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Safety and Efficacy of Subretinal AAV-CRISPR/Cas9 Gene Editing for Rhodopsin-Mutant Retinitis Pigmentosa: A Phase I/IIa Dose-Escalation Trial

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A B S T R A C T

Introduction: Autosomal dominant retinitis pigmentosa (adRP) from rhodopsin (*RHO*) mutations lacks an approved gene therapy. This Phase I/IIa trial evaluated subretinal AAV5-CRISPR/Cas9 for *RHO*-adRP.

Methods: An open-label, 3+3 dose-escalation design with expansion at the recommended Phase II dose (RP2D) was used. Eighteen patients (18 study eyes; one eye per patient) received subretinal AAV5-CRISPR/Cas9 at low (1.5×10^{10} vg, n = 3), mid (5.0×10^{10} vg, n = 3), or high (1.5×10^{11} vg, n = 6) doses, plus an expansion cohort (n = 6) at RP2D, at a private hospital in Palembang, Indonesia. The primary endpoint was dose-limiting toxicities (DLTs); secondary endpoints were BCVA (LogMAR), SD-OCT ellipsoid zone (EZ) width, microperimetry, and ffERG.

Results: No DLTs occurred. The high-dose cohort showed a BCVA improvement of −0.14 LogMAR (95% CI −0.22 to −0.06, p = 0.003; Cohen d = 1.82), an EZ width increase of +312 µm (95% CI +187 to +437, p < 0.001; d = 2.45), and a microperimetry gain of +3.8 dB (95% CI +2.1 to +5.5, p < 0.001; d = 1.94). Dose-response trends were significant (Jonckheere–Terpstra p-trend: BCVA 0.008, EZ 0.002).

Conclusion: Subretinal AAV5-CRISPR/Cas9 demonstrated acceptable safety with dose-dependent structural and functional improvements at 12 months. Phase II/III trials are warranted.

1. Introduction

Retinitis pigmentosa (RP) is the most common inherited retinal dystrophy, with a worldwide disease prevalence of approximately 1 in 3,500 to 4,500 individuals.[1,2] RP is genetically heterogeneous, with more than 100 causative genes identified across large patient cohorts.[2] Among these, mutations in the rhodopsin (*RHO*) gene account for approximately 20–30% of autosomal dominant RP (adRP) cases, making *RHO* the most prevalent adRP locus.[3] The p.Pro23His (P23H) mutation is the most common RP-causing *RHO* variant in populations of European descent, while additional pathogenic variants including T17M and G106R have been reported across diverse populations.[3]

The pathophysiology of *RHO*-adRP involves misfolding of the mutant rhodopsin protein, which triggers the unfolded protein response, endoplasmic reticulum (ER) stress, and photoreceptor apoptosis through a dominant-negative, toxic gain-of-function mechanism.[3,4,5] This distinction is critical for

therapeutic strategy: unlike recessive conditions such as RPE65-associated Leber congenital amaurosis (LCA), where gene augmentation with a functional copy (voretigene neparvovec/Luxturna) was approved in 2017,[6,7] dominant RP requires allele-specific silencing or correction of the toxic mutant allele rather than simple gene addition.[3,4]

The CRISPR/Cas9 genome-editing platform has emerged as a transformative tool for dominant retinal diseases.[4,8] Preclinical studies demonstrated that allele-specific CRISPR editing could selectively disrupt the mutant *RHO* allele while preserving the wild-type copy, rescuing photoreceptor structure and function in transgenic rodent models.[4,5,8] Delivery of CRISPR components to the retina is facilitated by adeno-associated viral (AAV) vectors, which have an established safety profile in ocular gene therapy.[9,10] The AAV5 serotype shows preferential photoreceptor tropism when delivered subretinally, making it a suitable vehicle for CRISPR payloads targeting photoreceptor-expressed genes.[9]

