PHARMACOKINETICS AND ANTI-ANGIOGENIC EFFICACY OF A TOPICALLY ADMINISTERED ANTISENSE OLIGONUCLEOTIDE TARGETING INSULIN RECEPTOR SUBSTRATE-1

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Aganirsen is an antisense oligonucleotide that inhibits insulin receptor substrate-1 (IRS-1) expression and promotes regression of pathological corneal neovascularization. In this study, we examined the ocular pharmacokinetics and anti-angiogenic activity of Aganirsen following topical administration.

Iris/ciliary body and retina were isolated 15-120 min after applying Aganirsen (86 μg) to corneas of adult male New Zealand albino rabbits. Retinal exposure was also evaluated in African green monkeys (AGM) following topical delivery (21.5, 43 and 86 μg). Efficacy was evaluated by fluorescein angiography and optical coherence tomography in an AGM laser-induced choroidal neovascularization (CNV) model following repeat daily topical dosing (from 2 days prior to 14 days post-laser photocoagulation).

Peak Aganirsen levels in rabbit iris/ciliary body and retina were observed 90 min after dosing with an estimated 0.83 % retinal penetration of active compound. In monkeys, significant dose-dependent increases in retinal penetration of Aganirsen were observed 90 min and 8 hours ($p<0.05$; 21.5 vs. 86 μg) after dosing. Retinal IRS-1 protein levels were significantly lower in eyes receiving 43 or 86 μg doses than with those receiving a 21.5 μg dose ($p<0.05$).

In the CNV model, Aganirsen significantly and dose-dependently attenuated development of grade IV neovascular lesions ($p<0.05$; vehicle vs. 86 μg Aganirsen) and CNV complex formation ($p<0.001$; vehicle vs. 86 μg).

Pharmacokinetics studies demonstrated retinal penetration of Aganirsen at therapeutically relevant doses following topical dosing. Proposed kinetics of Aganirsen following topical delivery will be further discussed. Anti-angiogenic efficacy in the retina was confirmed following topical delivery. This work strongly supports clinical phase II testing of Aganirsen for human retinal neovascular diseases.