Advancing *PRPF31*-Related Retinitis Pigmentosa Treatment: Key Insights from the VP-001 Phase 1B Study

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OHSU

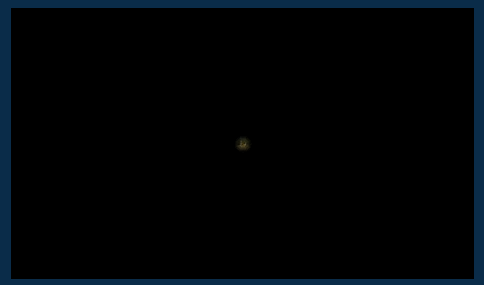
Retinitis Pigmentosa type 11 (RP11) is a progressive blinding eye disease for which there are no treatment options (*PRPF31*)

Degenerative sight of an RP11 patient

6 YEARS OLD

26 YEARS OLD

46 YEARS OLD



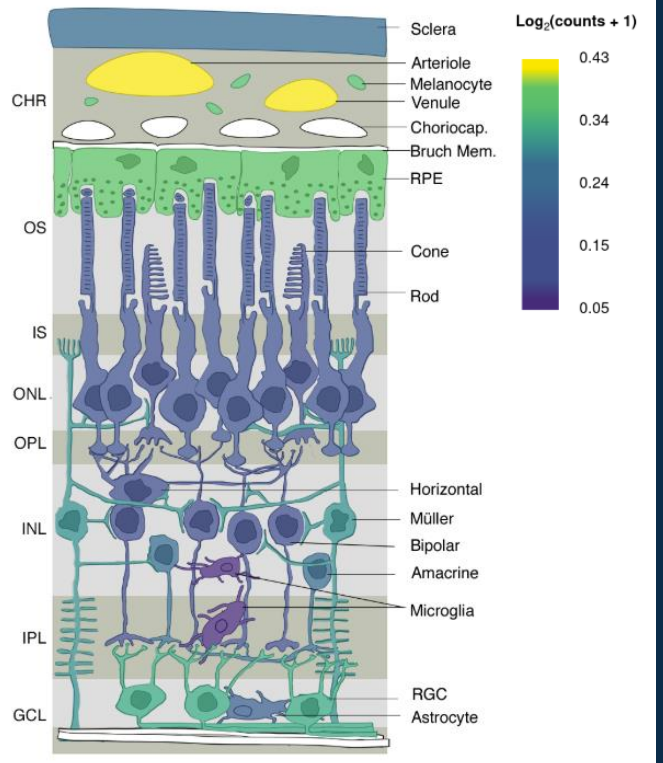
Retinitis Pigmentosa (RP)[1,2]

- A severe and progressive blinding eye disease that begins in childhood
- Affects 1 in every 3,500 people (RP11 accounts for ~3% of RP)
- RP11 is an autosomal dominant form of RP due to haploinsufficiency of *PRPF31* (high rates of non-penetrance)
- Patients experience night blindness followed by loss of peripheral and then central vision - legal blindness occurs in the 4th or 5th decade of life
- Patients with RP11 have no treatment options available

1. Daiger S et al. ‘Genes and Mutations Causing Autosomal Dominant Retinitis Pigmentosa’ Cold Spring Harb. Perspect. Med. 5 (2014)
2. Ellingford J et al. ‘Molecular findings from 537 individuals with inherited retinal disease’ J Med Genet 53, 761-776 (2016)

RP11 is caused by insufficient expression of *PRPF31* in the retina and RPE

PRPF31 expression



https://plae.nei.nih.gov/

Unaffected individual

PRPF31 DNA → *PRPF31* RNA → PRPF31 Protein

Functional *PRPF31* expression = 100%

RP11 patient

PRPF31 DNA → *PRPF31* RNA → PRPF31 Protein

Functional *PRPF31* expression = ~50%

PRP31 is a crucial splicing factor in the retina and regulates the synthesis of key proteins involved in vision, including Rhodopsin[2]

1. Hafler BP, et al. Course of Ocular Function in PRPF31 Retinitis Pigmentosa. Semin Ophthalmol. 2016;31:1-2
2. Yuan L, et al. Mutations in PRPF31 Inhibit Pre-mRNA Splicing of Rhodopsin Gene and Cause Apoptosis of Retinal Cells. Journal of Neuroscience. 2005 Jan 19;25(3):748–57.