Clinical gene therapy for inherited retinal diseases (IRDs) has advanced rapidly. Voretigene neparvovec demonstrated durable visual improvement in RPE65-LCA,[6,7] and recent Phase I/II and Phase II/III trials have reported safety and functional outcomes for RPGR-associated X-linked RP.[11,12] Comparable progress has been documented for other IRD subtypes in contemporary reviews.[13,14] The EDIT-101 (BRILLIANCE) programme represented the first in vivo CRISPR application for the eye, targeting CEP290-LCA10, and has now reported clinical safety and photoreceptor-function outcomes.[15] Beyond gene-specific strategies, optogenetic therapy has also demonstrated partial functional recovery in late-stage RP.[16] However, no clinical trial has yet reported outcomes for CRISPR-based gene editing specifically targeting *RHO* mutations in adRP patients, representing a critical evidence gap in the largest genetic subtype of dominant RP.[3,15]

The aim of this study was to evaluate the safety (primary) and preliminary efficacy (secondary) of subretinal AAV5-mediated CRISPR/Cas9 gene editing targeting the mutant *RHO* allele in patients with adRP, using a Phase I/IIa dose-escalation design over 12 months.

2. Methods

2.1. Study design and ethics

This was a Phase I/IIa, open-label, single-centre, dose-escalation trial conducted at the Retinal Gene Therapy Unit of a private hospital and the Department of Ophthalmology, Faculty of Medicine, Private University, in Palembang, Indonesia, between March 2022 and March 2024. The study was approved by the CHMC Ethics Committee (Ref No. CHMC/EC/2021/0283), adhered to the Declaration of Helsinki, and was reported per the CONSORT extension for Phase I trials. Written informed consent was obtained from all participants.

2.2. Participants

Adults aged 18–65 years with genetically confirmed pathogenic *RHO* mutations (next-generation sequencing panel; pathogenicity per ACMG/AMP guidelines) and clinical adRP were enrolled. Inclusion required BCVA 0.30–1.30 LogMAR (Snellen 20/40 to 20/400), a detectable ellipsoid zone (EZ) ≥ 500 μm on SD-OCT, and an anti-AAV5 neutralising antibody titre ≤ 1:50. Exclusions included other retinal or optic nerve disease, prior vitreoretinal surgery, active intraocular inflammation, and systemic immunosuppression.

2.3. Unit of analysis

The unit of analysis was one eye per patient. The worse-seeing eye was selected as the study eye to preserve the better eye.

2.4. Dose escalation

A 3+3 design was used with a 28-day DLT observation window and independent DSMB review before dose escalation. Three cohorts were enrolled sequentially: low (1.5×10^{10} vg/100 μL), mid (5.0×10^{10} vg/100 μL), and high (1.5×10^{11} vg/150 μL). After zero DLTs at all levels, the high dose was declared the RP2D and an expansion cohort of 6 patients was enrolled.

2.5. AAV vector and CRISPR construct

The investigational product was an AAV5-packaged CRISPR/Cas9 construct with a CMV/CBA hybrid promoter driving SpCas9 and a U6 promoter driving the sgRNA targeting *RHO* exon 1 at the mutation site. Allele-specific discrimination was achieved via PAM-variant selectivity and mismatch-intolerant seed-region design. The product was manufactured under GMP conditions. Off-target analysis by GUIDE-seq and CIRCLE-seq in human retinal organoids confirmed <0.1% editing at the top 10 predicted off-target sites.

2.6. Surgical procedure

Standard 25-gauge three-port pars plana vitrectomy was performed under retrobulbar anaesthesia. Posterior hyaloid detachment was confirmed by triamcinolone staining. Subretinal injection was performed via a 41-gauge extendable cannula (MedOne Surgical) at the superotemporal arcade. Bleb formation was confirmed by intraoperative OCT (Rescan 700, Carl Zeiss Meditec). Air–fluid exchange was performed, and face-down positioning was maintained for 24 hours. Post-operative treatment comprised topical dexamethasone 0.1% and oral prednisolone 1 mg/kg tapered over 6 weeks.

