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FOR IMMEDIATE RELEASE

Gene Signal announces positive data from Phase III trial of aganirsen eye drops for corneal neovascularisation due to inflammation, a rare eye disease with European Orphan Drug designation.

The journal *Ophthalmology* publishes results of the I-CAN study, the first randomised trial of a topical inhibitor of corneal angiogenesis:

- **Topical applications of aganirsen are safe and well-tolerated**
- **Significantly reduces the relative area of corneal neovascularisation**
- **Significantly reduces need for corneal transplantation in identified patient group**

Lausanne, Switzerland, May 12th 2014 – Gene Signal, a biotechnology company focused on developing innovative drugs to manage angiogenesis-based medical conditions, and the Department of Ophthalmology, University of Cologne Medical Centre, Germany, today announced that positive data from the I-CAN study of aganirsen eye drops (GS-101) was published in Ophthalmology, the Journal of the American Academy of Ophthalmology[1]

The European Phase III study of sixty nine (69) patients was designed to test the efficacy and safety of aganirsen, a first-in-class eye drop therapy, on patients who suffer from abnormal blood vessel growth in the front of the eye (corneal neovascularisation or CNV) due to inflammation (keratitis). In order to prevent blindness, these patients may need to have the diseased cornea replaced with a new cornea, known as a graft. There are long waiting lists for this operation, and untreated CNV can lead to an increased rate of graft failure and rejection. Currently, there are no approved therapies for this indication, for which aganirsen has an Orphan Drug Designation in Europe.

The company has been working hand-in-hand with regulators and key opinion leaders over several years as the understanding and clinical best practice for this condition has developed. The next step for the company is to discuss the results of the I-CAN study with the regulatory authorities to design a short confirmatory and pivotal study.

Eric Viaud, CEO and Co-Founder of Gene Signal, commented: “We are very encouraged by these results which demonstrate that aganirsen reduces corneal vascularisation and that it is safe. The data strongly support our experience since 2010 of using aganirsen in named patient sales in four European countries, where the clinical benefit has been accepted. We are confident that these results will enable us to agree with the regulatory authorities a short

confirmatory and pivotal study. Our goal is to move quickly to bring a much-needed therapy to the estimated 20,500 corneal neovascularisation graft patients across Europe. Aganirsen is set to become a break-through topical therapy for a range of ophthalmic diseases."

Professor Claus Cursiefen, MD, Principal Investigator of the I-CAN Study and Head of Department of Ophthalmology, University of Cologne Medical Centre, Germany, said: "Overall, the I-CAN study results demonstrate that aganirsen has important clinical benefits as a novel topical therapy for patients who are awaiting corneal transplants. There is a real unmet patient need, as current therapies do not target neovascularisation, and the longer patients go untreated, the greater the risk of graft failure or rejection."

"The fact that the need for corneal transplantation was significantly reduced in patients with viral keratitis and central neovascularisation, and that topical application of aganirsen was safe and well-tolerated, encourage us to continue clinical development of this therapy," he added.

Encouraging Efficacy Results

Visual Acuity (VA) has been traditionally used as an efficacy measure for back of the eye diseases such as age-related macular degeneration (AMD) and diabetic retinopathy (DR). The regulatory authorities recommended the I-CAN study to be the first randomised clinical trial in the front of eye disease CV to use VA as a primary endpoint. The results based on the whole patient population included in the study showed no statistical difference in VA scores between aganirsen and placebo patient groups. This confirmed a systematic review of a weak link between CNV and VA (Bachmann et al 2013)[2].

However the I-CAN study demonstrated a number of other efficacy results with positive data for topical aganirsen:

- Significantly reduced by 26.2% (p=0.014) the relative area of corneal neovascularisation after 90 days and this improvement persisted after 180 days (reduction of 26.6%, p=0.012)
- Tended to lower the need for cornea transplantation at day 180 (p=0.087) in the intent to treat (ITT) population
- However, in those patients with viral keratitis (inflammation) and central neovascularisation, it significantly reduced the need for cornea transplantation at both day 90 (p=0.014) and at day 180 (p=0.012)
- In those patients with traumatic/viral keratitis (inflammation), it tended to lower the risk of graft rejection at day 90 (p=0.162)
- In terms of Quality of Life, there were significant improvements in composite and near activity sub scores (p=0.039 and 0.026 respectively) at day 90 in the per protocol aganirsen population.

Excellent Safety & Compliance Results

The I-CAN study reiterated the excellent safety and tolerability profile of aganirsen, which has now been used in over 220 patients in clinical trials and for compassionate use:

- Similar numbers of treatment-emergent adverse events (TEAEs) were observed in both aganirsen and placebo patient groups

- Ocular TEAEs were lower in aganirsen patients (11.1%) compared to placebo patients (18.4%)
- Most TEAEs were of mild or moderate severity and there was no evidence of increased incidence of severe TEAEs in either patient group
- Patient compliance was 95% for aganirsen patients, a remarkable result for such a painful ophthalmologic condition.

About the I-CAN Study

I-CAN is the first randomised trial of a topical inhibitor of corneal angiogenesis**.** It was a European multicentre, double-masked, randomised placebo-controlled Phase III study. Sixty nine (69) patients with keratitis-related progressive corneal neovascularisation (CNV) were randomised to receive aganirsen (34) or placebo (35).