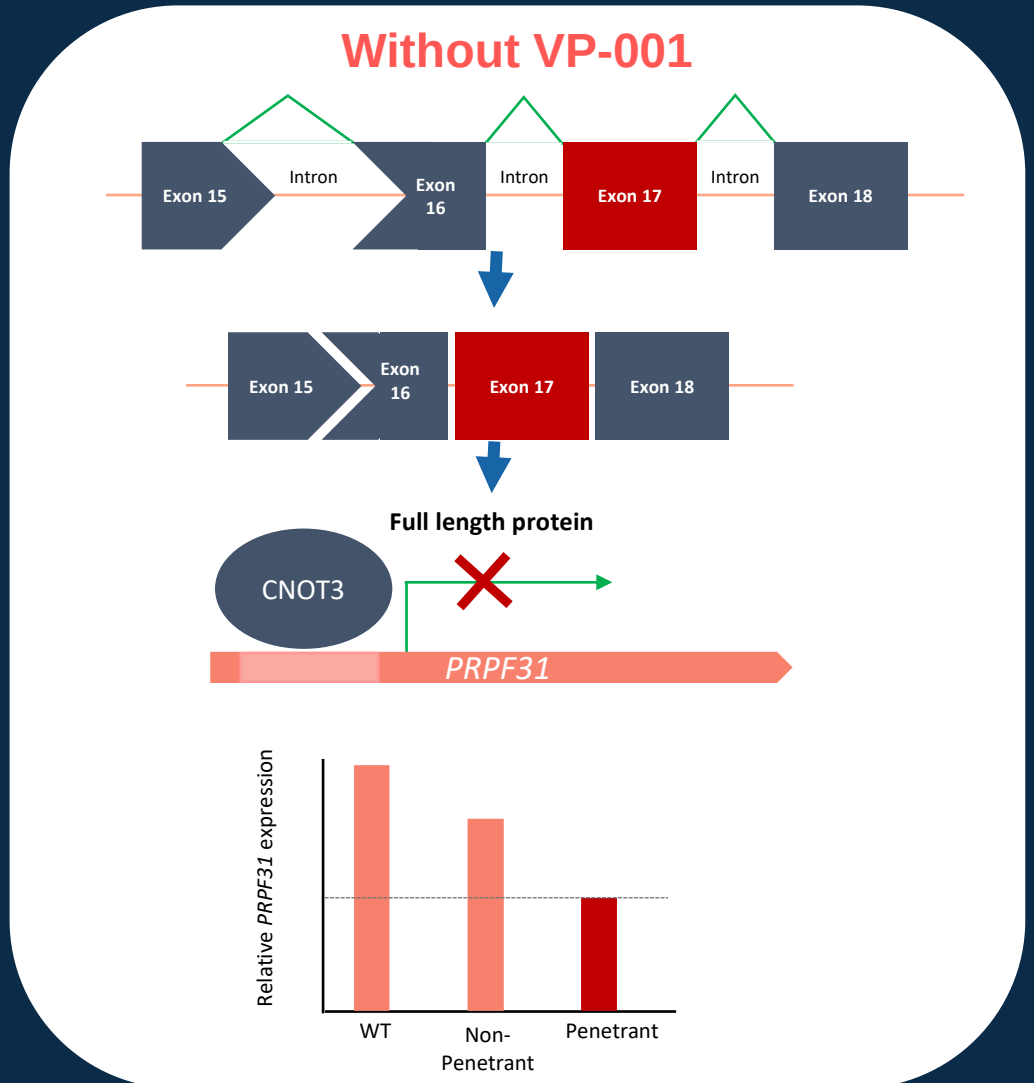
VP-001 is designed to address the underlying cause of RP11