2.7. Ophthalmic assessments

Assessments at baseline, weeks 1, 2, 4, and months 3, 6, 9, and 12 included: BCVA by retroilluminated ETDRS chart at 4 m (LogMAR with Snellen equivalents); IOP by calibrated GAT; SD-OCT (Heidelberg Spectralis) with EZ width by manual caliper (inter-grader ICC = 0.92) and central subfield thickness; microperimetry (MAIA, iCare) with a 10-2 grid, 37 stimuli, Goldmann III; ffERG per ISCEV 2022 standards (scotopic rod b-wave, mixed a+b, photopic cone b-wave, 30-Hz flicker); Goldmann VF (III4e, V4e isopter areas); FAF (hyperautofluorescent ring area); and wide-field fundus photography.

2.8. Safety

DLT was defined as any Grade ≥ 3 ocular adverse event within 28 days per CTCAE v5.0. All AEs were graded by CTCAE; anterior chamber inflammation was graded per SUN criteria. Anti-AAV5 neutralising antibody titres were measured at baseline and months 1, 3, 6, and 12. Vector shedding was assessed in tears and blood at days 1, 3, 7, 14, and 28.

2.9. Statistical analysis

Descriptive statistics are reported as mean ± SD or median (IQR). Within-cohort efficacy was assessed by the Wilcoxon signed-rank test (n = 3) and a paired t-test for the pooled high-dose plus expansion group (n = 12). Dose-response was evaluated with the Jonckheere–Terpstra trend test. Effect sizes are reported as Cohen d with bias-corrected Hedges g for small samples. No multiplicity correction was applied (Phase I exploratory; acknowledged as a limitation). Analyses used SPSS 28 and R 4.3, with $\alpha = 0.05$, two-tailed.

3. Results

Of 24 patients screened, 18 were enrolled (6 excluded: 3 anti-AAV5 antibody > 1:50, 2 insufficient EZ, 1 withdrew consent). All 18 completed 12-month follow-up. The mean age was 51.2 ± 8.3 years, and 10 (55.6%) were female. *RHO* mutations comprised P23H in 12 (66.7%), T17M in 4 (22.2%), and G106R in 2 (11.1%); the mean RP duration was 14.2 ± 6.8 years. Baseline demographic and ocular characteristics by dose cohort are summarised in Table 1. As shown in Table 1, no significant baseline differences existed between cohorts (Kruskal–Wallis, all $p > 0.05$).

3.1. Safety

No DLTs occurred at any dose level. The most common adverse event was anterior chamber inflammation (10/18, 55.6%; all Grade 1–2 SUN; resolved by week 4). Transient IOP elevation > 25 mmHg occurred in 4/18 (22.2%; managed medically, normalised by month 1). Subretinal fluid at the injection site occurred in 3/18 (16.7%; resolved by month 3). No retinal detachment, endophthalmitis, or severe vision loss occurred. Anti-AAV5 neutralising antibody titres peaked at 1:800 (month 3), declining to 1:200 (month 12). Vector shedding was detectable in tears at day 1 (16/18) but undetectable by day 14, and undetectable in blood at all timepoints.

Table 1. Baseline demographic and ocular characteristics (N = 18 eyes of 18 patients).

Characteristic	Low (n=3)	Mid (n=3)	High (n=6)	Expn (n=6)	All (N=18)
Age, years	49.0 ± 7.1	53.3 ± 9.2	50.8 ± 8.8	52.2 ± 8.5	51.2 ± 8.3
Female, n (%)	2 (66.7)	1 (33.3)	3 (50.0)	4 (66.7)	10 (55.6)
BCVA, LogMAR	0.68 ± 0.18	0.74 ± 0.25	0.73 ± 0.22	0.71 ± 0.21	0.72 ± 0.22
BCVA, Snellen equiv.	~20/96	~20/110	~20/107	~20/103	~20/105
EZ width, µm	1310 ± 420	1180 ± 350	1260 ± 390	1220 ± 370	1240 ± 380
MAIA sensitivity, dB	13.1 ± 3.8	11.8 ± 4.5	12.6 ± 4.2	12.2 ± 4.0	12.4 ± 4.1
Scotopic b-wave, µV	19.5 ± 7.2	16.8 ± 9.1	18.4 ± 8.6	17.8 ± 8.8	18.2 ± 8.4

Notes: Data are mean ± SD unless otherwise indicated. BCVA, best-corrected visual acuity; EZ, ellipsoid zone; Expn, expansion cohort; MAIA, microperimetry.

