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Lilly's Basal Insulin Peglispro Demonstrated HbA1c Superiority against Lantus® in Phase III Trials in Patients with Type 1 Diabetes

Core Phase III clinical trial program complete; BIL showed consistent HbA1c superiority against comparators
Lilly expects U.S. and European regulatory submissions by end of Q1 2015

INDIANAPOLIS, Sept. 4, 2014 /PRNewswire/ -- Eli Lilly and Company's (NYSE: LLY) basal insulin peglispro (BIL) demonstrated a statistically significant lower hemoglobin A1c (HbA1c) compared with insulin glargine (Lantus®) at 26 weeks and 52 weeks, respectively, in the IMAGINE-1 and IMAGINE-3 Phase III clinical trials in patients with type 1 diabetes. Patients in these trials were also taking mealtime insulin. Notably, patients in IMAGINE-1 continued treatment beyond 26 weeks, and the HbA1c superiority for BIL was maintained at 52 and 78 weeks.

The Phase III trials needed for submission are now complete. The trials, in both type 1 and type 2 diabetes, showed consistent superiority of HbA1c for BIL against comparators. Lilly is on track to file a submission with regulators by the end of the first quarter in 2015.

"These data are promising and give us further confidence in the clinical profile of BIL," said Enrique Conterno, president, Lilly Diabetes. "Lilly is committed to meeting the diverse needs of people living with diabetes who need therapies that will help them meet their individual goals. If approved, we believe BIL will be an important new basal insulin option for people with diabetes."

The primary efficacy endpoint of non-inferior HbA1c at the primary study endpoint compared with insulin glargine was met in both the IMAGINE-1 and IMAGINE-3 trials, and superiority was demonstrated. In addition, significantly more patients taking BIL versus those taking insulin glargine achieved an HbA1c of less than 7 percent, a target for glycemic control established by the American Diabetes Association.

Both trials also showed the rate of nocturnal hypoglycemia was significantly lower in patients taking BIL than in those taking insulin glargine. In both trials - in which patients were taking both mealtime and basal insulin - there was a statistically significant increase in the rate of total hypoglycemia for patients taking BIL compared with those taking insulin glargine due to a higher rate of daytime hypoglycemic events. In the open-label IMAGINE-1 trial, patients taking BIL reported a statistically significant higher rate of severe hypoglycemic events. However, in the larger, blinded IMAGINE-3 trial the rate of severe hypoglycemic events for treatment with BIL was numerically lower compared with insulin glargine, but was not statistically significant.

Additionally, both trials showed a statistically significant difference in weight. Patients taking BIL experienced weight loss—even with lower HbA1c—compared with weight gain in patients taking insulin glargine.

"All patients with type 1 diabetes depend on insulin to achieve and maintain their target blood glucose levels. For a number of those patients, current insulin options may not be optimal - particularly in those who experience nocturnal hypoglycemia or weight gain," said David Kendall, M.D., vice president, Medical Affairs, Lilly Diabetes. "Basal insulin peglispro may offer a useful option to help address these challenges."

Results of these two trials also showed patients taking BIL experienced changes in lipid parameters, including a small but statistically significant increase in triglycerides in both trials. In IMAGINE-3, there were small but statistically significant reductions and increases, respectively, in HDL (high-density lipoprotein) cholesterol and LDL (low-density lipoprotein) cholesterol in patients taking BIL compared with those taking insulin glargine. In addition, IMAGINE-3 showed patients taking BIL experienced small but statistically significant increases in systolic and diastolic blood pressure compared to insulin glargine (less than 2 mmHg mean difference at 52 weeks). Statistically significant differences in HDL and LDL cholesterol and blood pressure were not observed in IMAGINE-1. There were no major adverse cardiac events (MACE) in IMAGINE-1, and in IMAGINE-3, the MACE+ (cardiovascular death, non-fatal stroke, non-fatal MI and hospitalization due to unstable angina) event rate was lower for patients taking BIL compared with those taking insulin glargine.

In both trials, treatment with BIL was associated with a statistically significant higher incidence of patients with greater than three times the upper limit of normal range in the liver enzyme ALT (alanine aminotransferase) compared with patients taking insulin glargine. No cases of severe liver injury (Hy's Law) occurred in either of the trials. In a subset of patients whose liver fat

was measured using MRI imaging, BIL-treated patients had a statistically significant increase in liver fat compared to insulin glargine.

In both trials, there were significantly more injection site reactions observed in patients taking BIL compared to those taking insulin glargine.

Phase III Clinical Trial Program
Additionally, the IMAGINE-7 trial—a flexible dosing study of BIL in patients with type 1 diabetes—and the IMAGINE-6 trial, evaluating BIL compared to NPH insulin in patients with type 2 diabetes, have both completed. IMAGINE-7 showed there was no statistically significant difference in HbA1c between BIL dosed at the same time every day versus BIL dosed at variable times. IMAGINE-6 met its primary efficacy endpoint of non-inferior reduction in HbA1c compared with NPH insulin at 26 weeks and also demonstrated HbA1c superiority of BIL compared to NPH insulin. There were no new safety signals in either trial and the adverse events were similar to those seen in the other IMAGINE trials.

The core Phase III clinical trial program of BIL - consisting of seven IMAGINE trials in patients with type 1 and type 2 diabetes - is now complete, and superiority in HbA1c for BIL was seen in all six of the Phase III trials that were conducted against active comparators.

An analysis across all clinical trials in patients with type 1 and type 2 diabetes showed that the rates of major adverse cardiovascular events among patients taking BIL and those taking insulin glargine or NPH insulin were similar, with an observed hazard ratio below 1 and the upper limit of the 95 percent confidence interval below 1.4.

Data Disclosure and Regulatory Submission Plans
Detailed study results for all Phase III trials are expected to be disclosed in 2015.

Lilly plans to submit BIL for regulatory review to the U.S. Food and Drug Administration and the European Medicines Agency by the end of Q1 2015.

About the IMAGINE Clinical Trials
IMAGINE-1 is a Phase III, 78-week, open-label study designed to compare BIL (n=295) with insulin glargine (n=160) in combination with mealtime insulin in patients with type 1 diabetes.

IMAGINE-3 is a Phase III, 52-week, double-blind randomized study designed to compare BIL (n=664) with insulin glargine (n=450) in combination with mealtime insulin in patients with type 1 diabetes.

IMAGINE-6 is a Phase III, 26-week, open-label study designed to compare BIL (n=428) with NPH insulin (n=213) in insulin naïve patients with type 2 diabetes.

IMAGINE-7 is a Phase III, 36-week, randomized, cross-over study designed to compare BIL (n=182) administered once daily at a fixed time with BIL administered at a variable time of day in patients with type 1 diabetes.

About Basal Insulin Peglispro
Basal insulin peglispro (BIL), which was discovered and developed in Lilly Research Laboratories, is currently in Phase III clinical trials and is among several diabetes molecules in the Lilly late-stage pipeline. BIL is being studied as a once-daily treatment for type 1 and type 2 diabetes.

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

Lantus® is a registered trademark of Sanofi.

This press release contains forward-looking statements about an investigational compound basal insulin peglispro, which is currently in development for the treatment of diabetes. 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 novel basal insulin peglispro will receive required regulatory approvals or prove to be commercially successful. 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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