TITLE: OCULAR PHARMACOKINETICS AND ANTI-ANGIOGENIC EFFICACY OF AN ANTISENSE OLIGONUCLEOTIDE TARGETING INSULIN RECEPTOR SUBSTRATE-1

ROBIN GOODY, PHD [1], FRANK CLOUTIER, PHD[2], MATTHEW LAWRENCE, MD[1], STÉPHANIE LAMOUREUX, MSC[2], SALMAN AL-MAHMOOD, PHD[4], SYLVIE COLIN, PHD[4], ANTOINE FERRY, MD[4], JEAN-PASCAL CONDUZORGUES, DPHARM[5], AMEL HADRI, MSC[5], CLAUS CURSIEFEN, MD[6], PATRICIA UDAONDO, MD[7], ERIC VIAUD, MSC[4], ERIC THORIN, PHD[3,4], SYLVAIN CHEMTOB, MD, PHD[2].

[1] RxGen Inc., 100 Deepwood Drive, Hamden, CT 06517, USA, [2] Université de Montréal, Department of Pediatrics, Ophthalmology, Pharmacology, hôpital Ste-Justine, 3175, Chemin de la Côte-Sainte-Catherine Montreal H3T 1C5 Quebec, Canada, and [2] Université de Montréal, Department of Surgery, Montreal Heart Institute, 5000, Belanger Street, Montreal, H1T 1C8, Quebec, Canada, [4] Gene Signal Laboratories, Genopole Industries, 4 Rue Pierre Fontaine, 91000 Evry, France, [5] CRID Pharma, 17 Parc des Vautes, 34980 Saint Gély du Fesc, France, [6] Dept. of Ophthalmology, University of Cologne, Joseph-Stelzmann-Strasse 9D-50924 Köln, Germany and [7] Universidad Cardenal Herrera Oria, CEU, Nuevo Hospital Universitario y Politécnico La Fe, Bulevar Sur s/n, 46026 Valencia, Spain.

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

Iris/ciliary body and retina were isolated 15-120 minutes following administration of Aganirsen (86 μg) to corneas of adult male New Zealand albino rabbits. Retinal penetration was also evaluated in African green monkeys following topical administration (21.5, 43 and 86 μg). Efficacy was evaluated in a validated African green monkey laser-induced CNV model following repeat daily topical administration to eyes (16 days, beginning 2 days prior and continuing 14 days post-laser photocoagulation).

Aganirsen levels peaked in iris/ciliary body and retina 90 minutes after administration with retinal penetration estimated at 0.83% of active compound in rabbits. In monkeys, significant dose-dependent increases in retinal penetration were observed 90 minutes ($p<0.0001$; 21.5 μg vs. 86 μg) and 8 hours ($p=0.009$; 21.5 μg vs. 86 μg) after dosing between eyes receiving 21.5, 43 or 86 μg of Aganirsen. Significantly lower retinal IRS-1 protein levels were observed in eyes receiving 43 ($p=0.0039$) and 86 μg ($p=0.031$) doses compared with those receiving the 21.5 μg dose.

In the CNV model, Aganirsen significantly and dose-dependently attenuated laser-induced neovascular leakage ($p<0.05$; vehicle vs. 86 μg Aganirsen for incidence of grade IV lesions) and CNV complex formation ($p<0.001$; vehicle vs. 86 μg), determined by fluorescein angiography and optical coherence tomography respectively.

Pharmacokinetics studies demonstrated retinal penetration of Aganirsen at therapeutically relevant doses following topical dosing. Putative mechanisms of ocular kinetics of

Aganirsen following topical delivery will be further discussed. Anti-angiogenic efficacy was confirmed in the retina following topical delivery. This work strongly supports phase II testing of Aganirsen for human retinal neovascular diseases.