Evaluation of Novel Antisense Oligonucleotides Targeting Transforming Growth Factor beta (TGF-β) Isoforms for the Treatment of Ocular Diseases

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Transforming growth factor beta (TGF-β) represents a family of cytokines, which function as primary mediators for TGF-β signaling involved in a wide range of biological processes in human diseases, and in particular oncology, fibrosis and ocular diseases. Several different ocular diseases have been associated with TGF-β, including glaucoma, proliferative vitreoretinopathy (PVR), posterior capsule opacification (PCO: secondary cataract) and corneal diseases. Isarna Therapeutics has designed and developed highly potent and selective LNA-modified antisense oligonucleotide (ASO) gapmers targeting the various TGF-β isoforms, which have shown marked downregulation of target mRNAs in cell-based assays and tissues in vivo. In order to characterize the potential use of these ASOs in ocular diseases, we have initially conducted studies to evaluate the pharmacokinetic properties of the selected ASOs after intravitreal injection in the rabbit eye. In addition, we have analyzed the biodistribution and pharmacodynamic features of our compounds in aqueous humor, vitreous humor, lens, cornea, ciliary body & iris, choroid & retina, optic nerve, sclera tissue samples.

**ASP6_0036** represents an LNA-modified antisense oligodeoxynucleotide targeting the human TGF-β2 mRNA

ASP6_0036 is an oligodeoxynucleotide molecule consisting of 14 nucleotides linked by phosphorothioate bonds, and locked nucleic acids in the first (5’-end) and last (3’-end) 3 nucleotide positions.

Pharmacokinetic study in Balb/c mice following single intravenous administration of ASP6_0036 at 20 mg/kg animal body weight

Various major ocular diseases with high medical need do exist that appear to be TGF-β pathway driven or dependent and could benefit greatly from effective treatment with TGF-β specific ASO, providing attractive development opportunities within the ophthalmic disease landscape.

The link between TGF-β and glaucoma, glaucoma filtration surgery, proliferative vitreoretinopathy and posterior capsule opacification is scientifically well substantiated.

Glucoma is a progressive optic neuropathy characterized by gradually increasing loss of retinal ganglion cells, which manifests clinically with loss of optic disc and neuronal rim tissue, defects in the retinal nerve fiber layer, and deficits on functional visual field testing. Glaucoma is considered to be caused mainly by a chronic increase intraocular pressure.

Conclusions:
1. The highest concentration of ASP6_0036 was measured in ciliary body & iris, followed by choroid & retina and optic nerve.
2. The highest concentrations of ASP6_0036 were detected 24 h after oligonucleotide administration.
3. Multiple intravitreal administrations lead to accumulation of the ASO in choroid & retina, ciliary body & iris, cornea and vitreous humor.
4. Long-lasting downregulation of target mRNA expression was observed in choroid & retina, lens and optic nerve after ASP6_0036 treatment when compared to vehicle-treated animals. Multiple injections increase the downregulation compared to untreated animals.

ASP6_0036 is a powerful candidate for the evaluation in various ocular diseases!