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Gene Signal Novel Corneal Neovascularization Product Still On Track Despite Primary Endpoint Miss

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Executive Summary

Although visual acuity is no longer thought to be a useful primary endpoint for drugs targeting corneal neovascularization, Gene Signal will keep developing its first-in-class antisense product in that and other ophthalmic indications.

Swiss biotech Gene Signal International SA has learned the hard way that when you have a first-in-class compound that's the first potential therapy for a specific indication, the primary endpoint in your Phase III trial may not be particularly useful at the study's end compared with what was thought at the start of the trial.

The Lausanne-based company has been developing aganirsen, an antisense DNA oligonucleotide against insulin receptor substrate 1 (IRS-1) for the treatment of corneal neovascularization associated with inflammation, a front-of-the eye orphan indication, for a number of years. The company has been funded principally by a group of high-net-worth private individuals ("Gene Signal Will Expand Antisense Ophthalmic Studies With New Funds" — *"The Pink Sheet" DAILY*,Feb. 5, 2013).

Oligonucleotide-based therapies have seen a surge of interest over recent months, with RNAi firm Dicerna Pharmaceuticals Inc. going public with an $83.7 million IPO and Sanofi's Genzyme Corp. expanding its collaboration with Alnylam Pharmaceuticals Inc. ("Does Alnylam Lift All Oligo Boats? The Dicerna IPO" — *IN VIVO*,February 2014).

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The results of the Phase III I-CAN study, announced May 12, showed there was no difference in the primary endpoint, visual acuity, in patients with keratitis-related corneal neovascularization (CNV) treated for 90 days with aganirsen, compared with those treated with placebo. Sixty-nine patients were treated with one eye-drop of aganirsen, 6 mg/ml twice a day, or placebo, and were then followed for 180 days. The treatments were given on top of standard steroid, antiviral and immunosuppressant therapy.

However, other endpoints did show aganirsen was having statistically significant effects compared with placebo: the corneal neovascularization area was significantly reduced by 26.2% (p=0.014); the need for corneal transplant was significantly reduced at both day 90 (p=0.014) and day 180 (p=0.012); and there were significant improvements in quality of life. Aganirsen was also well tolerated with few treatment-emergent adverse effects.

“There have been shifts in the thinking of key opinion leaders since the I-CAN study was designed, and although visual acuity was believed to be a good endpoint four to five years ago for CNV, it is no longer thought to be so,” Gene Signal’s CEO and co-founder Eric Viaud said in an interview.

It is now believed there is little if any linkage between neovascularization and visual acuity. If patients have peripheral neovascularization it doesn’t affect vision, and if patients have central neovascularization, the condition is too advanced for aganirsen to make a difference, Viaud explained.

What seems to be important is that reducing the growth of new blood vessels through the use of aganirsen cleans the eye and makes it more receptive to a corneal graft, Viaud said. Previous Phase II results, and clinical experience in a couple of European countries where aganirsen is available on a named-patient basis, as well as the secondary endpoints, support this view.

Gene Signal is now discussing with EU and U.S. regulators the clinical endpoints necessary to show aganirsen has clinical benefits in a short confirmatory trial, likely to start in September this year.

Viaud is sanguine about the process, which he considers to be part and parcel of working in a new therapeutic area. And Gene Signal is not about to run out of funds. It has at least three years of funds available, including that supplied by private investors, various grants from institutions in Europe and Canada and a small amount from the named-patient supply of aganirsen.

Viaud expects Gene Signal will be able to market aganirsen in Europe in an orphan indication, if and when it is launched. And it is discussing collaborations for marketing the medicine outside Europe and in non-orphan indications.

Corneal transplants usually have a high success rate, partly because immune rejection is less common than in other sites. But invasion of the cornea by new, leaky, blood vessels – corneal neovascularization - increases the risk of rejection. IRS-1 is over-expressed in pathologic angiogenesis.

The company has many follow-on projects, including a new topical formulation of aganirsen that reaches the back of the eye and is about to be evaluated in a Phase II clinical study of patients with anterior-segment ischemic central retinal vein occlusion. Proof-of-concept Phase II studies should start in patients with age-related macular degeneration (AMD) in the third quarter of this year and in patients with diabetic macular edema early next year.

Aganirsen may have potential advantages in the treatment of back-of-the-eye conditions compared with conventional VEGF inhibitors, Viaud said. Aganirsen has little effect on normal blood vessels. VEGF inhibitors like ranibizumab (Novartis AG's *Lucentis*) and aflibercept (Bayer AG's *Eylea*) may also affect blood vessels involved in normal physiological processes, he noted.

Aganirsen in yet another formulation will be evaluated for the treatment of psoriasis after the ophthalmological studies are under way. A Phase IIa pilot study recently showed it significantly reduced inflammation and psoriatic lesion areas in patients with the condition.

Beyond aganirsen, Gene Signal has a number of monoclonal antibodies and peptides that are being evaluated in preclinical studies, including an oncology product that could be submitted for an IND 18 months from now.