



John Lechleiter

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Ruboxistaurin's future in doubt, despite promising study results

By Sean Henahan

ANTI-VEGF drugs are producing impressive initial clinical results in the treatment of diabetic retinopathy and macular oedema. However, if these results are confirmed in larger clinical trials, patients would need to receive intraocular injections every four to six weeks for the rest of their lives, a reality that could limit the usefulness of these agents.

Ruboxistaurin (Arxxant, Lilly), a drug that is administered in tablet form and also produced promising early results, would have transcended that problem. However, it is now uncertain whether Eli Lilly will continue to develop the drug, following a recent FDA decision mandating three years of additional clinical trials.

Ruboxistaurin mesylate is a specific inhibitor of PKC β , an enzyme that has been implicated in retinopathy. The results of a three-year multicentre clinical trial (PKC-DRS 2), first reported at the American Academy of Ophthalmology scientific sessions in Chicago, Illinois, recently appeared in the journal *Ophthalmology*, (December 2006, Vol. 113, Issue 12, 2221-2230).

The double-blind study randomised 685 patients at 70 clinical sites to oral ruboxistaurin (32mg/day) or placebo for 36 months. Inclusion criteria included a best-corrected visual acuity score of at least 45 letters, retinopathy level of at least 47A and no more than 53E, and no prior panretinal photocoagulation in at least one eye. The study included patients with Type 1 and Type 2 diabetes. Mean age of patients was 59 years.

Exclusion criteria included unstable angina, systolic blood pressure of 190 mmHg or diastolic blood pressure of 105 mmHg, a corrected QT interval of greater than 500 milliseconds, or malignancy within the past six months.

Patients underwent eye exams at screening and every three months, and retinopathy screening every six months. Retinopathy screening involved Early Treatment Diabetic Retinopathy Study (ETDRS) standard 7-field 30° colour stereoscopic fundus photography. Two independent graders determined the extent of retinopathy and macular oedema.

At three years, patients receiving the test drug had a 40 per cent risk reduction for sustained moderate visual loss compared to those receiving placebo. Vision loss occurred in 5.5 per cent of those on active treatment compared with 9.1 per cent in placebo-treated patients. The difference was statistically significant.

Patients on active treatment also had better mean visual acuity after 12 months. Ruboxistaurin treatment produced visual improvement of at least 15 letters and was more frequent in 4.9 per cent of cases, compared with 2.4 per cent for placebo. Patients on placebo were also more likely to

lose 15 letters over the course of the trial.

Patients on ruboxistaurin also fared better with macular oedema. These patients were less likely to develop progression of oedema to within 100 μ m of the centre of the macula than placebo recipients. They were also significantly less likely to require laser treatment for macular oedema.

Ruboxistaurin also appeared to be well tolerated, with no reported clinically significant adverse events or lab abnormalities. Dropout rates were the same for active treatment and placebo.

"The results of the current study are the first to demonstrate that an orally administered pharmacologic agent (ruboxistaurin) can be well tolerated and reduce vision loss in patients with diabetes over an extended period," the researchers said.

The researchers note that the effect of ruboxistaurin on macular oedema progression and vision is consistent with the hypothesis that hyperglycaemia induces synthesis of diacylglycerol, which activates PKC in the retina. This mediates vascular dysfunction and leads to increased vascular permeability, possibly through alterations in tight junction structure.

One disappointing result in this study was that ruboxistaurin did not appear to influence the progression of non-proliferative diabetic retinopathy to the proliferative form, nor did it appear to reduce the need for panretinal photocoagulation for diabetic retinopathy. The researchers note that several factors could account for this lack of effect. Those factors would include a limited follow-up time, retinopathy that was already too severe, insufficient dosing, or activation of compensatory mechanisms.

In spite of the lack of effect on retinopathy progression, Lilly had results suggesting potentially useful therapeutic effects. These results supported those from an earlier phase III trial (*Diabetes* 2005; 54: 2108-97). Accordingly, the company went ahead and submitted a new drug application (NDA) to seek approval from the US Food and Drug Administration for ruboxistaurin for the treatment of moderate to severe non-proliferative diabetic retinopathy in February 2006.

Much to the surprise of Lilly, the FDA responded by issuing an approvable letter, an indication that the agency wanted more information. The letter requested that Lilly submit additional data to support the clinical evidence from the PKC DR2 study. Lilly appealed the decision, hoping that it could provide sufficient data without conducting another study, but that appeal was rejected.

"We are certainly disappointed with this communication from the FDA. Diabetic retinopathy is a significant unmet medical need to which we have devoted more than a decade of clinical research with no guarantee

of approval. We still believe that ruboxistaurin has potential as a treatment for diabetic eye disease and are exploring the feasibility of further development of this molecule," said Dr John Lechleiter, president and chief operating officer of Eli Lilly and Company, in a media release.

Lloyd P Aiello MD, Harvard University, was the director of the PKC DR2 study. He told *EuroTimes* that he believes Lilly will support getting this drug to market in some manner for the benefit of patients. He commented that based on the current study results, the drug does look promising, and that he would like to see the research continue. He emphasised that the safety of the drug appeared to be excellent.

One scenario is that the FDA would require Lilly to conduct an additional three-year clinical study. This would literally cost millions of dollars. The company has not announced that they will not support such an investment, but neither have they said that they would. Even with the best possible scenario, a large clinical study that produced significant evidence of therapeutic benefit, the drug would not come to market for at least five years.

These recent developments also would push back the approval of ruboxistaurin in Europe. Lilly announced it would withdraw its marketing application from the European Medicines Agency (EMA) for the drug. The EMA's Committee for Medicinal Products for Human Use (CHMP) had also asked for additional data.

Two phase III studies and one phase II study are under way in the US at present. Two of these are looking at the effects of treatment on diabetic macular oedema in patients with Type 1 and Type 2 diabetes. The third trial is designed to measure the effects of treatment on early diabetic kidney in patients with Type 1 diabetes.

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