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Gene Signal International sees enough in aganirsen phase III data for follow-up trial

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Aganirsen, a topical antisense drug in development for treating inflammation-related corneal neovascularization (CNV), failed to reach the primary endpoint of visual acuity in a phase III trial, but its developer Gene Signal International SA plans to start a confirmatory trial later this year based on a different endpoint, having seen a significant reduction in the extent of neovascularization between the two treatment groups.

In order to maintain transparency and to allow the passage of light into the eye, the cornea does not normally contain any blood vessels. Injury or inflammation – due to viral infection, for example – can lead to neovascularization, however, and this may necessitate corneal transplant. Neovascularization is also one of the risk factors for graft failure.

Aganirsen inhibits expression of insulin receptor substrate 1 (IRS-1), a protein that modulates expression of vascular endothelial growth factor (VEGF), which stimulates the formation of new blood vessels. The drug is already sold through a compassionate use program in Germany, France, Spain and Switzerland.

The present study, which was published online on May 8, 2014, in *Ophthalmology* in a paper, titled "Aganirsen Antisense Oligonucleotide Eye Drops Inhibit Keratitis-Induced Corneal Neovascularization

and Reduce Need for Transplantation," recruited 69 patients with CNV due to inflammation. (The term "keratitis" refers to inflammation of the cornea.)

These were assigned to receive either aganirsen twice daily (n = 34) or placebo (n = 35) for 90 days. Patients were followed for 180 days in total. There was no significant difference in visual acuity between the two groups. The study detected a trend in lowering the need for corneal transplant in the intent-to-treat population, and that effect was significant in a subgroup with keratitis due to viral infection and central neovascularization.

A durable effect on neovascularization was apparent also. The area of corneal neovascularization was 26.2 percent less in the drug treatment group as compared with the control group at 90 days ($p = 0.014$) and 26.7 percent less at 180 days ($p = 0.012$).

"I think it's the first evidence of disease modification by angiogenesis inhibition in the cornea," Claus Cursiefen, head of the ophthalmology department of the University of Cologne Medical Center, in Germany, who was principal investigator on the trial, told *BioWorld Today*.

Lausanne, Switzerland-based Gene Signal plans to continue development of the drug on this basis. It could increase the number of patients who are eligible to receive a corneal graft, by cleaning up the cornea in advance of the procedure. It will need to employ a different endpoint in order to do so, however.

"We are first in class. Visual acuity is the traditional endpoint which is required by the regulatory authorities," Gene Signal co-founder and CEO Eric Viaud told *BioWorld Today*. "From our experience and knowledge, visual acuity is not a suitable endpoint."

Although visual acuity represents the gold standard for measuring clarity of vision – and is commonly used in back-of-the-eye indications – it may not distinguish between those on drug and placebo if the neovascularization process is at an early stage and does not yet have an impact on sight. Similarly, it may not be able to pick up a drug effect if the process is so far advanced that patients' vision has already deteriorated considerably.

"We have some ideas now for more meaningful clinical endpoints to discuss with the EMA and FDA in order to start a confirmatory study," Viaud said. "What we are looking for is an agreement with the authorities to get an endpoint which will be in line with the graft." If the firm can secure that agreement by September, the study could begin before the year end, he said.

"The obvious endpoint which works is we have an effect on neovascularization," said Cursiefen. In itself, that has no direct benefit for patients, however. "There is no direct link to visual acuity." A composite endpoint that encompasses reduction in the need for transplant, graft survival – in the event of a graft – and, ultimately, improved visual acuity arising from a successful graft, could capture

the compound's potential. "That is a long-term study," he said. It may need to obtain a narrower label in a shorter time frame first.

Gene Signal also plans to move aganirsen into a phase II/III trial in another orphan ophthalmology indication this year, ischemic central retinal vein occlusion, which, if untreated, can lead to neovascular glaucoma and blindness. The company also will conduct a phase II trial of the drug in wet age-related macular degeneration, an indication that currently relies on injectable therapies. The company already has obtained animal data indicating that it can deliver the drug to the retina. "We have developed an emulsion which is a more lipophilic formulation," Viaud said.

The company has sufficient funds for the next three years. Its compassionate use program generates enough cash to fund about half of its development costs.