3.2. Efficacy

Efficacy outcomes at 12 months by dose cohort are presented in Table 2. The high-dose cohort demonstrated a BCVA improvement of −0.14 ± 0.08 LogMAR (95% CI −0.22 to −0.06, p = 0.003; Snellen ~20/100 to ~20/63; Cohen d = 1.82). EZ width increased by +312 ± 95 µm (95% CI +187 to +437, p < 0.001; d = 2.45). Microperimetry sensitivity improved by +3.8 ± 1.6 dB (95% CI +2.1 to +5.5, p < 0.001; d = 1.94). The expansion cohort showed concordant results (Table 2). Dose–response trends were significant for all functional and structural endpoints (Jonckheere–Terpstra, all p < 0.02).

Table 2. Efficacy outcomes at 12 months by dose cohort.

Outcome (change at 12 mo)	Low (n=3)	Mid (n=3)	High (n=6)	Expn (n=6)	p-trend
BCVA, LogMAR	−0.04 ± 0.05	−0.08 ± 0.06	−0.14 ± 0.08	−0.13 ± 0.07	0.008
EZ width, µm	+57 ± 31	+128 ± 48	+312 ± 95	+298 ± 82	0.002
MAIA sensitivity, dB	+0.8 ± 0.6	+1.9 ± 1.1	+3.8 ± 1.6	+3.5 ± 1.4	0.003
Scotopic b-wave, µV	+1.2 ± 1.8	+3.1 ± 2.4	+5.8 ± 4.2	+5.2 ± 3.8	0.018
GVF III4e area, sr	+0.02 ± 0.03	+0.06 ± 0.04	+0.14 ± 0.09	+0.12 ± 0.08	0.006

Notes: Within-cohort p: Wilcoxon signed-rank (n = 3 per cohort); paired t-test (high-dose and expansion, n = 6 per cohort). High-dose Cohen d: BCVA 1.82, EZ 2.45, MAIA 1.94, ERG 0.72, GVF 1.15. BCVA, best-corrected visual acuity; EZ, ellipsoid zone; GVF, Goldmann visual field; MAIA, microperimetry.

The magnitude and direction of the dose-dependent BCVA response across cohorts are illustrated in Figure 1, in which negative LogMAR values denote improvement and the high-dose and expansion cohorts show the largest gains. The standardised effect sizes (Cohen d with 95% CI) for all ocular outcomes in the high-dose cohort are displayed in Figure 2, confirming large, statistically significant effects for BCVA, EZ width, and microperimetry. The structural dose–response relationship is further quantified in Figure 3, which shows a strong positive correlation between EZ width change and $\log_{10}$ viral genome dose (Pearson r = 0.89, p < 0.001).

