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Basal Insulin Peglispro Studies Demonstrate Superiority to Insulin Glargine Across Multiple Measures in People with Type 1 Diabetes

Phase III Data Presented at the 2015 American Diabetes Association Scientific Sessions®

INDIANAPOLIS, June 6, 2015 /PRNewswire/ -- In newly released Phase III trial data, Eli Lilly and Company's (NYSE: LLY) basal insulin peglispro (BIL) demonstrated statistically significantly lower hemoglobin A1c (HbA1c) compared to insulin glargine at 26 and 52 weeks in people with type 1 diabetes. Detailed results from the IMAGINE-1 and IMAGINE-3 clinical trials were presented today at the American Diabetes Association's (ADA) 75th Scientific Sessions in Boston.^{1,2} People with type 1 diabetes in these trials were also taking mealtime insulin.^{1,2}

BIL has a hepato-preferential activity profile derived from its reduced effect in peripheral tissue, making it more similar to endogenous insulin compared to other exogenous insulins with a conventional activity profile.

"In many people with type 1 diabetes, current insulin treatments may not be optimal for a variety of reasons," said Melanie Davies, M.D., professor of diabetes medicine, University of Leicester, United Kingdom. "Results from the IMAGINE trials showed that BIL has a unique combination of benefits, including superior glycemic control, reduced nocturnal hypoglycemia and weight loss, all of which could be beneficial for people who need basal insulin treatment."

In IMAGINE-1 and IMAGINE-3, BIL demonstrated superiority in HbA1c compared to insulin glargine.^{1,2} Significantly more patients taking BIL met the ADA's recommended HbA1c target of less than 7 percent and experienced lower rates of nocturnal hypoglycemia compared to those taking insulin glargine.³ 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.^{1,2}

In both trials, patients treated with BIL experienced mean weight loss compared to weight gain in patients who took insulin glargine.^{1,2}

In both trials, patients taking BIL had an increase in triglycerides compared to insulin glargine. In IMAGINE-3, patients taking BIL had an increase in LDL cholesterol, a decrease in HDL cholesterol and increases in systolic and diastolic blood pressure compared to insulin glargine. The rate of major adverse cardiac events MACE+ (cardiovascular death, non-fatal stroke, non-fatal MI and hospitalization due to unstable angina) was lower for patients taking BIL compared with those taking insulin glargine in IMAGINE-3. There were no MACE+ events in IMAGINE-1.

Additionally, in both studies, patients taking BIL had an increase in the liver enzyme ALT (alanine aminotransferase). Four weeks after BIL was discontinued these levels decreased toward baseline. Liver fat was measured by MRI in a subset of patients in both studies and was higher in patients treated with BIL compared to insulin glargine.^{1,2}

"These unprecedented results are meaningful not only to people with type 1 diabetes but also for those in the scientific and clinical community," said David Kendall, M.D., vice president, Medical Affairs, Lilly Diabetes. "Lilly is committed to developing innovative treatments to help people with diabetes achieve their goals. To that end, we are excited to continue development of promising investigational treatments such as BIL."

Lilly also presented results from IMAGINE-7, a study investigating flexible dose-timing of BIL in people with type 1 diabetes. There was no statistically significant difference in HbA1c or nocturnal and total hypoglycemia rates between people taking BIL dosed at variable times throughout the day.⁴

BIL Type 1 Clinical Data

BIL showed consistency in various measurements of glucose control across type 1 diabetes trials:^{1,2}

- Patients taking BIL showed lower HbA1c at the primary endpoints compared to those on insulin glargine in the IMAGINE-1

- trial at 26 weeks (7.1 percent vs. 7.4 percent) and in the IMAGINE-3 trial at 52 weeks (7.4 percent vs. 7.6 percent).^{1,2}
- Significantly more patients taking BIL reached the ADA's recommended target HbA1c of less than 7 percent compared to insulin glargine in the IMAGINE-1 trial at the primary endpoint of 26 weeks (44.9 percent vs. 27.5 percent) and in the IMAGINE-3 trial at the 52-week primary endpoint (35.3 percent vs. 26.1 percent).^{1,2}

BIL reduced the risk of nocturnal hypoglycemia in type 1 trials:^{1,2}

- In both studies, patients taking BIL had lower rates of nocturnal hypoglycemia compared to insulin glargine:
 - IMAGINE-1 at 26-week primary endpoint: 1.7 vs. 2.7 events/patient/30 days
 - IMAGINE-3 at 52-week primary endpoint: 1.3 vs. 2.5 events/patient/30 days.^{1,2}

BIL showed higher rates of total hypoglycemia:

- Patients taking BIL had higher rates of total hypoglycemia compared to insulin glargine in IMAGINE-1 at the 26-week primary endpoint (16.0 vs. 12.4 events/patient/30 days) and in IMAGINE-3 at the 52-week primary endpoint (15.3 vs. 13.9 events/patient/30 days).^{1,2}
- In an integrated analysis of IMAGINE-1 and IMAGINE-3, there were no significant differences in rates of severe hypoglycemia between BIL and insulin glargine. However, patients taking BIL had higher rates of severe hypoglycemia compared to insulin glargine in IMAGINE-1 at 26 weeks (39.0 vs. 16.2 events/100 patient years) and similar rates of severe hypoglycemia compared to insulin glargine in IMAGINE-3 at 52 weeks (19.7 vs. 22.5 events/100 patient years).^{1,2}

BIL showed consistent weight loss in type 1 trials:^{1,2}

- Patients taking BIL experienced mean weight loss while patients taking insulin glargine experienced mean weight gain in both IMAGINE-1 at the primary endpoint of 26 weeks (-1.2 kg vs. +0.7 kg) and IMAGINE-3 at the primary endpoint of 52 weeks (-0.6 kg vs. +1.2 kg).^{1,2}

