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Lilly Announces Detailed Results from Two Phase III Studies Testing Both Doses of Dulaglutide vs. Insulin Glargine

AWARD-2: Once-Weekly Dulaglutide 0.75 mg Non-Inferior, 1.5 mg Superior in HbA1c Reduction from Baseline with Sustained Weight Loss and Lower Risk for Hypoglycemia

AWARD-4: Both Doses of Once-Weekly Dulaglutide Superior in HbA1c Reduction from Baseline with Relative Weight Benefit; Lower Risk for Hypoglycemia with 1.5 mg

SAN FRANCISCO, June 16, 2014 /PRNewswire/ -- Eli Lilly and Company (NYSE: LLY) today released detailed results from two AWARD trials that showed treatment with once-weekly dulaglutide 1.5 mg resulted in superior reductions in HbA1c from baseline compared to insulin glargine, with a lower risk for hypoglycemia.^{1,2} Dulaglutide is an investigational glucagon-like peptide-1 (GLP-1) receptor agonist being studied for the treatment of type 2 diabetes. Results were presented at the 74th American Diabetes Association Scientific Sessions in San Francisco.

"Many patients with type 2 diabetes reach a point when oral medicines alone may no longer be effective enough. In these cases, many healthcare professionals choose to intensify treatment with an injectable medicine," said Francesco Giorgino, MD, professor of endocrinology and metabolism, University of Bari, Italy. "Data from these two studies comparing once-weekly dulaglutide with insulin glargine, in combination with other diabetes treatments, provide important information about a GLP-1 receptor agonist that, if approved, may be appropriate for patients with type 2 diabetes."

Study Results Overview

Results from the AWARD-2 trial, which evaluated the safety and efficacy of two doses of once-weekly dulaglutide compared to insulin glargine as add on to combination therapy with sulfonylurea and metformin, showed that once-weekly dulaglutide 1.5 mg provided superior blood sugar control at 52 and 78 weeks. Significantly more dulaglutide 1.5 mg-treated patients reached target HbA1c levels of less than 7 percent. Further, once-weekly dulaglutide 0.75 mg was non-inferior to insulin glargine in reducing HbA1c levels. Both doses of dulaglutide were associated with sustained weight loss, while insulin glargine showed weight gain.¹

Results from the AWARD-4 trial - the first Phase III study to evaluate a GLP-1 receptor agonist in combination with a mealtime insulin - showed that once-weekly dulaglutide 1.5 mg and 0.75 mg combined with mealtime insulin lispro provided superior blood sugar control at 26 and 52 weeks compared to the traditional basal/bolus combination of insulin glargine and mealtime insulin lispro. Further, at the 26-week primary endpoint, significantly more dulaglutide-treated patients reached target HbA1c levels of less than 7 percent, and patients treated with the dulaglutide-mealtime insulin lispro combination had 30 percent less total insulin dose. Both doses of dulaglutide, in combination with mealtime insulin lispro, were associated with relative weight benefit compared to the basal/bolus therapy of insulin glargine and mealtime insulin lispro.²

Hypoglycemia rates were lower in dulaglutide 1.5 mg-treated patients compared to insulin glargine in both studies.^{1,2} In AWARD-2, the 0.75 mg dose also had a lower rate of hypoglycemia compared to insulin glargine.

Adverse events were similar for dulaglutide-treated patients in both studies. The most frequently reported events were gastrointestinal-related, including nausea, diarrhea and vomiting. Nausea, which was mostly mild to moderate, was the most commonly reported event. These findings are consistent with prior studies of once-weekly dulaglutide.^{1,2}

"These results show that, compared to a commonly used basal insulin, once-weekly dulaglutide improves glycemic control, provides weight benefits and has a lower risk for hypoglycemia," Sherry Martin, M.D., senior medical director, Lilly Diabetes. "If approved, dulaglutide will be the only ready-to-use, weekly GLP-1 therapy that may be an alternative for patients with type 2 diabetes who need to intensify their treatment."

Once-weekly dulaglutide, an investigational GLP-1 receptor agonist being studied as a treatment for type 2 diabetes, has been submitted to the U.S. Food and Drug Administration (FDA), the European Medicines Agency (EMA) and other regulatory bodies. Five AWARD registration trials (1-5) were submitted as part of the regulatory package. If approved, dulaglutide will be marketed under the brand name Trulicity™.