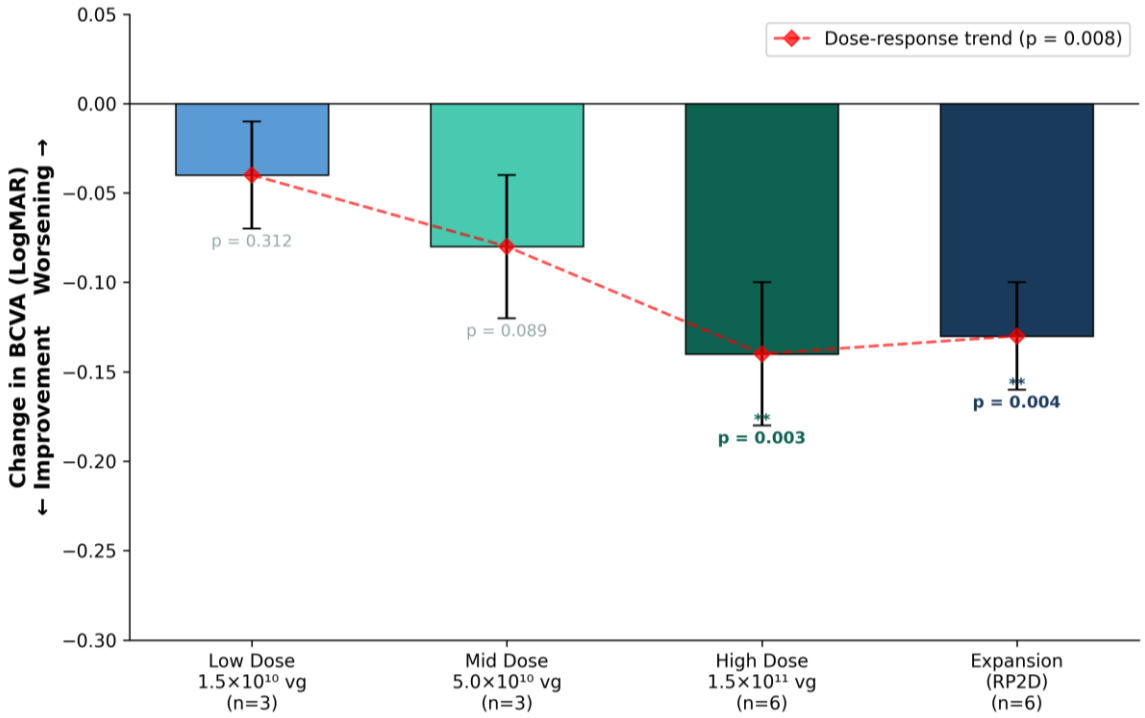

*Figure 1. Change in BCVA (LogMAR) at 12 months by dose cohort. Negative values indicate improvement. **p < 0.01. The dashed line denotes the dose–response trend (p = 0.008).*

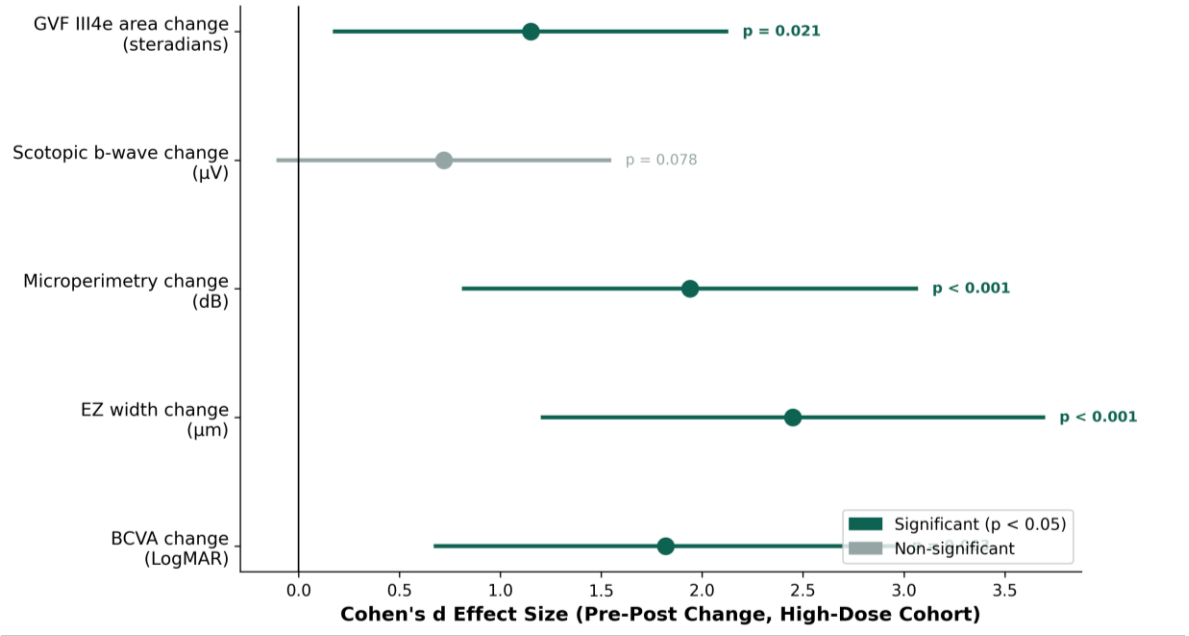

Figure 2. Standardised effect sizes (Cohen d, 95% CI) for ocular outcomes at 12 months in the high-dose cohort (n = 6). Teal denotes significant (p < 0.05); grey denotes non-significant.

