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Investigational Treatment Ruboxistaurin Demonstrated Promise in Reducing the Occurrence of Vision Loss Caused by Diabetic Retinopathy

Phase 3 data presented at 66th Annual ADA Scientific Sessions

WASHINGTON, D.C., June 11, 2006 /PRNewswire-FirstCall via COMTEX News Network/ -- Eli Lilly and Company (NYSE: LLY) today announced encouraging results from an analysis of pooled data from two, three-year phase 3 trials that showed ruboxistaurin mesylate reduced the risk of sustained moderate vision loss by 41 percent when compared to placebo in patients with moderate to severe, nonproliferative diabetic retinopathy (DR). Vision loss occurred in only 6.1 percent of patients treated with ruboxistaurin compared to 10.2 percent of patients treated with placebo.(1) Ruboxistaurin (proposed brand name Arxxant (TM)) is an investigational drug for the treatment of DR, a diabetic eye disease.

The findings were presented in an oral session at the American Diabetes Association's (ADA) 66th Annual Scientific Sessions in Washington, DC, and are included in Lilly's new drug application (NDA) submitted to the FDA in February 2006.

"These data are exciting because they show that ruboxistaurin has the potential to be the first oral therapy to specifically reduce the risk of vision loss caused by diabetic retinopathy," said Lloyd Paul Aiello, MD, PhD, lead investigator of the study, director, Beetham Eye Institute & Section on Eye Research, Joslin Diabetes Center, and associate professor of ophthalmology, Harvard Medical School in Boston, MA. "This could be an important clinical development for the millions of people(2) around the world who are at risk for vision loss caused by this serious disease."

Study Details

Vision loss (measured in the study as sustained moderate vision loss or SMVL) occurred in only 6.1 percent of patients treated with ruboxistaurin compared to 10.2 percent of patients treated with placebo, equaling a 41 percent relative risk reduction ($P=0.011$) over three years.(1) Vision loss (SMVL) was defined as a three-line loss on the eye chart that was sustained for at least 6 months.(1)

Comprised of data from the PKC-DRS and PKC-DRS2 studies, the combined analysis examined a total of 813 patients treated with 32 mg per day of ruboxistaurin ($n=412$) or placebo ($n=401$) derived from two multi-center, randomized, placebo-controlled, double-masked, phase 3 trials that were similar in design and implementation.(1) The analysis examined whether ruboxistaurin could reduce the risk of long-term, or sustained moderate vision loss caused by diabetic retinopathy.(1) Patients had moderate to severe nonproliferative diabetic retinopathy at the start of the study.(1) The beneficial effect of ruboxistaurin was not accompanied by a reduction in the progression of study patients from nonproliferative to proliferative diabetic retinopathy.

Clinical Safety Evaluation

A separate analysis of data from 11 studies, of the safety of 32 mg per day of ruboxistaurin in patients with at least one diabetic microvascular complication (including diabetic retinopathy), also presented at the ADA Scientific Sessions, found ruboxistaurin was generally well tolerated and had an overall adverse event profile, as well as a serious adverse event profile similar to placebo. Serious adverse events occurred in 23.2 percent of patients taking placebo compared to 20.8 percent of patients taking ruboxistaurin.(3) In addition, ruboxistaurin had no effect on glucose or blood pressure control.(3) This data presentation reported on a clinical safety data base which includes a total of 2,804 patients with type 1 or type 2 diabetes combined from 11 phase 2 and 3 placebo-controlled, double-masked trials, for up to four years.(3) The only treatment-emergent adverse event that occurred with a frequency of greater than or equal to two percent and occurred significantly more often in the ruboxistaurin group was indigestion.(3)

About Diabetic Retinopathy

Diabetic retinopathy is a relatively common microvascular complication in individuals with diabetes that can lead to a sudden and debilitating impact on vision.(4) In the United States, an estimated 4.1 million adults aged 40 and older have diabetic retinopathy (40.3% of persons with diabetes mellitus) with 899,000 having vision-threatening retinopathy (8.2%).(5) For persons with type 1 diabetes, the crude prevalence of diabetic retinopathy is about 80%.(6)

