

12-Month Safety and Efficacy Evaluation of HORA-PDE6B, a Gene Therapy Targeting Patients with Retinitis Pigmentosa Due to Biallelic PDE6B Gene Mutation.

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Abstract

Purpose : Retinitis Pigmentosa (RP) is a diverse hereditary disease leading to blindness after decades of irreversible progression. One form is associated with an autosomal recessive mutation in the Phosphodiesterase 6 Beta Gene (PDE6B). HORA-PDE6B is a clinical-stage gene therapy targeting RP patients with PDE6B mutations. It employs an Adeno-Associated Virus serotype 5 (AAV2/5) vector carrying the human PDE6B isoform 1 cDNA, controlled by the photoreceptor-specific human rhodopsin kinase promoter that targets Rods photoreceptors. A phase I/II study with HORA-PDE6B is currently underway, evaluating safety, efficacy, and immune response profiles. This work presents interim analysis results from the first 17 adult patients after 12 months of follow-up (FU).

Methods : The treatment is given via subretinal injection in the worth seeing eye, with the fellow eye used as control. Patients are observed for five years, testing two dose levels: 3.4×10^{11} vg and 6.4×10^{11} vg per eye. Safety is assessed by Adverse Events (AEs)/ Serious Adverse Events (SAEs), while efficacy measures include Visual Field (VF), Visual Acuity (VA), Full-Field Stimulus Testing (FFST), Microperimetry, Mobility Test and Ellipsoid Zone (EZ) via Optical Coherence Tomography (OCT).

Results : Seven patients received the low dose, 10 got the high dose. Both doses were well tolerated, with 2 SAEs linked to HORA-PDE6 (one VA decrease and one chorioretinitis). The injection volume was reduced from 800 to 400 μ l to mitigate the risk of retinal detachments reported in 2 out of 4 patients receiving 800 μ l. Primary efficacy analysis was done in 5 patients at a less advanced disease stage receiving the higher dose. Treated eyes exhibited a favorable trend suggesting a potential therapeutic effect requiring confirmation through the coming 24-month data. For most parameters, the untreated eyes kept declining per disease's natural course, while stabilization occurred in most tests in the treated eyes (VA, VF, microperimetry, mobility test, and horizontal line of EZ). Blue light FFST improved, suggesting rods photoreceptors transduction cascade reactivation.

Conclusions : Over a short 12-month period, HORA-PDE6B has shown a favorable safety profile and potentially efficacy, encouraging the continued development of HORA-PDE6B.

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Visual Parameters after 12-Month Follow-Up in the Sub-Group of Interest (Change from Baseline).

ETDRS LogMAR	TRT	NT
N	5	5
Mean (+/-SD)	0.00 (+/-0.08)	0.05 (+/-0.10)
95% CI	[-0.10; 0.10]	[-0.07; 0.18]
Microperimetry, mean overall sensitivity (dB)	TRT	NT
N	5	5
Mean (+/-SD)	0.35 (+/-1.18)	0.18 (+/-0.94)
95% CI	[-1.11; 1.82]	[-0.99; 1.35]
Microperimetry, mean sensitivity of the 4 central loci (dB)	TRT	NT
N	5	5
Mean (+/-SD)	0.40 (+/-1.34)	-1.25 (+/-1.58)
95% CI	[-1.27; 2.07]	[-3.21; 0.71]
Mobility Score*	TRT	NT
N	5	5
Mean (+/-SD)	0.00 (+/-0.71)	-0.40 (+/-0.89)
95% CI	[-0.88; 0.88]	[-1.51; 0.71]
Total retina - Foveal line horizontal axis (µm)	TRT	NT
N	4	4
Mean (+/-SD)	-41.25 (+/-285.36)	-241.75 (+/-275.10)
95% CI	[-495.31; 412.81]	[-679.50; 196.00]
FST B455 (dB) - Blue light	TRT	NT
N	4	4
Mean (+/-SD)	2.25 (+/-1.71)	-1.25 (+/-2.06)
95% CI	[-0.47; 4.97]	[-4.53; 2.03]

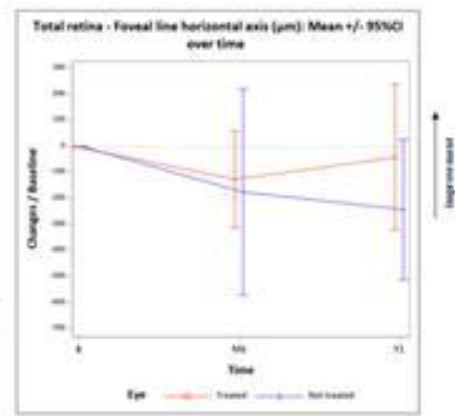
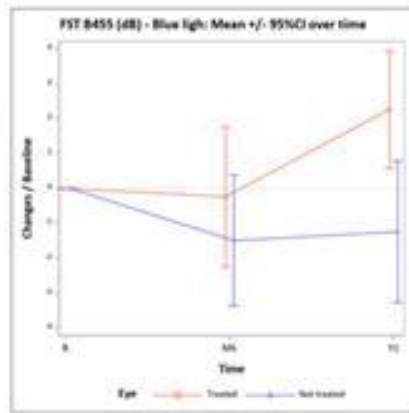
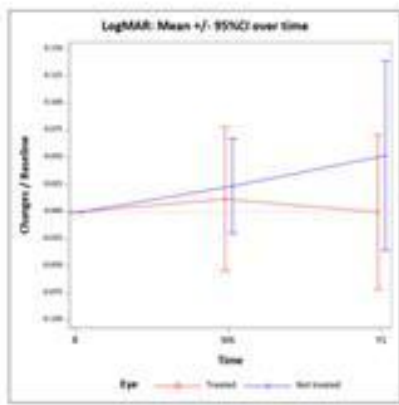
*: ORA® mobility test

TRT: Treated Eye

NT: Non-Treated Eye

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