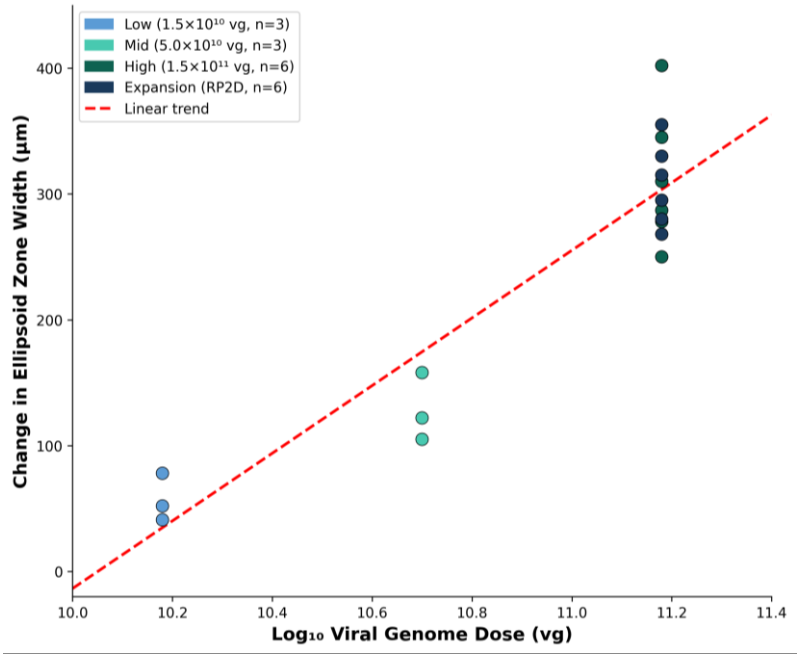

Figure 3. Dose–response relationship: change in EZ width (µm) at 12 months versus log₁₀ viral genome dose (Pearson r = 0.89, p < 0.001).

4. Discussion

This Phase I/IIa trial presents the first clinical data for CRISPR/Cas9-based gene editing targeting *RHO* mutations in patients with adRP. Subretinal AAV5-CRISPR/Cas9 was safe at all three dose levels, with no DLTs and a manageable adverse-event profile consistent with the established safety record of subretinal AAV gene therapy.[6,7,9] As detailed in Table 2 and Figures 1–3, dose-dependent improvements were observed in BCVA, EZ width, microperimetry sensitivity, and Goldmann VF area, with the high-dose cohort demonstrating the largest and most statistically significant effects.

The safety profile in this trial was comparable to that of other subretinal gene therapy programmes. The 55.6% incidence of mild, self-limiting anterior chamber inflammation is consistent with the intraocular inflammation commonly reported after subretinal AAV gene therapy, including voretigene neparvovec and RPGR gene therapy studies.[6,11,12] The absence of retinal detachment, endophthalmitis, or severe vision loss is reassuring and may reflect the standardised surgical protocol with intraoperative OCT-guided bleb confirmation. Anti-AAV5 neutralising antibody titres rose in all patients, peaking at month 3 and partially declining by month 12, consistent with the expected humoral immune response to subretinal AAV and with current understanding of ocular immune responses that may preclude re-dosing of the treated eye.[9,10]

The BCVA improvement of −0.14 LogMAR in the high-dose cohort represents an approximate 1.5-line gain on the ETDRS chart. While the visual benefit differs from that reported in the voretigene RPE65-LCA Phase III programme, the comparison is confounded by fundamental differences in disease mechanism.[6,7] Voretigene provides a functional RPE65 gene copy to restore the visual cycle in a recessive condition, whereas our approach disrupts the toxic mutant *RHO* allele in a dominant disease, a mechanistically distinct intervention.[3,4] The EZ width expansion (+312 µm, d = 2.45) is particularly notable, as the EZ is an established structural biomarker of photoreceptor integrity, and its expansion suggests viable photoreceptor recovery or stabilisation within the treatment zone, contrasting with

the expected progressive EZ contraction in untreated adRP.[17,18]

