Trulicity® (dulaglutide) significantly reduced major cardiovascular events for broad range of people with type 2 diabetes

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REWIND data showed a consistent effect in people with and without established cardiovascular disease

INDIANAPOLIS, June 9, 2019 /PRNewswire/ -- Detailed results from REWIND, the Trulicity® (dulaglutide) cardiovascular outcome trial, showed a significant 12 percent reduction in major cardiovascular events (MACE), a composite endpoint of non-fatal myocardial infarction (heart attack), non-fatal stroke or CV death. REWIND data showed a consistent MACE 3 effect in people with and without established CV disease. The CV risk reduction was sustained throughout the trial's duration.[1] The highly anticipated data for Eli Lilly and Company's (NYSE: LLY) once-weekly Trulicity were presented during a symposium today at the American Diabetes Association's® 79th Scientific Sessions® and simultaneously published in *The Lancet*.[1]

REWIND is the longest cardiovascular outcome trial in the GLP-1 receptor agonist class (median 5.4 years) and consisted primarily of people without established CV disease. While all participants had CV risk factors, only 31 percent of study participants had established CV disease. The study also had one of the lowest median baseline A1Cs of any diabetes CV outcome trial to date (7.2 percent) and had a balanced ratio of women (46.3 percent) to men (53.7 percent). This patient population is more representative of people with type 2 diabetes typically seen in clinical practice.[2]

"Dulaglutide is the first type 2 diabetes medicine to significantly reduce major adverse cardiovascular events (MACE 3) in a study population where the majority of participants had CV risk factors without established CV disease," said Hertzel Gerstein, M.D., MSc, FRCPC, professor of medicine and deputy director of the Population Health Institute at McMaster University and Hamilton Health Sciences, and REWIND study chair. "REWIND showed that adding dulaglutide to the therapeutic regimen of type 2 diabetes will benefit a broad range of people."

REWIND compared the effect of Trulicity 1.5 mg to placebo, both in addition to standard of care, on the risk of MACE 3 in 9,901 adults with type 2 diabetes. The risk reduction shown by Trulicity for the overall study (HR=0.88, 95% CI: 0.79-0.99) was consistent across subgroups, including: [1]

- established cardiovascular disease: HR=0.87, 95% CI: 0.74-1.02;
- no established cardiovascular disease: HR=0.87, 95% CI: 0.74-1.02;
- baseline A1C greater than or equal to 7.2 percent: HR=0.86, 95% CI: 0.74-1.00;
- baseline A1C less than 7.2 percent: HR=0.90, 95% CI: 0.76-1.06;
- women: HR=0.85, 95% CI: 0.71-1.02; and
- men: HR=0.90, 95% CI: 0.79-1.04.

All three components contributed to the significant reduction Trulicity provided in MACE 3, including CV death (HR=0.91, 95% CI: 0.78-1.06), non-fatal heart attack (HR=0.96, 95% CI: 0.79-1.16) and non-fatal stroke (HR=0.76, 95% CI: 0.61-0.95). Trulicity further showed reductions in composite microvascular outcomes (HR=0.87, 95% CI: 0.79-0.95), characterized by fewer composite renal outcomes.[1] Analysis of the renal outcomes suggests long-term Trulicity use was associated with reduced progression of renal disease in people with type 2 diabetes.[3]

In addition to the long-term follow-up assessing CV outcomes, REWIND provides additional evidence of Trulicity's efficacy in treating diabetes. Trulicity reduced A1C across the study from a median baseline of 7.2 percent compared to placebo (A1C: -0.46 percent [Trulicity], +0.16 percent [placebo]; Weight: -2.95 kg [Trulicity], -1.49 kg [placebo]). [1]

Trulicity's safety profile was consistent with the GLP-1 receptor agonist class. The most common adverse events leading to the discontinuation of Trulicity were gastrointestinal events.[1]

"Trulicity is already well-known for helping people with type 2 diabetes reach their blood glucose goals with a weekly dose," said Brad Woodward, M.D., global development leader, Incretins, Lilly. "Detailed results from our landmark REWIND trial demonstrate a cardiovascular benefit in a more representative population of people with type 2 diabetes. These data suggest Trulicity can help physicians and people with type 2 diabetes better manage blood glucose and cardiovascular risk over the long-term."

