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Data Indicate That Lilly's Ruboxistaurin May Have A Potentially Beneficial Effect on Diabetes-Induced Eye Disease

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Confirmatory Phase 3 Clinical Trials Are Ongoing

Eli Lilly and Company's investigational compound ruboxistaurin may reduce vision loss from diabetes-induced eye disease, according to new analyses of previously reported data presented at the 2004 Joint Meeting of the American Academy of Ophthalmology and the European Society of Ophthalmology in New Orleans, La.

The analyses showed that diabetic macular edema (DME) — a serious manifestation of diabetic retinopathy that occurs when fluid builds up in the retina and causes swelling¹ — was associated with lower visual acuity when it involved the center of the macula. The severity of central involvement was associated with the severity of vision loss, according to the analyses.

Patients who received 32 mg per day of ruboxistaurin appeared to have better visual acuities (better vision) at equivalent levels of involvement of the center of the macula than placebo-treated patients (data from a trial with approximately 63 patients per treatment group). In addition, there was a trend toward less progression of DME to involve the center of the macula in patients receiving 32 mg of ruboxistaurin (data from a trial with 170 patients per treatment group).

"A key to preventing vision loss from diabetic eye disease is to prevent macular edema from involving the center of the macula, where it affects the part of the retina that is most important for detailed vision," said Lloyd Paul Aiello, MD, PhD, associate director of the Beetham Eye Institute at the Joslin Diabetes Center, Harvard University Medical School.

"These data suggest that ruboxistaurin may have the potential to decrease the progression of diabetic macular edema to involve the center of the macula. A Phase 3 clinical trial is underway to further explore these preliminary findings."

Details

These analyses involved data from two Phase 3 placebo-controlled trials of ruboxistaurin in patients with diabetic eye disease, one with a 30-month minimum duration and one with a three-year minimum duration. The trials enrolled a total of more than 900 patients with diabetic retinopathy and different degrees of DME. Over the course of the studies, patients had both their visual acuity and extent of DME measured at multiple visits.

One analysis examined 540 different concurrent determinations of visual acuity and distance of DME from the center of the macula in 122 eyes of patients receiving placebo treatment only. The results showed that visual acuity was close to normal in eyes with macular edema that did not involve the center of the macula (approximately 80 letters correct, equivalent to about 20/25 vision, on the ETDRS visual acuity protocol - the standard measure used in visual acuity research). The visual acuity was significantly lower in eyes with macular edema that involved the center of the macula (approximately 65 letters correct, corresponding to about 20/50 vision, $p < 0.001$.)

In a second analysis, patients ($n=67$) with eyes showing center involvement who were taking 32 mg per day of ruboxistaurin had higher average visual acuity than the eyes of placebo patients ($n=61$) -- 71 letters correct versus 60 letters, $p < 0.01$. This difference was not seen at lower doses of ruboxistaurin. In addition, there was a trend toward less progression of DME from outside of 500 microns to the center of the macula in patients taking 32 mg of ruboxistaurin ($n=168$) than in placebo-treated patients ($n=176$) -- 20 percent versus 31 percent, $p = 0.083$. This difference was not seen at lower doses of ruboxistaurin.

Findings from a previously conducted analysis of these two combined clinical trials showed that side effects were equally distributed among experimental and placebo groups and that ruboxistaurin was generally well tolerated by the patients. While no cause and effect relationship was established between ruboxistaurin and any event, the most common side effects seen in the trials were nasopharyngitis, headache, cough and hypertension.

About Diabetic Macular Edema

Diabetic macular edema is a manifestation of diabetic retinopathy that occurs when fluid buildup causes the macula, or the

center of the retina, to swell. This can cause blurriness and vision loss.² Diabetic retinopathy, one of three major diabetic microvascular complications, affects the small blood vessels in a part of the eye called the retina.

Currently there is no prescription therapy in the United States or Europe approved to target the underlying process of microvascular damage that leads to diabetic retinopathy. Pre-clinical data show that ruboxistaurin, currently being investigated for treatment of diabetic retinopathy and other diabetic microvascular complications, is a specific inhibitor of PKC β . PKC β is an enzyme that has been implicated in the underlying process of microvascular damage.

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.

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.

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.

1. American Diabetes Association, Diabetes Dictionary. Available at:

<http://www.diabetes.org/diabetesdictionary.jsp?pageID=3&exitDictionaryTo=>. Accessed August 9, 2004.

2. National Eye Institute, Diabetic Retinopathy: What You Should Know. Available at:

<http://www.nei.nih.gov/health/diabetic/retinopathy.asp>. Accessed August 9, 2004.