Detailed Study Results

AWARD-2

AWARD-2 was a randomized, 78-week, open-label comparison of the effects of once-weekly dulaglutide and insulin glargine on glycemic control in patients with type 2 diabetes taking concurrent metformin and glimepiride. The primary objective of the study, conducted in 807 patients with poorly controlled type 2 diabetes, was to evaluate whether once-weekly dulaglutide 1.5 mg was non-inferior to insulin glargine in reducing HbA1c from baseline at 52 weeks. Insulin glargine-treated patients were titrated using a treat-to-target algorithm. Superiority testing was performed since the statistical criterion for non-inferiority was satisfied. Results showed:

- Once-weekly dulaglutide 1.5 mg was superior to insulin glargine in reducing HbA1c at 52 (-1.08 percent vs. -0.63 percent) and 78 weeks (-0.90 percent vs. -0.59 percent).
- Significantly more patients treated with once-weekly dulaglutide 1.5 mg reached target HbA1c levels of less than 7 percent compared to insulin glargine-treated patients at 52 (53 percent vs. 31 percent) and 78 weeks (49 percent vs. 31 percent).
- Patients treated with once-weekly dulaglutide 1.5 mg lost weight at 52 weeks (-1.87 kg) and 78 weeks (-1.96 kg) compared to insulin glargine-treated patients, who gained weight (+1.44 kg [52 weeks], +1.28 kg [78 weeks]).

The study also evaluated dulaglutide at the 0.75 mg dose, showing that:

- Once-weekly dulaglutide 0.75 mg was non-inferior to insulin glargine in reducing HbA1c at 52 weeks (-0.76 percent vs. -0.63 percent) and 78 weeks (-0.62 percent vs. -0.59 percent).
- Similar percentages of patients treated with once-weekly dulaglutide 0.75 mg and insulin glargine reached target HbA1c levels of less than 7 percent at 52 weeks (37 percent vs. 31 percent) and 78 weeks (34 percent vs. 31 percent).
- Patients treated with once-weekly dulaglutide 0.75 mg lost weight at 52 weeks (-1.33 kg) and 78 weeks (-1.54 kg) compared to insulin glargine-treated patients, who gained weight (+1.44 kg [52 weeks], +1.28 kg [78 weeks]).

Safety-related endpoints showed that:

- At the final endpoint of 78 weeks, the average documented, symptomatic hypoglycemia rate (blood glucose less than or equal to 70 mg/dL) was lower in patients treated with once-weekly dulaglutide 1.5 mg and 0.75 mg (1.7 events/patient/year for both doses) compared to insulin glargine (3 events/patient/year), with minimal rates of severe hypoglycemia in all treatment arms.
- The most commonly reported adverse events were gastrointestinal-related, with more dulaglutide-treated patients experiencing nausea (15 percent [dulaglutide 1.5 mg], 8 percent [dulaglutide 0.75 mg]) and diarrhea (11 percent [dulaglutide 1.5 mg], 9 percent [dulaglutide 0.75 mg]) compared to insulin glargine (2 percent and 6 percent).¹

AWARD-4

AWARD-4 was a randomized, 52-week, open-label comparison of the effects of once-weekly dulaglutide and insulin glargine, both in combination with insulin lispro, in patients with type 2 diabetes poorly controlled on a conventional insulin regimen. The goal was to determine whether dulaglutide in combination with mealtime insulin could be an alternative to insulin intensification in patients who were potential candidates for basal-bolus insulin therapy. Patients were allowed to take stable doses of metformin. The primary objective of the study, conducted in 884 patients, was to evaluate whether once-weekly dulaglutide 1.5 mg, in combination with insulin lispro, was non-inferior to insulin glargine in combination with insulin lispro, in reducing HbA1c from baseline at 26 weeks. All insulin doses were titrated to target. Superiority testing was performed since the statistical criterion for non-inferiority was satisfied. Results showed:

