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## **Pilot Study of Ruboxistaurin Showed Favorable Effects on Kidney Damage and Function in People with Type 2 Diabetes and Nephropathy**

**Approximately 40 percent of people with diabetes develop nephropathy, the leading cause of kidney failure**

SAN DIEGO, June 12, 2005 /PRNewswire-FirstCall via COMTEX/ -- Eli Lilly and Company (NYSE: LLY) today announced encouraging results from a one-year pilot study examining the effect of ruboxistaurin mesylate in persons with type 2 diabetes and kidney disease (also known as "diabetic nephropathy"). Data reported at the American Diabetes Association (ADA) Annual Meeting in San Diego showed that in patients being treated with angiotensin converting enzyme inhibitors (ACE inhibitors), angiotensin receptor blockers (ARBs), or both, ruboxistaurin significantly reduced albuminuria (an indicator of diabetic kidney damage) by 24%, compared to a nonsignificant 9% reduction in patients taking placebo.

"The results from this study are very encouraging for people with type 2 diabetes who suffer from diabetic nephropathy," said Katherine R. Tuttle, MD, lead investigator of the study, from Providence Medical Research Center and The Heart Institute of Spokane, Spokane, Wash. "The significant improvement of albuminuria with ruboxistaurin in patients already treated with ACE inhibitors or ARBs suggests that the drug may be helpful in further slowing the progression of kidney disease."

Albuminuria is a condition in which the kidneys lose increased amounts of albumin (a protein marker of kidney damage) into the urine, and is considered the first clinical indication of diabetic nephropathy. Diabetic nephropathy is a diabetic microvascular complication (DMC) caused by damage to the small blood vessels in the kidneys. It occurs in approximately 40 percent of people with diabetes and is the leading cause of kidney failure in the United States and the developed world.

Reductions in albuminuria with ruboxistaurin were seen after one month of treatment and remained consistent throughout the study. In addition, patients taking placebo experienced a significant loss of kidney function after 1 year, however kidney function was stable in patients treated with ruboxistaurin.

### **About the Study**

In this multicenter, randomized, double-blinded, parallel placebo- controlled trial, 123 subjects were randomized at 17 clinical sites in the United States to receive either 32 mg/day of ruboxistaurin or placebo. Participants were required to be taking stable doses of either ACE inhibitors, ARBs, or both, for 6 months prior to the study and these agents were continued throughout the trial. Baseline characteristics did not differ significantly between treatment groups. Blood glucose and blood pressure control was similar at the beginning and throughout the study.

Analyses of adverse events in this trial revealed no significant differences between the ruboxistaurin (15 reported) and placebo (9 reported) groups, except in the placebo group for episodes of hypertension requiring intervention (8% of placebo participants had an episode of hypertension requiring intervention compared with 0% in ruboxistaurin treated group). The most frequently reported adverse event in this clinical trial was hypertension. Three ruboxistaurin-treated participants withdrew due to adverse events (decreased libido, impaired mental status, and metastatic cancer). Based upon the results of this pilot study, ruboxistaurin was well tolerated; but the small sample size and limited duration of follow-up precludes a firm conclusion about safety.

### **About Ruboxistaurin**

Ruboxistaurin is a specific protein kinase C beta (PKC  $\beta$ ) inhibitor, the first of a new class of compounds being investigated for the treatment of diabetic peripheral neuropathy (damage to the nerves), diabetic retinopathy (damage to the eyes) and diabetic nephropathy, the three major diabetic microvascular complications (DMCs) associated with type 1 and type 2 diabetes. Metabolic factors associated with diabetes often lead to damage to the small blood vessels in the nerves, eyes and kidneys, ultimately leading to DMCs.

Pre-clinical data show that ruboxistaurin is a specific inhibitor of PKC  $\beta$ . PKC  $\beta$  is an enzyme that has been implicated in the underlying process of microvascular damage caused by diabetes. Lilly has previously announced that it plans to submit a marketing application (or NDA) to seek approval from the U.S. Food and Drug Administration for ruboxistaurin for the treatment of symptoms of diabetic peripheral neuropathy in the second half of 2005.

## Lilly's Leadership in Diabetes

Through a long-standing commitment to diabetes care, Lilly provides patients with breakthrough treatments that enable them to live longer, healthier and fuller lives. Since 1923, Lilly has been the industry leader in pioneering therapies to help health care professionals improve the lives of people with diabetes, and research continues on innovative medicines to address the unmet needs of patients. For more information about Lilly's current diabetes products visit [www.lillydiabetes.com](http://www.lillydiabetes.com) .

### About Lilly

Lilly, a leading innovation-driven corporation, is developing a growing portfolio of first-in-class and best-in-class pharmaceutical products by applying the latest research from its own worldwide laboratories and from collaborations with eminent scientific organizations. Headquartered in Indianapolis, Ind., Lilly provides answers -- through medicines and information -- for some of the world's most urgent medical needs. Additional information about Lilly is available at [www.lilly.com](http://www.lilly.com) . P-LLY

This press release contains forward-looking statements about the potential of the investigational compound ruboxistaurin for the treatment of diabetic microvascular complications and reflects Lilly's current beliefs. However, as with any pharmaceutical product under development, there are substantial risks and uncertainties in the process of development and regulatory review. There is no guarantee that the product will receive regulatory approvals, or that the regulatory approval will be for the indication(s) anticipated by the company. There is also no guarantee that the product will prove to be commercially successful. For further discussion of these and other risks and uncertainties, see Lilly's filings with the United States Securities and Exchange Commission. Lilly undertakes no duty to update forward-looking statements.

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