Hepatic (liver) safety findings:

- In an integrated analysis of type 1 studies, patients taking BIL had a mean increase in the liver enzyme ALT compared to insulin glargine (the mean difference between treatment groups at 52 weeks was 7.2 IU/L). Four weeks after BIL was discontinued these levels decreased toward baseline. Additionally, more BIL-treated patients had an ALT level greater than or equal to three times the upper limit of normal compared to insulin glargine (ALT $\geq$ 3X ULN: 4.4 percent vs. 1.5 percent). No cases of severe drug-induced liver injury (Hy's Law) occurred in these studies.^{1,2}
- Liver fat was measured using magnetic resonance imaging (MRI) in a subset of patients from both studies. Results showed BIL-treated patients had an increase in liver fat content from baseline compared to those treated with insulin glargine (the mean difference between treatment groups was 2.2 percent at 52 weeks).^{1,2}
- In the IMAGINE-7 trial, patients taking BIL experienced an increase in the level of ALT from baseline (10.59 IU/L), but four weeks after BIL was discontinued these levels decreased toward baseline. No patients met the criteria for severe drug-induced liver injury (Hy's Law) in the study.⁴

Non-hepatic safety findings:

- In both IMAGINE-1 and IMAGINE-3, patients taking BIL had an increase in triglycerides.
- An analysis across all trials - including type 2 - 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.
- In IMAGINE-3, BIL-treated patients experienced small but statistically significant increases in systolic and diastolic blood pressure compared to insulin glargine patients (less than 2 mmHg mean difference at 52 weeks).
- In IMAGINE-3, patients on BIL also had increases in LDL cholesterol levels and reductions in HDL cholesterol levels compared to those taking insulin glargine.²
- There were significantly more injection site reactions in patients treated with BIL than those treated with insulin glargine.^{1,2}

About the Studies

IMAGINE-1

IMAGINE-1 is a Phase III, 78-week (primary endpoint at 26 weeks), open-label, randomized, study of 455 patients designed to compare BIL (n=295) to insulin glargine (n=160) in combination with mealtime insulin in patients with type 1 diabetes. Patients were randomized to bedtime BIL (n=295) or insulin glargine (n=160). Patients in both groups had a mean baseline HbA1c of 7.8

percent.¹

IMAGINE-3

IMAGINE-3 is a Phase III, 52-week, double-blind, randomized study of 1,114 patients with type 1 diabetes designed to compare BIL (n=664) to insulin glargine (n=450) in combination with mealtime insulin. Patients in both groups had a mean baseline HbA1c of 7.9 percent.²

IMAGINE-7

IMAGINE-7 is a Phase III, 36-week, randomized, crossover study of 212 patients designed to compare BIL administered once daily at a fixed time to BIL administered at a variable time of day in patients with type 1 diabetes. Patients were randomized to two 12-week treatment periods comparing fixed time dosing to variable time dosing. Patients had a mean baseline HbA1c of 7.5 percent.⁴

About Basal Insulin Peglispro

Basal insulin peglispro, discovered in Lilly Research Laboratories, is currently in Phase III clinical trials and is being studied as a once-daily treatment for type 1 and type 2 diabetes. BIL is a hepato-preferential basal insulin. Its activity profile is derived from its reduced effect in peripheral tissue, making it more similar to endogenous insulin compared to other exogenous insulins with a conventional activity profile.

In the clinical trial program to date, consisting of more than 6,000 patients, approximately 3,900 patients have been treated with BIL. In the core Phase III clinical trial program consisting of seven IMAGINE trials in patients with type 1 and type 2 diabetes, superiority in HbA1c was seen in five trials for BIL against active comparators.

About Diabetes

Approximately 29 million Americans⁵ and an estimated 387 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.⁶

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 newsroom.lilly.com/social-channels.

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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 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.

¹ Garg S, Hideaki J, Dreyer M, et al. Greater HbA1c Reduction with Basal Insulin Peglispro (BIL) v Insulin Glargine (GL) in an Open-label, Randomized Study in T1D Patients 9 (pts): IMAGINE 1. Abstract 95-OR. Presented at 75th American Diabetes Association (ADA) Scientific Sessions; June 5-9, 2015; Boston, MA.

² Bergenstal R, Lunt H, Franek E, et al. Superior Reduction of HbA1c in a Double-blind, Randomized Study of Basal Insulin Peglispro (BIL) v Insulin Glargine (GL) in Patients (pts) with T1D: IMAGINE 3. Abstract 986-P. Presented at 75th American

Diabetes Association (ADA) Scientific Sessions; June 5-9, 2015; Boston, MA.

³ Standards of Medical Care in Diabetes. Diabetes Care. January 2014. 37:1. Accessed at: http://care.diabetesjournals.org/content/37/Supplement_1/S14.full

⁴ Garg S, Selam J, Bhargava A, et al. HbA1c Reduction and Hypoglycemia with Variable Time (VT) and Fixed Time (FT) Dosing of Basal Insulin Peglispro (BIL) in Type 1 Diabetes (T1D): IMAGINE 7. Abstract 1018-P. Presented at 75th American Diabetes Association (ADA) Scientific Sessions: June 5-9, 2015; Boston, MA.

⁵ Centers for Disease Control and Prevention. National Diabetes Statistics Report, 2014. Available at: <http://www.cdc.gov/diabetes/pubs/statsreport14/national-diabetes-report-web.pdf>. October 2014.

⁶ International Diabetes Federation. IDF Diabetes Atlas, 6th edn. Brussels, Belgium: International Diabetes Federation, 2014. <http://www.idf.org/diabetesatlas/update-2014>.

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