Isarna Therapeutics
www.isarna-therapeutics.com

Looking beyond the standard of care for eye diseases

Isarna Therapeutics' antisense therapy targeting transforming growth factor beta 2, ISTH0036, is about to enter phase 2 clinical development for two retinal diseases: wet age-related macular degeneration and diabetic macular edema.

Age-related macular degeneration (AMD) and diabetic macular edema (DME) are leading causes of blindness in the developed world[1]. Both diseases involve the leakage of fluid from abnormal or damaged small blood vessels into part of the retina called the macula, leading to blurred and impaired vision. In the case of wet AMD, vision loss can occur quite suddenly, whereas in DME, a complication of diabetic retinopathy, it can progress over months.

Intravitreal (IVT) injections every 4–8 weeks of vascular endothelial growth factor (VEGF)-A inhibitors have revolutionized the treatment of these conditions, by preventing further vision loss in a subset of patients[2]. However, long-term vision improvement is rare, and studies have shown that up to 61% of patients with AMD develop macular fibrosis after seven years of continuous treatment with anti-VEGF[3,4]. "Current drugs are doing a good job of controlling early disease, but they aren't preventing damaged cells from scarring and irreversible loss of vision," said René Rückert, Chief Operating Officer at Isarna Therapeutics.

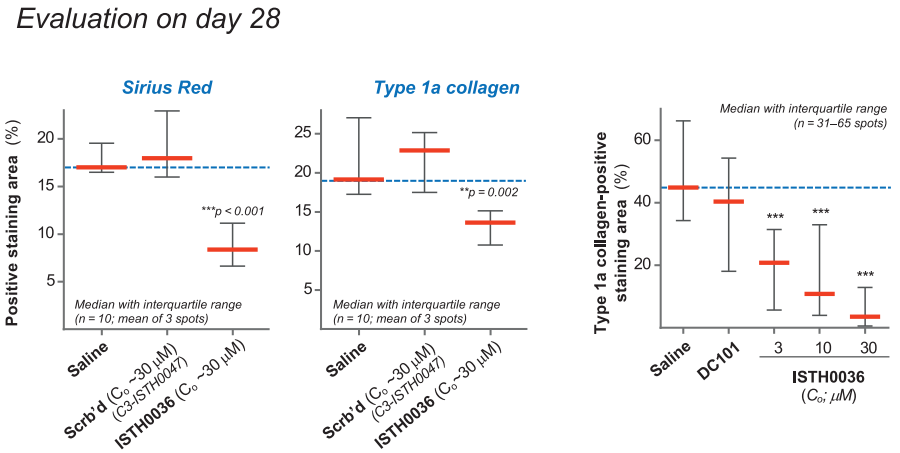

Fig. 1 | ISTH0036 significantly inhibits fibrosis in a murine CNV model. Intravitreal administration of ISTH0036 (C_o ~3–30 µM) statistically significantly inhibits fibrosis in a sequence-dependent and dose-dependent manner. By contrast, the model reference by blocking VEGF signaling (using DC101, a VEGFR2 antibody) does not show any significant effect on fibrosis.

Lead candidate targeting TGF-β

Isarna Therapeutics is focused on developing a pipeline of next-generation oligonucleotides that target the various isoforms of transforming growth factor beta (TGF-β), a family of proteins implicated in fibrosis and cancer. Its lead compound, ISTH0036, selectively targets the messenger RNA (mRNA) of human TGF-β2, which has a critical role in the regulation of cells in ocular tissues. TGF-β2 can stimulate angiogenesis by upregulating VEGF-secretion from retinal pigment epithelial (RPE) and endothelial cells[5]. Furthermore, it can drive epithelial-to-mesenchymal transformation of RPE cells and other retinal components, which leads to photoreceptor degeneration and fibrosis.

ISTH0036 has been shown to downregulate TGF-β2 mRNA and protein in a dose-dependent manner in both cell-based assays and key ocular tissues in vivo. Following IVT administration in animals, ISTH0036 downregulated TGF-β2 in the retina for up to four months. It demonstrated similar anti-angiogenic activity compared to the gold-standard anti-VEGF therapy, Zaltrap (aflibercept). Importantly, it also had anti-fibrotic effects after glaucoma filtration surgery and laser-induced choroidal neovascularization (CNV), a well-established method for assessing therapies for wet AMD and macular fibrosis in animals.

The first-in-human, single-dose phase 1 study in patients undergoing glaucoma filtration surgery, confirmed that ISTH0036 is safe and well tolerated. The results warrant a phase 2 study that is expected to start enrolling pre-treated and treatment naïve patients with wet AMD or DME in July 2021. "The favorable pharmacokinetic and pharmacodynamic properties of ISTH0036 support prolonged treatment with potentially fewer IVT administrations than current VEGF inhibitors," Rückert explained.

The compound's anti-fibrotic effects may not just stop the development of fibrosis (Fig. 1), but could also reverse its progression, as TGF-β signalling has been shown to disrupt the wound response[6] and cause senescence-associated changes in RPE cells as seen in early AMD[7]. Thus, ISTH0036 could prevent the transition from early to advanced AMD that is associated with increased levels of TGF-β2 and the onset of a dysregulated RPE wound response.

"Although TGF-β has been identified as a drug target in the 80s, few therapies that target the cytokine directly have reached the clinic," said Marion R. Munk, Chief Medical Officer at Isarna Therapeutics. "By selectively intracellularly blocking the production of TGF-β2 in the retina using targeted antisense, rather than inhibiting a pathogenic factor once it has already been produced and released as its current standard of care, our antisense therapy could become a first and best in class treatment option for patients with wet AMD and/or DME," she added.

Future outlook and partnering

ISTH0036 may offer a true alternative to current standard of care treatments for two blockbuster indications. The global retinal disorder treatment market size was valued at $11.4 billion in 2020 and is expected to grow by 6.4% until 2028 as the incidence of these conditions is increasing. Isarna Therapeutics has been granted a composition of matter patent protecting ISTH0036 until at least 2034.

Given the role of TGF-β in fibrosis in other organs and cancer, the company is also carrying out preclinical work exploring the potential of ISTH0036 and antisense oligonucleotides against other TGF variants (TGF-β1 and TGF-β3) for the treatment of lung, kidney and liver fibrosis as well as various cancers.

Isarna Therapeutics' team of retina experts, and its lead investor, MIG Verwaltungs AG, are open for financing and partnering discussions aimed at driving their promising antisense oligonucleotide platform forward.

1. Taylor, H. R. et al. *Brit. J. Ophthalmol.* **85**, 261–266 (2001).
2. Emerson, M. V. et al. *BioDrugs* **21**, 245–257 (2007).
3. Daniel, E. et al. *Ophthalmology* **121**, 656–666 (2014).
4. Rofagha, S. et al. *Ophthalmology* **120**, 2292–2299 (2013).
5. Bian, Z.-M. et al. *Exp. Eye Res.* **84**, 812–822 (2007).
6. Radeke, M. J. et al. *Genome Med.* **7**, 58 (2015).
7. Yu, A. L. et al. *Invest. Ophth. Vis. Sci.* **50**, 926–935 (2009).

CONTACT
René Rückert, Chief Operating Officer
Isarna Therapeutics
Munich, Germany
Tel: +49 171 20 80 410
Email: r.ruckert@isarna-therapeutics.com