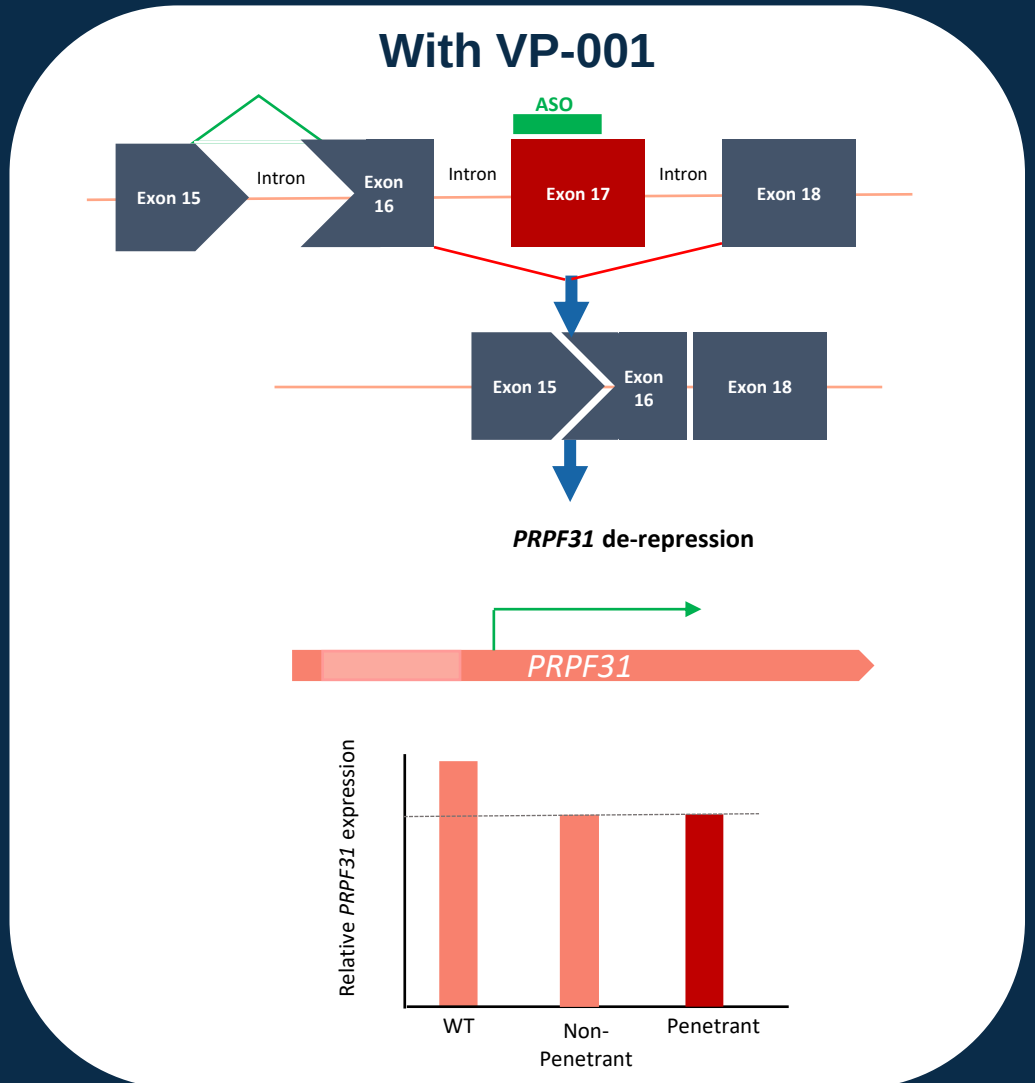
- **Cell-penetrating peptide conjugated to an oligonucleotide to modulate *CNOT3* expression**
- **Intravitreal injection (50 µl)**

