in the process of drug development and commercialization. There is no guarantee that future study results and patient experience will be consistent with study findings to date, or that the investigational combination tablet of empagliflozin and linagliptin will be commercially successful, or that it will receive regulatory approvals. For further discussion of these and other risks and uncertainties, please see Lilly's latest Forms 10-Q and 10-K filed with the U.S. Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.

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