

## Isarna Presents Positive Preclinical Results Supporting Development of ISTH0036 for the Treatment of Glaucoma

-- Oral and Poster Presentations Given at ARVO 2015 Annual Conference --

**Munich, Germany, May 11, 2015** – Isarna Therapeutics, the leader in transforming growth factor beta (TGF- $\beta$ ) isoform targeted antisense therapeutics, today announced the presentation of preclinical data for its lead candidate ISTH0036, a locked nucleic acid-modified antisense oligonucleotide, currently in phase I development for the treatment of advanced-stage glaucoma. Isarna presented supporting preclinical results in one podium presentation and two poster publications at the Annual Meeting of the Association for Research in Vision and Ophthalmology (ARVO) held May 3-7 in Denver, Colorado.

As described in the podium presentation, ISTH0036 was administered to evaluate its therapeutic potential in murine models of glaucoma filtration surgery (GFS) and laser-induced choroidal neovascularization (CNV). In the murine GFS model, upon intraocular administration, ISTH0036 was able to significantly prolong bleb survival, as compared to control oligonucleotide- and saline-treated eyes. In addition, ISTH0036 was able to significantly decrease the extent of fibrosis in the bleb area in a sequence-specific manner.

Furthermore, in a murine CNV model, intravitreal administration of ISTH0036 was able to significantly reduce (40%) the process of angiogenesis, as compared to saline- and control oligonucleotide-treated eyes. This observation may open up development opportunities beyond glaucoma.

Also presented at the conference, two posters described the overall preclinical profile and the testing of ISTH0036 in which it successfully demonstrated excellent cellular uptake, potent TGF- $\beta$ 2 mRNA downregulation (target engagement) in cell-based assays and in relevant tissues of the eye. Long-lasting tissue distribution was consistent with the observed target engagement.

“We have clearly demonstrated in these animal models that intraocular administration of ISTH0036 leads to biological responses consistent with the expected molecular mechanism of action and with observed efficient and long-lasting distribution in relevant eye tissues,” said Dr. Michel Janicot, Head of Preclinical Research and Development at Isarna. “These preclinical data support the compound’s potential to protect glaucoma patients’ vision and we hope to reproduce these results in our ongoing clinical evaluation of the compound. In addition, based on these data we see several other high medical need diseases that could potentially benefit from TGF- $\beta$ -targeted treatment.”

Several diseases in ophthalmology have been linked to the modulation of TGF- $\beta$ , among them are glaucoma, proliferative vitreoretinopathy, diabetic retinopathy and corneal diseases. TGF- $\beta$ 2 has specifically been identified as having a critical role in the pathophysiology of glaucoma affecting changes in the ocular outflow region that can lead to open-angle glaucoma and has been linked in addition to having a direct, toxic effect on the optic nerve head.

### About Glaucoma

Glaucoma is the leading cause for irreversible blindness worldwide. The disease has been linked to elevated intraocular pressure, due to decreased fluid outflow (aqueous humor) from the eye, based upon alteration of the trabecular meshwork. Recent scientific data indicate that glaucoma progression is associated with elevated levels of TGF- $\beta$ 2 resulting in alteration of the trabecular meshwork (Prendes et al. 2013; Br J Ophthalmol.) and a potential direct toxic effect on the optic nerve (Fuchshofer 2011; Exp Eye Res.). Approximately 10% of glaucoma patients lose vision despite optimum treatment. More information on glaucoma can be found at [www.glaucoma.org](http://www.glaucoma.org), a website of the Glaucoma Research Foundation.

### About ISTH0036

ISTH0036 is a locked nucleic acid-modified antisense oligonucleotide selectively targeting the messenger ribonucleic acid (mRNA) of TGF- $\beta$ 2. TGF- $\beta$  (transforming growth factor beta) plays an

important role in key pathways such as cell proliferation, cell differentiation, immune response and tissue modeling. Because TGF- $\beta$  is chronically elevated in many diseases, including ophthalmic and fibrotic diseases and cancer, and involved in their pathophysiology, it is an extremely versatile drug target throughout the body. Preclinical studies have demonstrated that ISTH0036 is highly potent and shows selective target engagement (TGF- $\beta$ 2 mRNA and protein downregulation) and long-lasting tissue uptake and pharmacodynamic effects.

### **About Isarna Therapeutics**

Isarna Therapeutics has an unmatched commitment to developing selective TGF- $\beta$  inhibitors to fight cancer and to effectively treat ophthalmic and fibrotic diseases. We are advancing a unique pipeline of novel oligonucleotides and combination modalities to transcend clinical response and improve patient outcomes. Isarna is established in the Netherlands, Germany, and the United States. [www.isarna-therapeutics.com](http://www.isarna-therapeutics.com).

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