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Data Show Reduced Symptoms of Diabetic Peripheral Neuropathy for Patients Taking Lilly's Ruboxistaurin

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Additional analyses show reliability of NTSS-6-SA testing, symptom relief from ruboxistaurin independent of the simultaneous use of pain medications, and impact of symptoms on quality of life

Eli Lilly and Company announced encouraging results from analyses of prior study data this week for patients with diabetic peripheral neuropathy (DPN). Data reported at the European Association for the Study of Diabetes (EASD) Diabetic Neuropathy Study Group's (NeuroDiab) Annual Meeting demonstrated that patients with DPN who took Lilly's ruboxistaurin experienced relief of a broad range of symptoms of DPN independent of the simultaneous use of pain palliative oral medications. Ruboxistaurin is not approved for use in Germany, Europe or elsewhere in the world. These analyses are from a data set from a previously reported study. In that study patients were administered the Neuropathy Total Symptom Score-6 test (NTSS-6), a questionnaire that measures the frequency and intensity of six positive sensory symptoms of DPN - numbness, prickling, aching pain, burning pain, lancinating pain, and allodynia (a condition in which ordinarily non-painful stimuli such as a bed sheet or socks evoke pain).

In two additional analyses subsequently presented at EASD's 40th Annual Meeting, one demonstrated the validity of a self-administered version of the NTSS-6 and another revealed outcomes data showing a strong correlation between the presence of positive sensory symptoms characteristic of DPN and a lower quality of life.

"We are very encouraged by this early evidence of ruboxistaurin's ability to reduce a broad range of symptoms, but it is also important to improve the recognition and diagnosis of diabetic nerve damage," said Vladimir Skljarevski, M.D., neurologist, senior clinical research physician and investigator for Lilly's ruboxistaurin effort. "These data suggest physicians can encourage patients to take this simple test (NTSS-6-SA) with reliability to help detect diabetic peripheral neuropathy earlier. To succeed against this potentially devastating condition and improve quality of life, we need to attack diabetic peripheral neuropathy on all fronts."

About Diabetic Neuropathy

Diabetic peripheral neuropathy, along with diabetic retinopathy (eye damage) and diabetic nephropathy (kidney damage), is one of the three diabetic microvascular complications.¹ DPN is caused by microvascular (small blood vessel) damage that affects nerves primarily in the hands and feet and can lead to a broad range of symptoms and ultimately, foot ulcers and amputations.² It is the leading cause of non-traumatic lower-limb amputations.³

There is no prescription therapy in the United States or Europe currently approved to target the underlying process of microvascular damage that leads to DPN. Pre-clinical data show that ruboxistaurin, currently being investigated for treatment of DPN 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.

Findings - Ruboxistaurin's Impact Independent of Use of Palliative Medications

Data from the study presented at the NeuroDiab meeting evaluated the concomitant use of pain palliative oral medications and ruboxistaurin in 83 patients with clinically significant symptoms of DPN. The analysis compared the effect on symptoms in patients treated with ruboxistaurin alone to patients who took palliative oral medications at any point in the study.

Data showed patients taking ruboxistaurin alone or together with palliative medications had significant improvement in symptoms from baseline. Researchers concluded that ruboxistaurin's favorable effects on symptom reduction were independent of the use of palliative medications, suggesting that ruboxistaurin may work via a different mechanism to treat the disease directly, not just the symptoms. Previous studies have similarly demonstrated ruboxistaurin's effect on NTSS-6 outcomes.

Findings - NTSS-6-SA

Analyses presented during EASD evaluated a self-administered version of the NTSS-6 (NTSS-6-SA), and found it consistently reliable when compared to the original clinician-administered version. Researchers administered the NTSS-6-SA via an 11-

page questionnaire to randomly selected members of the Kaiser Permanente Northwest diabetes registry. Participants were categorized according to their NTSS-6-SA results, then a subset of patients participated in a clinical exam where they were evaluated with the original clinician-administered version of the NTSS-6. Patients also were assessed for pressure sensitivity with a monofilament and vibratory detection threshold (VDT).

Data showed the NTSS-6-SA to be a valid and reliable alternative to the original NTSS-6 for the assessment of positive sensory symptoms characteristic of DPN. The results suggest that the NTSS-6 can be self-administered and does not require intensive clinician-assessment, which potentially may increase awareness of all major DPN symptoms, especially numbness and tingling that have often been ignored. Results also suggest NTSS-6-SA may facilitate dialogue with physicians, and improve overall testing. The findings also confirm that symptoms of DPN often occur before the neurological damage of DPN is detected by the predominantly used monofilament test and can be captured by NTSS-6 testing.

"Increasing testing for DPN is half the battle - the earlier we catch it the greater chance for effective treatment," said Dr. Pawel Fludzinski, team leader for Lilly's ruboxistaurin effort.

Findings - DPN Symptoms and Quality of Life

Analyses presented during EASD evaluated 281 patients randomly selected from the same Kaiser Northwest registry to assess the relationship between worsening positive sensory symptoms characteristic of DPN and functional health status and overall quality of life. Study participants were evaluated based on results from the NTSS-6-SA, the Short-Form 12 Health Survey, the EuroQol quality of life instrument and an 8-item Patient Health Questionnaire depression diagnostic tool.

Data showed a significant link between the presence and severity of positive sensory symptoms of DPN as measured by NTSS-6-SA and a lower quality of life and a lower self-reported health status for people with diabetes. A total of 62 patients who showed no signs of DPN had the most favorable scores on each of the health quality tests. Comparatively, the 112 patients with the most severe symptoms of DPN scored least favorably in overall self-reported health status and quality of life - indicating the severe and negative impact of positive sensory symptoms of DPN.

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 an 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 Eli Lilly and Company

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.

This news release contains forward-thinking statements that reflect management's current beliefs about the potential for ruboxistaurin as a treatment of diabetic microvascular complications. However, as with any pharmaceutical under development, there are significant risks and uncertainties in the process of development and regulatory review. This product has not yet been proven safe and effective. There are no guarantees that the product will receive necessary regulatory approvals or prove to be commercially successful. For additional information about the factors that affect the company's business, see the company's filings with the United States Securities and Exchange Commission. The company 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 17, 2004.

2. American Diabetes Association, Neuropathy and Nerve Damage.

Available at: <http://www.diabetes.org/type-1-diabetes/nerve-damage.jsp>
Accessed August 17, 2004.

3. American Diabetes Association, National Diabetes Fact Sheet.

Available at: <http://www.diabetes.org/diabetes-statistics/national-diabetes-fact-sheet.jsp>
Accessed August 17, 2004.