Diabetic retinopathy is recognized as the leading cause of blindness in the working aged population, which exacts huge human

and financial costs.(7,8) Yet blindness is only a part of the story. Even mild vision loss can lead to difficulties in reading, driving, employment, and mobility as well as an increased risk of accidental injuries.(9,10,11) For the diabetes patient, vision loss can lead to additional issues as functional difficulties further exacerbate patients' ability in disease self-management that leads to a worsening of metabolic control.(12)

Nonproliferative diabetic retinopathy (NPDR) occurs when the smallest blood vessels in the retina are damaged.(6) Patients with NPDR can develop diabetic macular edema (DME), which is the most common cause of vision loss in patients with NPDR. (8) DME occurs when the macula (the area of the retina that allows sharp vision) swells with fluid.

In the most advanced or proliferative stage of diabetic retinopathy (PDR), new blood vessels grow abnormally from the back of the eye(6) and they may subsequently cause severe vision loss.(6)

About Ruboxistaurin

Ruboxistaurin limits protein kinase C beta (PKC beta) overactivation, and it is the first of a new class of compounds being investigated for the treatment of diabetic retinopathy.

The laboratory of George L. King, MD, research director at Joslin Diabetes Center and professor of medicine at Harvard Medical School, first proposed that PKC beta activation is responsible for the development of diabetic retinopathy and other microvascular damages induced by diabetes.

Lilly submitted a new drug application (or NDA) to seek approval from the U.S. Food and Drug Administration for ruboxistaurin for the treatment of diabetic retinopathy in February 2006. The FDA has informed Lilly that it will conduct a priority review of Lilly's NDA submission for ruboxistaurin.

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.

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, IN, 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.

About Joslin Diabetes Center

Joslin Diabetes Center, dedicated to conquering diabetes in all of its forms, is the global leader in diabetes research, care and education. Founded in 1898, Joslin is an independent nonprofit institution affiliated with Harvard Medical School. Joslin research is a team of more than 300 people at the forefront of discovery aimed at preventing and curing diabetes. Joslin Clinic, affiliated with Beth Israel Deaconess Medical Center in Boston, the nationwide network of Joslin Affiliated Programs, and the hundreds of Joslin educational programs offered each year for clinicians, researchers and patients, enable Joslin to develop, implement and share innovations that immeasurably improve the lives of people with diabetes. For more information on Joslin, call 1-800-JOSLIN-1 or visit www.joslin.org.

This press release contains forward-looking statements about the potential of the investigational compound ruboxistaurin for the treatment of diabetic retinopathy 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.

(1) Aiello, L, et al. Effect of Ruboxistaurin (RBX) on Diabetic Macular Edema (DME) and Visual Loss: Meta-Analysis of the PKC-DRS and PKC DRS2.

(2) Prevent Blindness America; National Eye Institute, Vision Problems in the U.S. Available at: <http://www.nei.nih.gov/eyedata/pdf/VPUS.pdf>. Accessed May 3, 2006.

(3) King, G., et al. Evaluation of the clinical safety of the selective PKC beta isoform inhibitor, ruboxistaurin, in patients with diabetic microvascular complications.

(4) Ciulla, et al. Diabetes Care, 26:2653-2664 (2003).

(5) Kempen, et al. Arch Ophthalmol, 122:552-563 (2004).

(6) Roy, et al. Arch Ophthalmol, 122:546-551 (2004).

(7) The Centers for Disease Control and Prevention. National Diabetes Fact Sheet: General Information and National Estimates on Diabetes in the United States, 2000. Available at: <http://www.cdc.gov/diabetes/pubs/estimates.htm>. Accessed May 3, 2006.

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(9) Wulsin, et al. Psychomatic Medicine, 53:109-117 (1991).

(10) Coyne et al. Family Practice, 21:445-451 (2004).

(11) Legood et al Injury Prevention 8:155-160 (2002)

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