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FOR IMMEDIATE RELEASE

Gene Signal announces publication of positive results from Phase IIa study of topical aganirsen in psoriasis.

- **First topical therapy for psoriasis with dual anti-angiogenic and anti-inflammatory properties**
- **Significantly reduces inflammation and psoriatic lesion areas**
- **First study to demonstrate benefits of down-regulating IRS-1 in psoriasis**
- **Excellent safety profile**
- **Phase IIa results justify further large-scale clinical studies**

Lausanne, Switzerland, April 10th 2014 – Gene Signal, a company focused on developing innovative drugs to manage angiogenesis based conditions, today announced positive results from a Phase IIa study in psoriasis which demonstrated that topical application of aganirsen (GS-101), an antisense oligonucleotide, reduced the size of psoriatic lesions and inflammation compared to placebo. Psoriasis is a common chronic skin disease occurring in approximately one to three percent of general populations; there is no known cure. The results were published in *The Journal of Pharmacology and Experimental Therapeutics*[i].

Eric Viaud, CEO and Co-Founder of Gene Signal, commented: "We are very pleased by these results which strongly suggest that aganirsen is a dual anti-angiogenic and anti-inflammatory agent that could represent an innovative, safe and effective topical therapy for psoriasis. These results merit further large-scale clinical trials for psoriasis, and also add to the body of evidence that aganirsen is a first-in-class therapy with great potential for a range of angiogenesis-based diseases including ophthalmology and dermatology."

Significant efficacy results and first study to demonstrate IRS-1 as valid target

Topical application of both doses of 0.86 mg/g or 1.72 mg/g aganirsen once per day for 6 weeks led to a significant reduction of -14.4% and -12.9% respectively ($p<0.05$) in the area of the treated psoriatic lesions compared to placebo. By contrast an increase in the lesion area (+24.5%) was observed in placebo-treated patients. Least square mean differences with placebo were -38.9% and -37.4% for the low and high doses of aganirsen, respectively. A significant treatment effect with aganirsen was also observed as early as 3 weeks.

It was particularly interesting to note that aganirsen had the power as a topical therapy to normalize expression levels of the major inflammatory factors involved in psoriasis. Most importantly, this study is the first to demonstrate the therapeutic benefit in psoriasis of down-regulating the expression of insulin receptor substrate-1 (IRS-1).

The results unveil IRS-1 as a new and original target which underlies the chronic multifactor inflammation as well as the aberrant angiogenesis. Aganirsen also inhibited the over-expression of vascular endothelial growth factor (VEGF) and consequently the aberrant angiogenesis. The topical application of aganirsen on psoriatic lesions was shown to inhibit tumor necrosis factor alpha (TNFα), which is elevated in psoriasis as part of the human immune response system, and to restore normal levels of CD4+ and CD3+ lymphocytes in psoriatic skin.

About the clinical trial

The randomized, double blind, placebo-controlled six-week exploratory Phase IIa study involved 36 lesions in 12 patients. Each patient with three identified plaque psoriasis (at least two in refractory sites) received topical applications of 0.86 mg/g and 1.72 mg/g of aganirsen or placebo once per day over six weeks. The two doses of aganirsen and placebo were administered consistently to the same psoriasis plaques throughout the treatment period.

Aganirsen's safety was excellent, without any reported adverse events. Patients reported no irritation, burning or exudation.

The study did not reveal a dose-dependent effect. Results suggest that the two doses tested induced a maximal effect within the current protocol; lower daily doses of aganirsen combined with a longer period of treatment will have to be tested in further clinical studies.

The results were recently published in *The Journal of Pharmacology and Experimental Therapeutics* (J Pharmacol Exp Ther 2014;349:107-117) in a paper entitled 'The Antiangiogenic Insulin Receptor Substrate-1 Antisense Oligonucleotide Aganirsen Impairs AU-Rich mRNA Stability by Reducing 14-3-3β-Tristetraprolin Protein Complex, Reducing Inflammation and Psoriatic Lesion Size in Patients'. http://dx.doi.org/10.1124/jpet.113.209346)

About psoriasis

Psoriasis is a chronic inflammatory skin condition ranging from mild to severe and occurring at any age occurring in one to three percent of the general population. It is caused partly when an overactive immune system mistakes a normal skin cell for a pathogen triggering an overproduction of new skin cells. These new skin cells grow ten times faster than normal skin cells and rather than exfoliate the cells amass forming red, raised patches of skin, or plaques. Psoriasis is often mistaken for other skin disorders such as eczema or dermatitis; it is not contagious and cannot be spread by contact. To date there is no known cure and because of its chronic recurrent nature it is difficult to treat.

Psoriasis skin presents many vascular abnormalities, such as enlarged, hyperpermeable and tortuous vessels that are commonly found in the diseased skin. Angiogenesis plays an important role in psoriasis as immunostaining demonstrates a significant increased development of the microvasculature in comparison with healthy skin (Simonetti 2006ii, Rosenberg 2007iii). Vascular endothelial growth factor (VEGF), known to play a central role in angiogenesis, is also up-regulated in psoriasis (Canavese 2011[iv]).

Conventional systemic therapies for psoriasis, such as methotrexate, cyclosporine A, retinoids or psoralen and ultraviolet A (PUVA) therapies can result in long-term toxicity and may not be effective.

About aganirsen antisense oligonucleotide

Gene Signal's compound, aganirsen (GS-101), is a novel topical compound which has the ability to inhibit unwanted angiogenesis.

An antisense DNA oligonucleotide,[v] aganirsen inhibits Insulin Receptor Substrate 1 (IRS-1) which is over-expressed in pathological angiogenesis.[vi]IRS-1 is a high angiogenic-specific target and in particular for angiogenesis-related pathologies. Aganirsen, by preventing the expression of IRS-1 in pro-angiogenic conditions, prevents the angiogenic process. This has been demonstrated both *in vitro* and *in vivo* (Al-Mahmood 2009[vii]vii, Jiang 2003[viii]viii Araki 1994i[ix]) and in humans in the cornea of the eye.

Additionally, antisense oligonucleotides confer distinctive advantages versus other biologics: they can be readily transported 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. Four 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 a European Phase III trial for the treatment of neovascular-associated corneal graft rejection. Aganirsen is the beneficiary of an EU grant for the Phase II STRONG trial for the orphan indication neovascular glaucoma. The compound is also being prepared for Phase II trials in age-related macular degeneration, diabetic macular oedema, and 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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[v]An antisense Oligonucleotide is a short strand of DNA designed to prevent translation of messenger RNA into an unwanted protein

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