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Gene Signal Raises New Cash for Its Antisense Drug Trials

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Thursday, January 24, 2013

With data due from a pivotal Phase III trial of its lead drug candidate around midyear, Gene Signal International SA raised an undisclosed investment from its longstanding syndicate of private investors to keep its pipeline of antisense and peptide-based drugs moving forward.

Although it has maintained a relatively low profile since its formation in 2000, the Lausanne, Switzerland-based biotechnology firm has a topical antisense compound, aganirsen (GS-101), undergoing a pivotal Phase III trial in neovascular-associated corneal graft rejection (NV-CGR). The trial has two main endpoints: visual acuity and effect on corneal neovascularization.

Gene Signal has ambitions to market the product in that indication, for which it has orphan drug status. It already has treated more than 100 patients under a compassionate use program, which is authorized in Germany, Switzerland, Spain and France. The company also is looking to progress aganirsen into larger ophthalmology indications, including age-related macular degeneration (AMD) and diabetic retinopathy.

"Now we are in a position where we have raised enough money to cover the next three years of development, in orphan and non-orphan indications," Gene Signal CEO and co-founder Eric Viaud toldBioWorld Today. Prior to the latest injection of cash, the company had raised some €20 million (US$26.6 million) in total.

To maintain visual acuity and transparency, the cornea normally lacks any blood or lymphatic vessels, a state known as "angiogenic privilege," However, that can become compromised during pathological processes, including inflammation. Corneal revascularization is a major cause of corneal transplants; it is also a significant risk factor for their failure. "If you're not treating neovascularization, the risk of graft failure is about 50 percent," Viaud said.

Aganirsen, a 25-mer phosphorothioate oligonucleotide, inhibits expression of the gene encoding insulin receptor substrate 1 (IRS-1), a protein that mediates signals from insulin and insulin-like growth factor-1 (IGF-1), and which has downstream effects on vascular endothelial growth factor (VEGF), a major target of existing anti-angiogenic therapies. "We are physiologically modulating overproduction of VEGF," Viaud said. "In a normal situation, you don't have any effect."

The drug is administered twice daily in an eye drop formulation, which, Viaud said, is sufficient to deliver an optimal daily dose of 86 mcg. Phase II data indicated that dose significantly inhibited and reversed corneal neovascularization.

Should aganirsen reach the market, the company envisages treating candidates for corneal transplant for three months before they undergo the procedure. High-risk patients would receive another three months of therapy after completing the transplant. Peak sales in Europe could top €200 million in that indication, Viaud said.

Next up is a Phase II/III trial of aganirsen in more than 300 patients with neovascular glaucoma. That trial will employ an emulsion formulation of the drug, which allows it to penetrate further into the eye. It has conducted wide-ranging pharmacokinetic studies in numerous animal models, which have examined the relationship between viscosity of the emulsion and the efficiency of drug delivery. "We are able to clearly identify the pathway of the product into the different compartments of the eye," Viaud said. Gene Signal also will use emulsified forms of the drug for Phase II trials of back-of-the-eye conditions, such as AMD and diabetic retinopathy.

Although VEGF inhibitors, such as Lucentis (ranibizumab, Genentech), off-label Avastin (bevacizumab, Genentech) and Eylea (aflibercept, Regeneron Pharmaceuticals Inc.), currently hold sway in AMD, Princeton, N.J.-based Ophthotech Corp. reported last year that a combination of its anti-PDGF aptamer Fovista (E10030) and Lucentis was superior to Lucentis alone. Viaud said a combination of aganirsen and a VEGF inhibitor also should have additive effects, but the company has no immediate plans to test that idea in a trial. Its main competitive differentiator against its competitors would be its topical delivery method. (SeeBioWorld Today, June 14, 2012.)

It does plan to conduct a Phase II trial of aganirsen in psoriasis. A pilot study is already under way. The company also plans to move into the clinic several preclinical programs involving peptides, small proteins and antibodies, which are in development for wound healing and cancer indications.