

Safety of Ad_{GV}PEDF.11D Administered by Subtenon Injection Following Laser Disruption of the Bruch's Membrane in Cynomolgus Monkey Eyes

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Introduction:

Ad_{GV}PEDF.11D

- Second generation (E1, E4 and partial E3 deleted) adenoviral vector containing the antiangiogenic factor, PEDF (Pigment Epithelium-Derived Factor).
- Prevents choroidal neovascularization in preclinical animal models for wet age-related macular degeneration given by intravitreal, subretinal or periocular administration.
- Currently in Phase I clinical trial given by intravitreal administration.

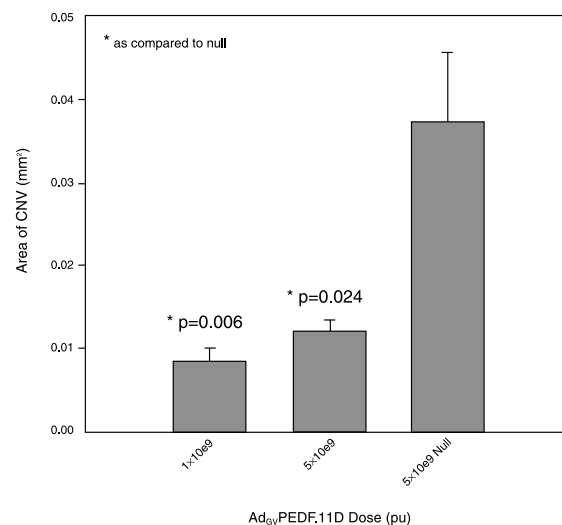


Figure 1. Ad_{GV}PEDF.11D Inhibits Mouse Choroidal Neovascularization

- Mice received laser treatment to the eye to disrupt the Bruch's membrane in 3 locations. After laser treatment, Ad_{GV}PEDF.11D was administered to one eye and Ad_{GV}Null.11D to the contralateral eye by periocular injection.
- Each bar represents the mean (± SEM) area of choroidal neovascularization measured by image analysis following periocular injection. (Gehlbach et al, Gene Therapy, Apr; 10(8):637-646, 2003).

Purpose:

To determine the safety of single and repeat doses of Ad_{GV}PEDF.11D administered by subtenon injection following laser disruption of the Bruch's membrane in cynomolgus monkey eyes.

Subtenon Administration



Dose Groups:

Group No.	Number of Males/Females	Treatment		Dose Day(s)	Number Necropsied	
		Left Eye	Right Eye		Day 43	Day 85
1	2/1	Vehicle	Vehicle	1	-	-
2	2/1	1x10 ⁸ pu	Vehicle	1	2/1	-
3	2/1	1x10 ⁹ pu	Vehicle	1	2/1	-
4	2/1	1x10 ¹⁰ pu	Vehicle	1	2/1	-
5	2/1	1x10 ⁹ pu	Vehicle	1, 22, 43	-	2/1

Methods:

- Model: Cynomolgus monkey
 - Disruption of Bruch's membrane was produced by laser treatment to the macula of eyes.
 - Immediately following laser treatment, a dose of Ad_{GV}PEDF.11D (left eye) or vehicle (right eye) was administered by subtenon injection (150 µL per eye). Group 1 received vehicle in both eyes.

Study Measurements:

Measurement	Frequency
Clinical Observations	Twice Daily
Food Consumption	Once Daily
Body Weight	Prior to Dosing, Weekly Thereafter
Ophthalmic Exams (Indirect Ophthalmoscopic and Biomicroscopic Exams)	Prestudy, Prior to Dosing, Weekly and Prior to Necropsy
Electroretinograms (ERG)	Prestudy (Groups 1-5), Day 19 (Group 5), Day 40 (Groups 1-5) and Day 82 (Group 1 and 5)
Clinical Pathology (Hematology, Clinical Chemistries and Coagulation Parameters)	Prestudy, Day -1, 21, 42 (Group 5); Day 43 (Groups 1-4) and Day 85 (Group 1 and 5)
Gross and Microscopic Pathology	Day 42 (Groups 2-4) and 85 (Group 5)

Conclusions:

- Ad_{GV}PEDF.11D administered by subtenon injection following laser disruption of the Bruch's membrane in cynomolgus monkey eyes was:
 - Safe and did not produce any adverse systemic or ocular effects at single doses of up to 1x10¹⁰ pu; and
 - No adverse systemic or ocular effects after repeat administration of 1x10⁹ pu once every 3 weeks for a total of 3 doses.

Table 1. Ad_{GV}PEDF.11D Related Effects

Dose Group	Clinical Observations/Clinical Pathology	Ophthalmic Exams	ERG	Systemic Histopathology	Ocular Histopathology	
					Ad _{GV} PEDF.11D (left eye)	Vehicle (right eye)
Control (Vehicle)	NA	NA	NA	NA	NA	NA
Group 2 1x10 ⁸ pu	none	none	none	none	none	NA
Group 3 1x10 ⁹ pu	none	none	none	none	NDR ^a	NA
Group 4 1x10 ¹⁰ pu	none	none	none	none	NDR ^a	NA
Group 5 1x10 ⁹ pu x 3	none	none	none	NDR ^b	NDR ^a	NA

Table 1: Safety of Ad_{GV}PEDF.11D in monkey eye with laser disrupted Bruch's membrane

- None: no effects
- NA: not applicable
- NDR: nondrug-related effects
- ^aMinimal nonsuppurative inflammation was observed in control-treated and drug-treated eyes in Groups 3 and 4. This observation is not dose-related and may be related to the injection procedure. In Group 5, minimal nonsuppurative inflammation was observed in Ad_{GV}PEDF.11D treated eyes and repeated administration did not result in an increase in severity.
- ^bSplenic lymphoid hyperplasia was observed in Group 5. This finding occurs sporadically in naïve animals and is not clearly related to Ad_{GV}PEDF.11D administration.

Table 1 Conclusion: No adverse drug-related and/or dose-related effects occurred in monkeys treated with Ad_{GV}PEDF.11D given by subtenon injection.