CNOT3 Pre-mRNA

CNOT3 mRNA

PRPF31 mRNA expression

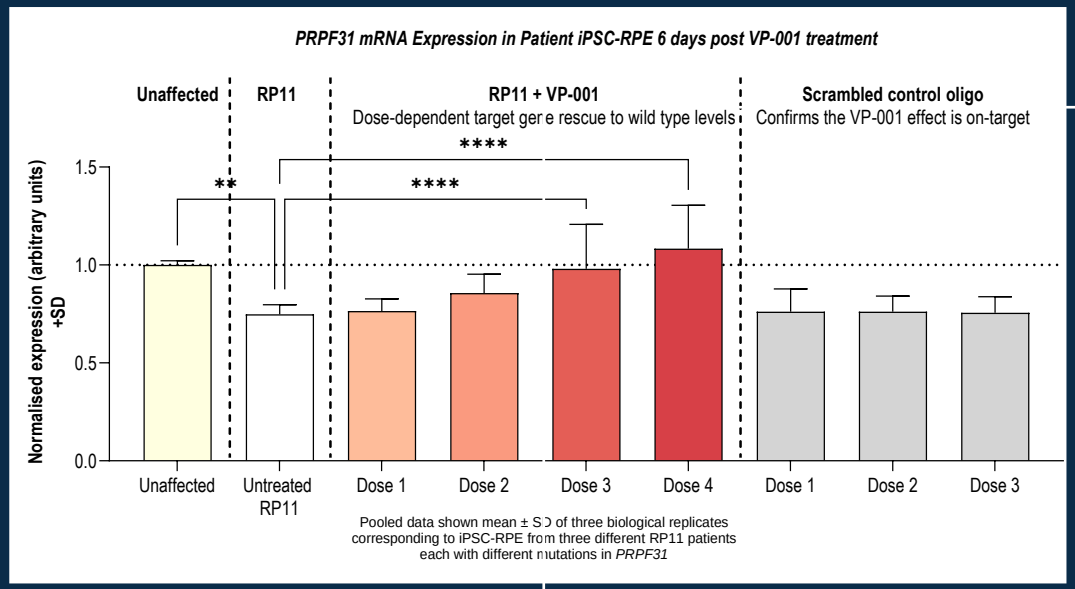




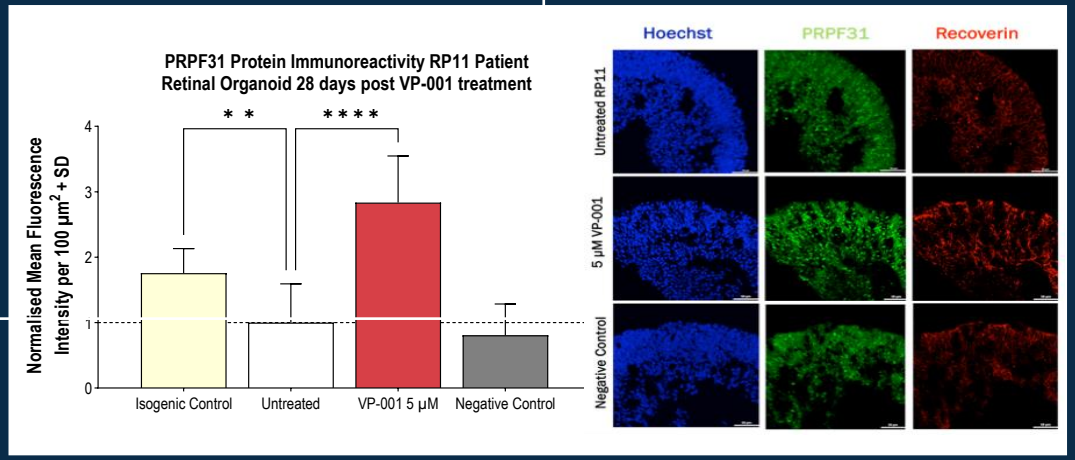
VP-001's Robust Preclinical Proof of Concept

VP-001 shows the ability to rescue *PRPF31* haploinsufficiency in patient-derived models

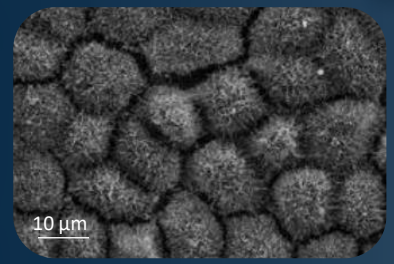
1) Upregulates *PRPF31* **mRNA** in RP11 iPSC-RPE



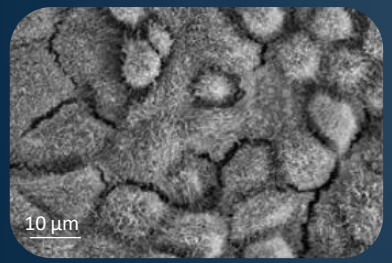
2) Upregulates PRPF31 **protein** in RP11 3D retinal organoid models