Patients applied aganirsen eye drops (GS-101) with one drop twice a day of a 86 mg/ml solution or placebo, for 90 days treatment with a follow up at 180 days. **Aganirsen was administered on top of current standard of care (e.g. corticoids, antiviral and immunosuppressant therapies).**

The I-CAN study results have been published online in *Ophthalmology*, the Journal of the American Academy of Ophthalmology (http://www.aaojournal.org/article/S0161-6420(14)00315-7/abstract)

About Corneal Neovascularisation in Graft Patients

Corneal transplantation, or replacement of a patient's damaged cornea with that of a donor cornea (graft), has a relatively high success rate. This is attributable to the privileged "immune status" of the cornea, which reduces rejection episodes common in other organ transplant situations. However, when sickly and leaky blood vessels invade the cornea – a condition known as pathologic corneal neovascularisation (CNV) - the situation changes, and the risk of graft rejection is again much higher. This is because the unwanted pathological vessels reduce the cornea's privileged immune status. In fact, a recent meta-analysis confirmed the association between presence of pathological corneal neovessels and increased risk of graft rejection. Consequently, and because of the long graft waiting lists that patients are faced with both in Europe and in the USA, it is desirable to apply a therapy such as aganirsen to reduce corneal neovascularisation and hence the risk of graft rejection. In Europe alone, there are an estimated 20,500 patients suffering from CNV.

About Aganirsen Antisense Oligonucleotide

Gene Signals' compound, aganirsen (GS-101), is a novel compound which is applied topically, i.e. in eye-drop formulation for front of the eye diseases and in eye-emulsion formulation for back of the eye diseases such as neovascular glaucoma. It has the ability to inhibit unwanted angiogenesis.

Early signs are that aganirsen, an antisense DNA oligonucleotide,[3] is topically effective. Formulated as a small complementary DNA fragment, aganirsen emulsion has demonstrated its ability to effectively inhibit neovascularisation in the cornea and to reach and act on the retina[4], when other drugs have to be injected.

Aganirsen inhibits the insulin receptor substrate 1 (IRS-1) which is over-expressed in pathological angiogenesis,[5] and it has been demonstrated to target pathological vessels without inhibiting normal vessel growth.[6] Thanks to its entirely novel mechanism of action,

this could potentially make aganirsen a topical and safe alternative to anti-VEGF intra-vitreal injections depending on the indication.

Additionally, antisense oligonucleotides confer distinctive advantages versus other biologics: they can be readily diffused across cell membranes, are associated with low immunogenicity, and can be produced by simple chemical synthesis, unlike larger proteins and monoclonal antibodies that require cell culture and complex purification steps.

About Gene Signal www.genesignal.com

Gene Signal is a Swiss-based biotechnology company pioneering the development of innovative therapies for angiogenesis-based diseases. Its product candidates are a new class of oligonucleotides, proteins and monoclonal antibodies which are derived from genes that are exclusively involved in the angiogenesis process. At least four official candidates are in development for eleven indications in ophthalmology, dermatology, vascular disorders and cancer.

The company's lead compound, aganirsen (GS-101), an antisense DNA oligonucleotide, completed in 2013 the European I-CAN Phase III trial for the treatment of corneal neovascularisation due to inflammation. The I-CAN study was published in 2014 and the company is planning a short confirmatory pivotal trial to lead to market authorisation. Aganirsen is the beneficiary of an EU grant for the Phase II STRONG trial for the treatment of ischemic central retinal vein occlusion (iCRVO). The compound is also being prepared for Phase II proof of concept (PoC) trials in age-related macular degeneration (AMD) and diabetic macular oedema (DME). Following a successful PoC study published in 2014, a larger Phase II trial is planned in Psoriasis.

Gene Signal's discovery program leverages a patented discovery platform, GENE-MAAP, which streamlines the identification process of genes exclusively involved in the regulation of angiogenesis, resulting in the identification and patenting of more than 94 such genes.

The company was founded in 2000, is privately owned, and is led by a team of highly qualified scientific and commercial talents. Its headquarters are in Lausanne (EPFL Swiss Federal Institute of Technology), Switzerland, with research programs based in France (Bioparc Genopole, Evry) and product development in Canada (Montreal).

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1 Cursiefen C. et al “Aganirsen antisense oligonucleotide eye drops inhibit keratitis-induced corneal neovascularization and reduce need for transplantation: the I-CAN study” Ophthalmology, e-pub 08 May 2014, http://www.aaojournal.org/article/S0161-6420(14)00315-7/fulltext

2 Bachmann B, Taylor RS, Cursiefen C. The association between corneal neovascularization and visual acuity: a systematic review. Acta Ophthalmol February 2013;91:12-9.

3 An antisense Oligonucleotide is a short strand of DNA designed to prevent translation of messenger RNA into an unwanted protein

4Cloutier F, Lawrence M. et al “Anti-angiogenic activity of Aganirsen in non-human primate and rodent models of retinal neovascular disease following topical administration” Invest. Ophthalmol. Vis. Sci. (IOVS) February 9, 2012 iovs.11-9064

5Al Mahmood S et al “Potent in vivo antiangiogenic effects of GS-101 (5'-TATCCGGAGGGCTCGCCATGCTGCT-3'), an antisense oligonucleotide preventing the expression of insulin receptor substrate-1”, J. Pharmacol Exp Ther. (JPET) 2009 May;329(2):496-504.

6Cloutier F. IOVS 2012