Objectives
To evaluate the ocular pharmacokinetics and anti-angiogenic efficacy of aganirsen, an antisense oligonucleotide that inhibits insulin receptor substrate-1 (IRS-1) expression, in African green monkeys following topical delivery.

Background
Aganirsen is an inhibitor of IRS-1 previously shown to dose-dependently inhibit corneal angiogenesis in animals and humans. Prior studies have confirmed aganirsen eyedrops are safe for human use and penetrate the posterior chamber of the eye in rabbits following topical delivery. A key role for IRS-1 in retinal angiogenesis has been confirmed. Together, these findings suggest aganirsen may be an effective treatment for retinal neovascular diseases via topical delivery.

Detailed Methods
All work was conducted in accordance with the ARVO Statement for the Use of Animals in Ophthalmic and Vision Research.

Ocular Pharmacokinetics
Adult New Zealand albino rabbits (n=60) received a topical application of 50 µL of ophthalmic emulsion, composed of carboxer, caprylc/acpc acid triglycerides, cetyl alcohol, glycerol, and polyethylene glycol stearates, sodium hydroxide, and water) containing aganirsen (1.72 mg/mL), giving a local delivery of 68 µg of active compound to each eye. Rabbits were euthanized 15-120 minutes after dosing, eyes enucleated and snap frozen and ocular tissues sub-dissected and homogenized for analysis by ion-exchange chromatoigraphy.

Twelve adult African green monkeys (Chlorocebus sabaeus) were recruited to this study. Each monkey received 16 twice daily topical doses of aganirsen (54 µL) of 21.5, 43 or 86 µg. Animals were euthanized, eyes enucleated, flash frozen and analyzed as above. Significant quantities of aganirsen are achieved in the retina. Studies are required to assess ocular pharmacokinetics.

Results (continued)
A single topical dose of 43 or 86 µg of aganirsen was sufficient to elicit significant reduction in retinal IRS-1 expression in African green monkeys (Fig. 3).

Conclusions
1. Significant quantities of aganirsen are delivered to the retina following topical instillation of a single 86 µg dose to the cornea.
2. Retinal levels obtained following single dose administration are dose-dependent.
3. Following topical delivery of a single 86 µg dose, bioactive levels of aganirsen are achieved in the retina.
4. A twice-daily 86 µg dosing regimen conferred significant attenuation of laser-induced CNV in a nonhuman primate model.
5. Retinal delivery is likely to occur via the trans-scleral route although further studies are required to assess ocular pharmacokinetics.

References