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# A One-week Study to Evaluate Safety, Tolerability, and Retinal Cell Transfection of Non-viral DNA Nanoparticles Administered by Suprachoroidal Injection

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## Purpose

- The results of a 1-week study evaluating safety, tolerability, and retinal cell transfection of non-viral DNA nanoparticles (DNPs) administered by suprachoroidal (SC) injection in a rabbit model will be presented.

## Methods

- New Zealand white rabbits were randomized to four treatment groups, four animals per group. On Day 0, animals in the SC administration arms received a single 100-µL injection of either saline (negative control), ellipsoid-shaped DNPs, or rod-shaped DNPs. Animals in the positive control arm received 50 µL of rod-shaped DNPs administered by subretinal (SR) injection. The DNPs consisted of a single copy of plasmid DNA with a polyubiquitin C/luciferase transcriptional cassette. All doses of DNPs were administered to the left eye. Ophthalmic examinations were performed to evaluate surface morphology and anterior segment inflammation, in addition to intraocular pressure and electroretinography, at baseline and Days 1 and 7 post-dose. One week post-injection, both eyes were enucleated, and their choroid and retina separated and processed for luciferase activity.

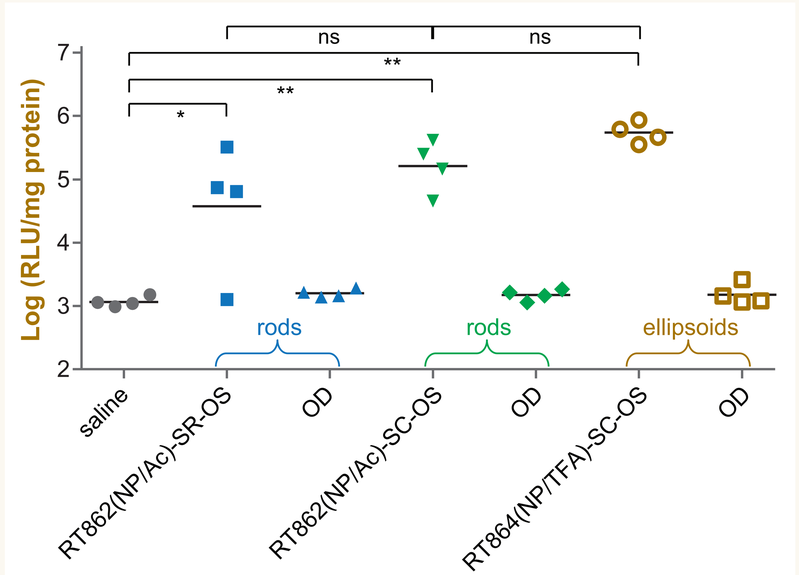
### Study Design

| Group ID | No. of Animals | Test Article/ Route | End Point Parameters | Time of Euthanasia |
|---|---|---|---|---|
| 1 | 4 | OS: vehicle (100 µL)/SC<br>OD: none | • Ocular Events (OE) at baseline, 24 h post-injection, and at harvest<br>• Intraocular Pressure (IOP) at baseline, 24 h, and weekly until harvest<br>• Electroretinogram (ERG) at baseline, and at harvest<br>• Luciferase activity | 1 week |
| 2 | 4 | OS: Active TA (ellipsoid luciferase) (100 µL)/SC<br>OD: none | • OE at baseline, 24 h post-injection, and at harvest<br>• IOP at baseline, 24 h, and weekly until harvest<br>• ERG at baseline, and at harvest<br>• Luciferase activity | |
| 3 | 4 | OS: Active TA (rod luciferase) (100 µL)/SC<br>OD: none | • OE at baseline, 24 h post-injection, and at harvest<br>• IOP at baseline, 24 h, and weekly until harvest<br>• ERG at baseline, and at harvest<br>• Luciferase activity | 1 week |
| 4 | 4 | OS: Positive Controls (rod luciferase) (50 µL)/SR<br>OD: none | • OE at baseline, 24 h post-injection, and at harvest<br>• IOP at baseline, 24 h, and weekly until harvest<br>• ERG at baseline, and at harvest<br>• Luciferase activity | |