The REWIND results have been submitted to regulatory authorities in the U.S. and Europe for review.

Lilly will host an investor call Monday, June 10, at 10:00 a.m. EDT (7:00 a.m. PDT) to discuss the company's presentations at the American Diabetes Association's 79th Scientific Sessions.

About the REWIND Study

REWIND (**R**esearching cardiovascular **E**vents with a **W**eekly **IN**cretin in **D**iabetes) was a multicenter, randomized, double-blind, placebo-controlled trial designed to assess the effect of Trulicity 1.5 mg, a weekly glucagon-like peptide 1 receptor agonist (GLP-1 RA), compared to placebo, both added to standard of care (according to local standard of care guidelines), on cardiovascular (CV) events in adults with type 2 diabetes. The primary CV

outcome was the first occurrence of MACE (the composite of CV death or non-fatal myocardial infarction or non-fatal stroke). Secondary outcomes include each component of the primary composite CV outcome, a composite clinical microvascular outcome comprising retinal or renal disease, hospitalization for unstable angina, heart failure requiring hospitalization or an urgent heart failure visit, and all-cause mortality. The 9,901 participants from 24 countries had a mean duration of diabetes of 10.5 years and a median baseline A1C of 7.2 percent. While all participants had CV risk factors, only 31 percent of the study participants had established CV disease. Prior (or established) cardiovascular disease in REWIND was defined as prior myocardial infarction, prior ischemic stroke, prior unstable angina, prior revascularization (coronary, carotid, or peripheral), prior hospitalization for ischemia-related events (unstable angina or myocardial ischemia on imaging, or need for percutaneous coronary intervention), or prior documented myocardial ischemia.

The REWIND trial's international scope, high proportion of women, high proportion of people without established cardiovascular disease and inclusion of participants with a lower mean baseline A1C suggest that the findings will be directly relevant to the typical type 2 diabetes patient seen in general practice throughout the world.

Indication and Limitations of Use for Trulicity®
Trulicity is a once-weekly injectable prescription medicine to improve blood sugar (glucose) in adults with type 2 diabetes mellitus. It should be used along with diet and exercise. Trulicity is not recommended as the first medication to treat diabetes. It has not been studied in people who have had inflammation of the pancreas (pancreatitis). Trulicity should not be used by people with type 1 diabetes, people with diabetic ketoacidosis, or people with a history of severe gastrointestinal (GI) disease. It is not a substitute for insulin. It has not been studied in children under 18 years of age.

Important Safety Information for Trulicity®

Patients should tell their healthcare provider if they get a lump or swelling in their neck, have hoarseness, trouble swallowing, or shortness of breath while taking Trulicity. These may be symptoms of thyroid cancer. In studies with rats or mice, Trulicity and medicines that work like Trulicity caused thyroid tumors, including thyroid cancer. It is not known if Trulicity will cause thyroid tumors or a type of thyroid cancer called medullary thyroid carcinoma (MTC) in people. Patients should not take Trulicity if they or any of their family members have ever had MTC or if they have Multiple Endocrine Neoplasia syndrome type 2 (MEN 2).

Patients should not take Trulicity if they have had an allergic reaction to dulaglutide or any of the other ingredients in Trulicity.

Trulicity should not be used in children under 18 years of age.

Trulicity may cause serious side effects, including:

- **Inflammation of the pancreas (pancreatitis).** If a patient has pain in their stomach area (abdomen) that is severe and will not go away, they should stop taking Trulicity and call their healthcare provider right away. The pain may happen with or without vomiting. It may be felt going from the abdomen through to the back.
- **Low blood sugar (hypoglycemia).** If patients are using another medicine that can cause low blood sugar (such as insulin or a sulfonylurea) while taking Trulicity, their risk for getting low blood sugar (hypoglycemia) may be higher. Signs and symptoms of low blood sugar may include dizziness, blurred vision, anxiety, irritability, mood changes, sweating, slurred speech, hunger, confusion or drowsiness, shakiness, weakness, headache, fast heartbeat, or feeling jittery. Patients should talk to their healthcare provider about low blood sugar and how to manage it.
- **Serious allergic reactions**. Patients should stop taking Trulicity and get medical help right away if they have symptoms of a serious allergic reaction including: swelling of the face, lips, tongue or throat; problems breathing or swallowing; severe rash or itching; fainting or feeling dizzy; or very rapid heartbeat.
- **Acute kidney injury.** In people who have kidney problems, diarrhea, nausea, and vomiting may cause a loss of fluids (dehydration). This may cause kidney problems to get worse.
- **Severe stomach problems.** Trulicity may cause stomach problems, which could be severe.