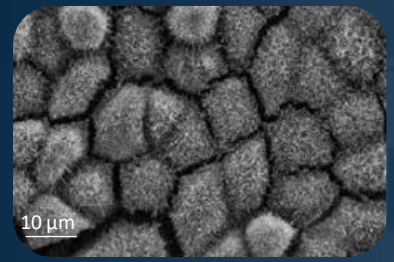
3) Rescues **morphology** of affected cells (iPSC-RPE)



Unaffected control

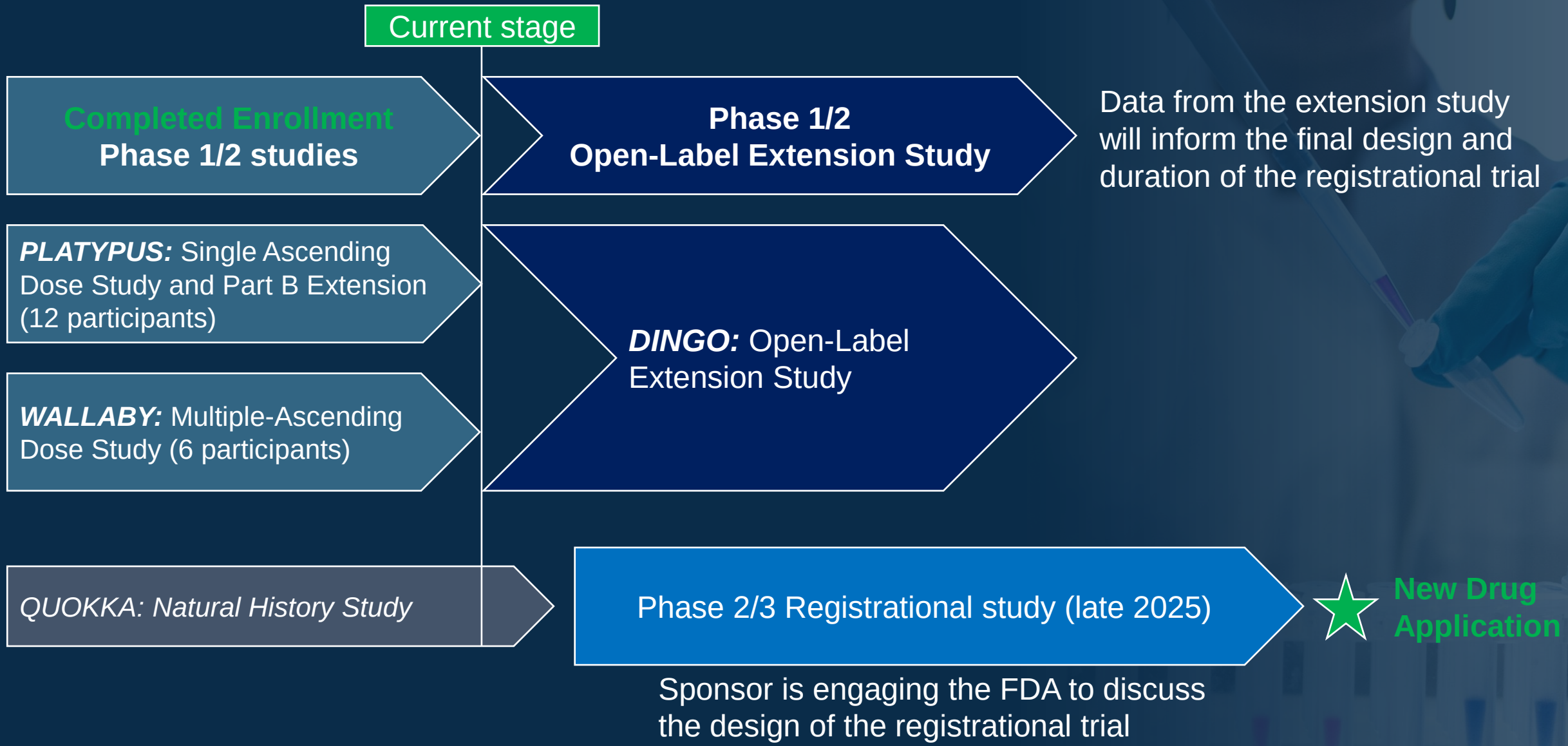


Retinitis Pigmentosa



RP + VP-001 treatment

Overview of VP-001 Clinical Trials



Overview of the Phase 1/2 studies of VP-001 in RP11

Overview of *PLATYPUS*

Primary Outcome: Safety & Tolerability

Single Ascending Dose (SAD) study

- n = 3 patients per cohort
- Patients receive unilateral injection of VP-001
- Patients monitored on outcome measures

