Lilly's Investigational Dual GIP and GLP-1 Receptor Agonist Shows Significant Reduction in HbA1c and Body Weight in People With Type 2 Diabetes

October 4, 2018

INDIANAPOLIS, Oct. 4, 2018 /PRNewswire/ -- Results from a phase 2b clinical trial of Eli Lilly and Company's (NYSE: LLY) dual GIP and GLP-1 receptor agonist (GIP/GLP-1 RA, LY3298176) showed strong and clinically meaningful blood sugar reduction and weight loss in people with type 2 diabetes. The six-month data —showing average HbA1c reductions of up to 2.4 percentage points and an average weight reduction up to 11.3 kg (12.7 percent) – were presented today at the 54th Annual Meeting of the European Association for the Study of Diabetes in Berlin and simultaneously published in ***The Lancet***.[1]

The weekly dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist integrates the action of both incretins into a single novel molecule, aiming to build upon the clinical benefits seen with a selective GLP-1 RA.

"These phase 2b clinical trial results for GIP/GLP-1 RA are unprecedented, and the impressive blood glucose and weight reductions seen may lead to a new treatment option for people with type 2 diabetes," said Juan P. Frias, M.D., President and Principal Investigator, National Research Institute. "The next wave of innovation in the study of incretins for treating type 2 diabetes is fascinating. We're taking the already proven benefits of GLP-1 receptor agonists and looking at a new molecule that integrates GIP action to see what additional benefits are possible."

Two statistical approaches were used to evaluate the efficacy of four doses of GIP/GLP-1 RA (1 mg, 5 mg, 10 mg, 15 mg) compared to placebo and dulaglutide 1.5 mg in people with type 2 diabetes. The first was a dose response model evaluating the effect regardless of discontinuation of treatment and use of rescue medication. An additional analysis identified the effect while on treatment and without use of rescue medication.*[1]

At 26 weeks, the primary analysis showed a robust dose response compared to placebo throughout the entire dose range of GIP/GLP-1 RA included in the study.[1]

The analysis of participants while on treatment comparing GIP/GLP-1 RA to dulaglutide and placebo showed significant improvements across endpoints.[1]

- **HbA1c reduction:** All GIP/GLP-1 RA doses and dulaglutide showed significant blood sugar improvement (mean absolute reduction) from baseline [GIP/GLP-1 RA: -1.6 percent (5 mg), -2.0 percent (10 mg), and -2.4 percent (15 mg); dulaglutide -1.1 percent (1.5 mg)] compared to placebo (0.1 percent).
- **HbA1c target:** The higher doses of GIP/GLP-1 RA provided the most significant HbA1c reductions, with up to 30 percent of people who received the 10 mg and 15 mg doses achieving HbA1c levels of less than 5.7 percent, which is in the normal range for people without diabetes [18 percent (10 mg) and 30 percent (15 mg)]. Further, up to 90 percent of people reached the recommended HbA1c target of 7 percent or less [GIP/GLP-1 RA: 69.1 percent (5 mg), 90.0 percent (10 mg), and 77.4 percent (15 mg); dulaglutide 51.9 percent (1.5 mg)].
- **Weight loss:** Participants taking GIP/GLP-1 RA achieved significant weight loss [-4.8 kg (5 mg), -8.7 kg (10 mg) and -11.3 kg (15 mg)], as did those taking dulaglutide [-2.7 kg (1.5mg)], compared to placebo (-0.4 kg). More than a third of people lost 10 percent or more of their starting body weight with GIP/GLP-1 RA 10 mg (39.2 percent) and 15 mg (37.7 percent), and a quarter of people lost 15 percent or more with the 15 mg dose.

The safety profile of GIP/GLP-1 RA was similar to the GLP-1 RA class. The most commonly reported side effects were gastrointestinal-related, and dose-dependent. These events included nausea [20 percent (5 mg), 22 percent (10 mg), 40 percent (15 mg)], diarrhea [24 percent (5 and 10 mg), 32 percent (15 mg)] and vomiting [8 percent (5 mg), 16 percent (10 mg), 26 percent (15 mg)], which were mild to moderate and generally temporary, most often occurring during the titration period. Dulaglutide 1.5 mg had a similar side effect profile to previous studies. No participants in any of the treatment groups experienced severe hypoglycemia.[1] A further study examining an optimal titration schedule to help manage GI side effects was conducted and will be presented next year.

"Despite the progress we've made in diabetes management, people living with type 2 diabetes often need additional treatments as their condition progresses. That's why our researchers continue innovating —to help make lives better," said Jeff Emmick, M.D., Ph.D., vice president of product development, Lilly Diabetes. "We set a high bar for this phase 2 study, and the results exceeded our expectations. We're excited to continue studying GIP/GLP-1 RA and hope to add it to our wide range of therapies for people with diabetes."

The safety and efficacy of Lilly's GIP/GLP-1 RA are being studied further in a large phase 3 clinical program that will be referred to as the SURPASS program. Phase 3 studies for type 2 diabetes are expected to begin no later than early 2019 and complete in late 2021. Lilly is evaluating next steps in the study of GIP/GLP-1 RA for obesity and other conditions.

Lilly will conduct a webcast today to discuss the company's presentations. Remarks will focus primarily on this Phase 2b data. The webcast will begin

at 7 p.m. Central European Time, or 1 p.m. Eastern Time. More information can be found in the press release.

About the Phase 2b Study[1]
The phase 2b study was a 26-week, randomized, placebo-controlled study comparing the effects of four doses (1 mg, 5 mg, 10 mg, 15 mg) of Lilly's novel long-acting dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptor agonist to dulaglutide 1.5 mg and placebo in people with type 2 diabetes. The primary objective of the study, conducted in 300 people with type 2 diabetes, was to evaluate whether GIP/GLP-1 RA, dosed once weekly, was superior to placebo in reducing HbA1c from baseline at 26 weeks.

Secondary objectives included change in mean body weight, fasting plasma glucose (FPG), waist circumference from baseline to 26 weeks, proportion of patients with less than or equal to 5 percent and 10 percent body weight loss from baseline to 26 weeks, proportion of patients reaching HbA1c targets, and change in lipid laboratory data from baseline to 26 weeks.

About Diabetes
Approximately 30 million Americans[2] and an estimated 425 million adults worldwide have diabetes.[3] 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.[2] 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

*Treatment effect of dulaglutide versus placebo for all randomized subjects while on treatment without use of rescue medication was assessed by Mixed Model for Repeated Measures (MMRM). The primary efficacy analysis was performed using a Bayesian dose-response model.

This press release contains forward-looking statements (as that term is defined in the Private Securities Litigation Reform Act of 1995) about GIP/GLP-1 RA as a potential treatment for patients with type 2 diabetes 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 GIP/GLP-1 RA will achieve its primary study endpoints or receive 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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1. Frias JP, Nauck MA, Van J, et al. Efficacy and safety of LY3298176, a novel dual GIP and GLP-1 receptor agonist, in patients with type 2 diabetes: a randomised, placebo-controlled and active comparator-controlled phase 2 trial. Lancet 2018; published online October 4. DOI: 10.1016/S0140-6736(18)32260-8. Available at: https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)32260-8/fulltext.
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