Patients should tell their healthcare provider if they:

- *have or have had problems with their pancreas, kidneys, or liver.*
- *have severe problems with their stomach, such as slowed emptying of the stomach (gastroparesis) or problems with digesting food.*
- *have any other medical conditions.*
- *are pregnant or plan to become pregnant, or if they become pregnant while taking Trulicity. It is not known if Trulicity will harm their unborn baby.*
- *are breastfeeding or plan to breastfeed. It is not known if Trulicity passes into breast milk. Patients should not use Trulicity while breastfeeding without first talking to their healthcare provider.*
- *are taking other medicines including prescription and over-the-counter medicines, vitamins, and herbal supplements. Trulicity may affect the way some medicines work and some medicines may affect the way Trulicity works.*
- *are taking other medicines to treat diabetes, including insulin or sulfonylureas.*

If patients take too much Trulicity, they should call their healthcare provider or go to the nearest emergency room right away.

The most common side effects with Trulicity may include: *nausea, diarrhea, vomiting, abdominal pain and decreased appetite. Patients should*

talk to their healthcare provider about any side effect that bothers them or does not go away. These are not all the possible side effects of Trulicity. Patients should call their doctor for medical advice about side effects.

Patients are encouraged to report side effects of prescription drugs to the FDA. Visit www.fda.gov/medwatch or call 1-800-FDA-1088.

Please click to access Prescribing Information, including Boxed Warning about possible thyroid tumors including thyroid cancer, and Medication Guide.

Please see Instructions for Use included with the pen.

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About Diabetes

Approximately 30 million Americans[4] and an estimated 425 million adults worldwide have diabetes.[5] Type 2 diabetes is the most common type internationally, accounting for an estimated 90 to 95 percent of all diabetes cases in the United States alone.[4] Diabetes is a chronic disease that occurs when the body does not properly produce or use the hormone insulin.

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. We offer a wide range of therapies and a continued determination to provide real solutions—from medicines and technologies to support programs and more. For the latest updates, visithttp://www.lillydiabetes.com/or follow us on Twitter: @LillyDiabetes and Facebook: LillyDiabetesUS.

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. P-LLY

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This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about Trulicity (dulaglutide) as a treatment for type 2 diabetes and as a potential treatment for the reduction of cardiovascular events 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 study findings to date, that Trulicity will receive additional regulatory approvals or that Trulicity will continue to be commercially successful. 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.

1. Gerstein HC, Colhoun HM, et al. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. The Lancet. 2019. S0140-6736(19)31149-3. Retrieved from https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)31149-3/fulltext.
2. Boye KS, Riddle MC, Gerstein HC, et al. Generalizability of Glucagon-Like Peptide-1 Receptor Agonist Cardiovascular Outcome Trials to the Overall Type 2 Diabetes Population in the United States. Diabetes Obes Metab 2019.
3. Gerstein HC, Colhoun HM, et al. Dulaglutide and renal outcomes in type 2 diabetes: an exploratory analysis of the REWIND randomised, placebo-controlled trial. 2019. S0140-6736(19)31150. Retrieved from: http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(19)31150-X/fulltext.
4. Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2017. Atlanta, GA: Centers for Disease Control and Prevention, U.S. Dept of Health and Human Services; 2017.
5. International Diabetes Federation. *IDF Diabetes Atlas*, 8th edn. Brussels, Belgium: International Diabetes Federation, 2017. http://www.diabetesatlas.org.

Refer to:
Dani Barnhizer; dbarnhizer@lilly.com; (317) 607-6119 (Media)
Kevin Hern; hern_kevin_r@lilly.com; (317) 277-1838 (Investors)

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