## Results

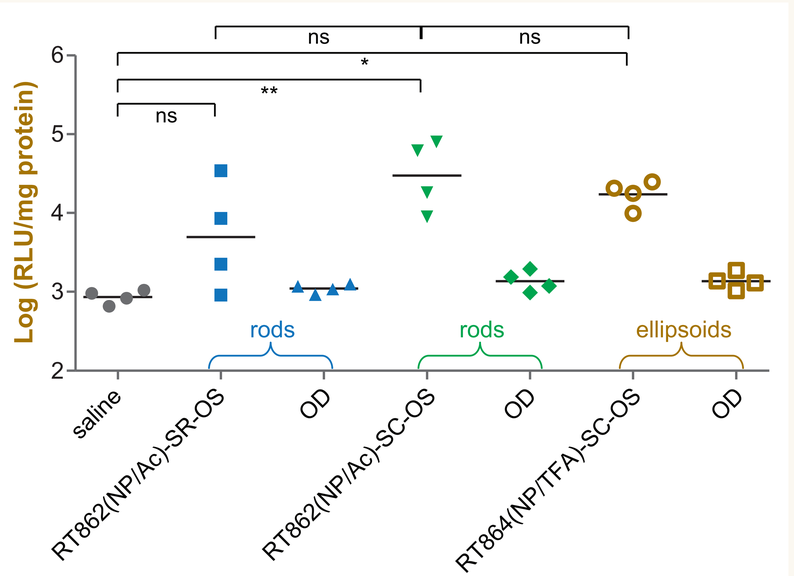
- Suprachoroidal injections of the non-viral DNPs were generally well-tolerated across groups. Transfection was observed in the retina and choroid of eyes that received SC and SR injections of DNPs. Eyes administered saline by SC injection had identical low levels of luciferase activity as untreated eyes. There was significant activity of both rod and ellipsoid DNPs following SC dosing and from rod DNPs from SR dosing. Transfection in the choroid was approximately 10-fold higher than in the retina in groups administered DNPs. No significant differences were observed in the choroid or retina between rod- and ellipsoid-shaped DNP groups, but the mean value was higher for ellipsoid-shaped DNPs in the choroid. One of the eyes in the positive control SR group showed no activity in either the choroid or the retina. Transfection was observed in every eye in all groups that received an SC injection of luciferase DNPs, with tightly clustered data points in each group. There were no significant abnormalities in OE, IOP, or ERG for any eye after SC injection.

### Figure 1. Luciferase Activity Analysis – Choroid




1-way ANOVA, p<0.0001. Bonferroni's multiple comparison test: *p<0.01, **p<0.0001. ns, non-significant.

### Figure 2. Luciferase Activity Analysis – Retina




1-way ANOVA, p<0.0001. Bonferroni's multiple comparison test: *p<0.001, **p<0.0001. ns, non-significant.

## Conclusions

- **Suprachoroidal administration of either rod- or ellipsoid luciferase DNPs produced activity that was comparable to that seen from subretinal injections of rod DNPs, and significantly greater than that seen from the negative control or untreated eyes. These data provide evidence that suprachoroidal injection of DNPs is well-tolerated with high levels of luciferase activity and should be further evaluated for ocular gene delivery.**

**Disclosures:** **Donna Taraborelli,** Clearside Biomedical Code I (Personal Financial Interest); **Glenn Noronha,** Clearside Biomedical Code I (Personal Financial Interest); **Robert Moen,** Copernicus Therapeutics Code I (Personal Financial Interest); **Jesse Yoo,** Clearside Biomedical Code I (Personal Financial Interest); **Ozge Sensenoglu Laird,** Copernicus Code I (Personal Financial Interest); **Mark J. Cooper,** Copernicus Code I (Personal Financial Interest).

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