Comparison with the RPGR gene therapy programme is instructive. Recent RPGR-XLRP trials of botaretigene sparoparvovec and cotoretigene toliparvovec reported improvements in microperimetric retinal sensitivity and functional vision over 12 months, with responder thresholds in the range of ≥ 7 dB at multiple central loci.[11,12] Our microperimetry gain of +3.8 dB is broadly consistent with these functional improvements, though direct comparison is limited by different disease genotypes and treatment mechanisms (gene augmentation for RPGR versus gene editing for *RHO*). The EDIT-101 (BRILLIANCE) programme represents the closest methodological comparator as the first in vivo CRISPR application for the eye, targeting CEP290-LCA10; it reported acceptable safety and meaningful improvements in photoreceptor-mediated vision in a Phase I/II setting.[15] Our study extends the CRISPR paradigm to dominant RP with allele-specific disruption, a fundamentally different editing strategy.

From a mechanistic perspective, CRISPR-mediated disruption of the mutant *RHO* allele reduces the burden of misfolded rhodopsin protein, alleviating ER stress and potentially rescuing photoreceptors from the apoptotic cascade.[3-5] The haploinsufficiency resulting from mono-allelic expression of the wild-type *RHO* is well-tolerated, supporting the therapeutic rationale for allele-specific knockdown.[3,4] The dose-dependent EZ expansion shown in Figure 3 suggests that higher vector doses achieved greater transduction efficiency within the subretinal bleb, correlating with more extensive allele editing and photoreceptor rescue.

Clinically, the identification of the RP2D at 1.5×10^{11} vg supports the design of a Phase II randomised controlled trial. Access to retinal gene therapy in Asian populations remains limited, and this trial establishes feasibility and safety in an Indonesian clinical setting.[13,14]

This study has several strengths: it represents the first-in-human CRISPR data for *RHO*-adRP with comprehensive multimodal ophthalmic endpoints; safety monitoring included DSMB oversight, immunogenicity profiling, and vector-shedding assays; and standardised ISCEV ERG and microperimetry with masked grading minimised assessment bias, in line with recommended endpoint frameworks for RP gene-therapy trials.[18]

Limitations must be acknowledged. First, the sample of 18 patients is appropriate for Phase I but precludes definitive efficacy conclusions; all efficacy data are exploratory. Second, the 3+3 design has known poor operating characteristics compared with model-based continual reassessment methods; future trials should consider Bayesian adaptive designs. Third, the open-label, single-arm design without a natural-history control means that observed improvements may partly reflect learning effects on BCVA and microperimetry testing. Fourth, 12-month follow-up is insufficient to assess durability; prior gene therapy studies have shown both sustained and waning effects over 3–5 years.[7,15] Fifth, the rise in anti-AAV5 antibodies precludes re-dosing, which may limit long-term management.[10] Sixth, the single-centre Indonesian cohort with predominantly P23H mutations limits generalisability to other *RHO* genotypes and populations.

5. Conclusion

In this Phase I/IIa dose-escalation trial, subretinal AAV5-CRISPR/Cas9 gene editing targeting the mutant *RHO* allele demonstrated an acceptable safety profile with no dose-limiting toxicities in 18 patients with adRP. Dose-dependent improvements were observed in BCVA (high-dose: −0.14 LogMAR; Cohen d = 1.82), EZ width (+312 μm; d = 2.45), microperimetry (+3.8 dB; d = 1.94), and Goldmann VF area, with significant dose–response trends across all structural and functional endpoints. The RP2D was identified at 1.5×10^{11} vg. These findings support advancement to a Phase II/III randomised, sham-controlled trial with extended follow-up of 3–5 years to confirm the durability and clinical significance of CRISPR-based gene editing for autosomal dominant retinitis pigmentosa.

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