- Once-weekly dulaglutide 1.5 mg and 0.75 were superior to insulin glargine - all combined with mealtime insulin lispro - in reducing HbA1c at 26 and 52 weeks.
 - Dulaglutide 1.5 mg: -1.64 percent (26 weeks), -1.48 percent (52 weeks)
 - Dulaglutide 0.75 mg: -1.59 percent (26 weeks), -1.42 percent (52 weeks)
 - Insulin glargine: -1.41 percent (26 weeks), -1.23 percent (52 weeks)
- Significantly more dulaglutide-treated patients reached target HbA1c levels of less than 7 percent without weight gain, nocturnal hypoglycemia or severe hypoglycemia at 26 and 52 weeks compared to insulin glargine.
 - Dulaglutide 1.5 mg: 33 percent (26 weeks), 20 percent (52 weeks)
 - Dulaglutide 0.75 mg: 25 percent (26 weeks), 19 percent (52 weeks)
 - Insulin glargine: 6 percent (26 weeks), 5 percent (52 weeks)
- Patients treated with once-weekly dulaglutide 1.5 mg lost weight at 26 (-0.87 kg) and 52 weeks (-0.35 kg) compared to insulin glargine-treated patients, who gained weight (+2.33 kg [26 weeks], +2.89 kg [52 weeks]).
- Dulaglutide 0.75 demonstrated a weight benefit, with less weight gain in dulaglutide-treated patients at 26 (+0.18 kg) and 52 weeks (+0.86 kg) compared to insulin glargine (+2.33 kg, +2.89 kg).
- At the final endpoint of 52 weeks, the average documented, symptomatic hypoglycemia rates were lower in patients treated with once-weekly dulaglutide 1.5 mg and similar with dulaglutide 0.75 mg (31 and 35 events/patient/year)

compared to insulin glargine (40 events/patient/year). There were 11 and 15 episodes of severe hypoglycemia with once-weekly dulaglutide 1.5 mg and 0.75 mg, respectively, and 22 events with insulin glargine.

- The most commonly reported adverse events were gastrointestinal-related, with more dulaglutide-treated patients experiencing nausea and diarrhea compared to insulin glargine.²

About Diabetes

Approximately 24.4 million Americans and an estimated 382 million people worldwide have type 1 and type 2 diabetes. Type 2 diabetes is the most common type, accounting for an estimated 90 to 95 percent of all diabetes cases. Diabetes is a chronic disease that occurs when the body either does not properly produce, or use, the hormone insulin.³

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>.

P-LLY

This press release contains forward-looking statements about dulaglutide that are based on Lilly's current expectations. Actual results could differ materially from these expectations. There are significant risks and uncertainties in the process of drug development and commercialization. There can be no guarantee that future study results and patient experience will be consistent with the study findings to date. There can also be no guarantee that dulaglutide will be approved by regulatory authorities or that it will prove to be commercially successful. For further discussion of these and other risks and uncertainties that could cause actual results to differ from Lilly's expectations, please see the company's latest Forms 10-K and 10-Q filed with the U.S. Securities and Exchange Commission. Except as required by law, the company undertakes no duty to update forward-looking statements.

REFERENCES

1. Giorgino, F, Benroubi, M, et al. Efficacy and Safety of Once-Weekly Dulaglutide vs. Insulin Glargine in Combination with Metformin and Glimepiride in Type 2 Diabetes Patients (AWARD-2). Abstract 330-OR. Presented at 74th American Diabetes Association (ADA) Scientific Sessions; June 13-17, 2014; San Francisco, CA.
2. Jendle, J, Rosenstock, J, et al. Better Glycemic Control and Less Weight Gain with Once-Weekly Dulaglutide vs. Once-Daily Insulin Glargine, Both Combined with Premeal Insulin Lispro, in Type 2 Diabetes Patients (AWARD-4). Abstract 962-P. Presented at 74th American Diabetes Association (ADA) Scientific Sessions; June 13-17, 2014; San Francisco, CA.
3. International Diabetes Federation. *IDF Diabetes Atlas, 6th edn*. Brussels, Belgium: International Diabetes Federation, 2013. <http://www.idf.org/diabetesatlas>.

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The Lilly logo is a stylized, red, cursive script of the word "Lilly". The letters are fluid and interconnected, with a prominent 'L' and a long, sweeping tail on the 'y'.

Logo - <http://photos.prnewswire.com/prnh/20031219/LLYLOGO>

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