**Suprachoroidally delivered non-viral DNA nanoparticles transflect chorioretinal cells in non-human primates and rabbits**

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**Purpose:**

Suprachoroidal delivery offers the potential to precisely target chorioretinal tissues while avoiding surgical risks associated with a subretinal injection, and may offer an office-based non-surgical gene therapy for the treatment of ocular diseases. The purpose of this research was to evaluate ocular tolerability and chorioretinal cell transfectability of suprachoroidally injected non-viral DNA nanoparticles (DNPs) in non-human primates (NHPs) and rabbits.

**Methods:**

Two separate studies evaluated chorioretinal cell transfectability and ocular tolerability of suprachoroidally injected non-viral DNPs in NHPs and in rabbits. The DNPs consisted of a single copy of plasmid DNA with a polyubiquitin C/luciferase transcriptional cassette. Cynomolgus monkeys (N=4 per group) received a single bilateral suprachoroidal injection (0.1 mL) of either saline (negative control), ellipsoid-shaped DNPs, or rod-shaped DNPs. New Zealand White rabbits (N=4 per group) received a single suprachoroidal injection (0.1 mL) of either saline (negative control), ellipsoid-shaped DNPs, or rod-shaped DNPs. A cohort of rabbits also received a single unilateral (left eye) subretinal injection of rod-shaped DNPs. Animals were assessed for anterior segment inflammation, intraocular pressure changes and for electroretinographic changes, at baseline, day 1, and day 7 post-dose in the rabbit study, and at baseline, day 1, day 8 and day 22 post-dose in the NHP study. Luciferase activity was measured in NHP ocular tissues at week 1, and week 3 post-injection, and at week 1 in rabbit ocular tissues by bioluminescence assay.

**Results:**

Suprachoroidally injected DNPs were generally well-tolerated in NHPs and rabbits. Luciferase activity was observed in the retina and choroid/RPE of eyes that received suprachoroidal injections in NHPs and rabbits. In NHPs, the persistence of luciferase activity was observed through day 22 (last study timepoint) with ellipsoid-shaped DNPs, while a decline (32% and 90% in retina and choroid/RPE, respectively) was observed with rod-shaped DNPs at day 22. In rabbits, suprachoroidally injected DNPs (both rod and ellipsoid) and subretinal DNPs (rod-shape) resulted in comparable luciferase activity at week 1 (last study timepoint).

**Conclusions:**

Suprachoroidal administration of non-viral DNPs resulted in an efficient chorioretinal transfection in NHPs and rabbits. Suprachoroidally injected DNPs were well tolerated, and will be further evaluated for their safety and efficacy.