Cohort 1 (3 µg)

Cohort 2 (10 µg)

Cohort 3 (30 µg)

Cohort 4 (75 µg)

SAD 'Part B' Extension study

Cohort 3 (30 µg)

Cohort 4 (75 µg)

Outcome measures

- Ocular and non-ocular adverse events (AEs)
- BCVA
- LLVA
- Microperimetry
- Perimetry
- FAF
- SD-OCT

Overview of *WALLABY*

Primary Outcome: Safety & Tolerability

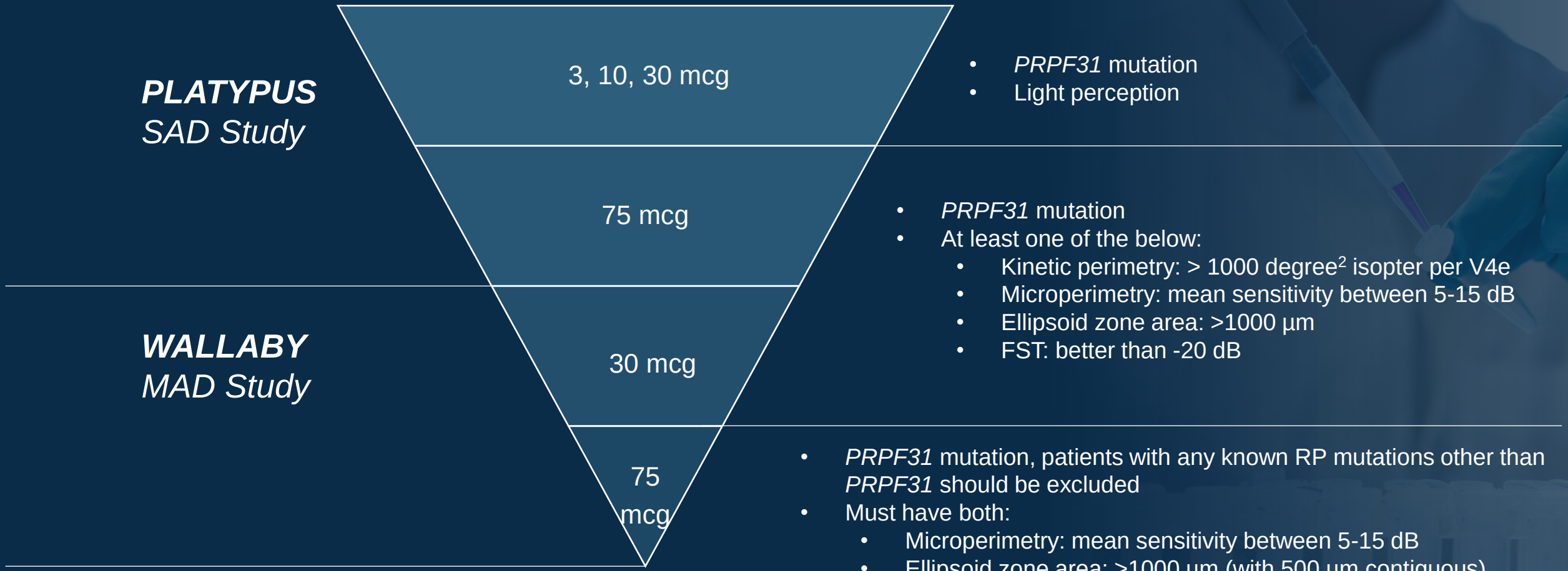
Multiple Ascending Dose (MAD) study

Cohort 1 (30 µg)

Cohort 2 (75 µg)

- n = 3 patients per cohort
- Patients receive unilateral VP-001 injection every 2 months
- Repeat injections of both 30 µg and 75 µg has already been confirmed safe and well-tolerated in the ongoing SAD 'Part B extension' study

The inclusion criteria was progressively refined to seek an accelerated efficacy signal in the ongoing studies of VP-001



Key outcomes from ongoing clinical studies of VP-001 in RP11

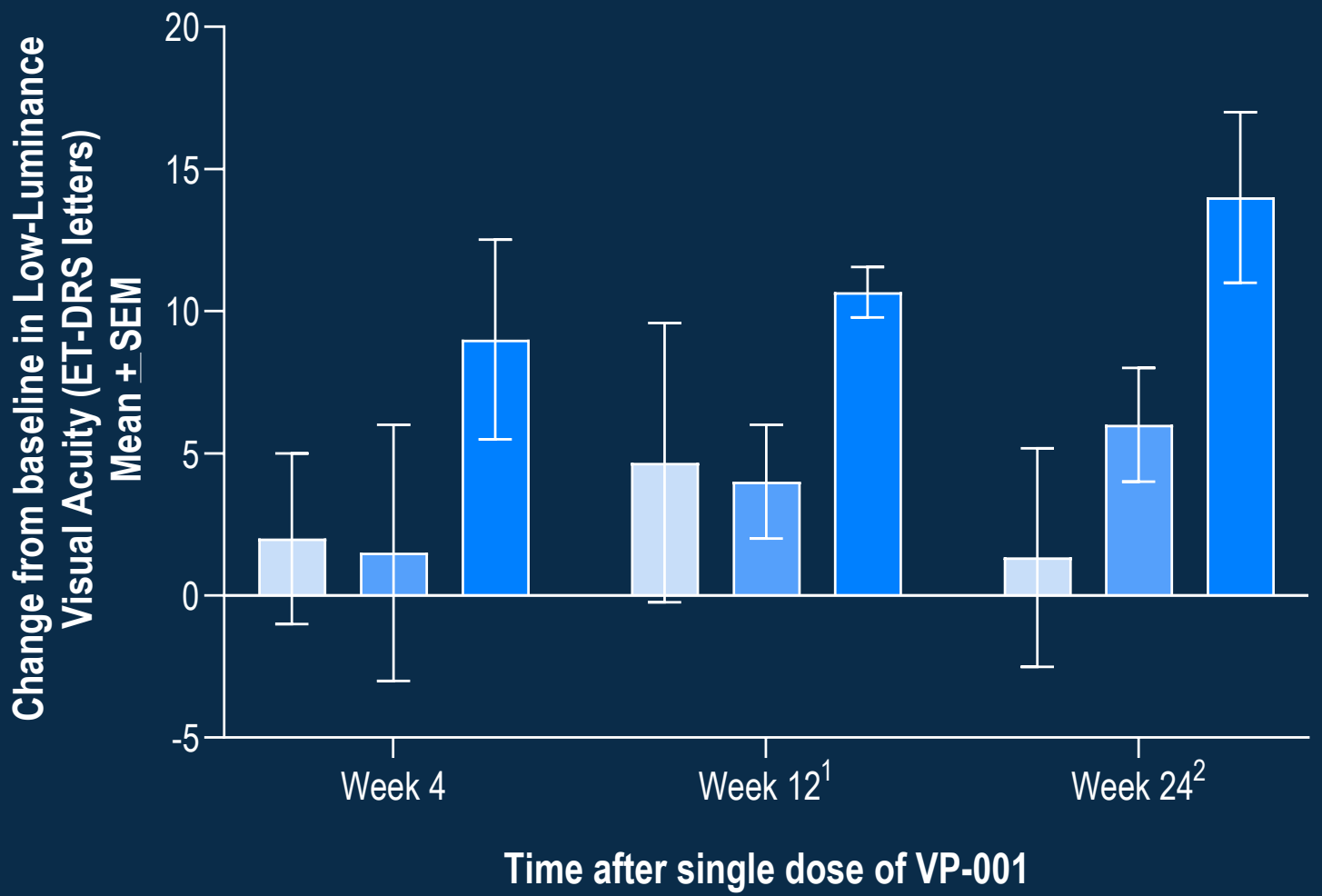
Overview of patient exposure to VP-001 in the Phase 1/2 trials

Study	Cohort	Patient ID	Received repeat doses of ≥ 30 µg VP-001	Number of doses ≥ 30 µg VP-001 patient has received
SAD	3 µg	Patient 1	Yes – patient was eligible for Part B study	2 (first dose was < 30 µg)
SAD	3 µg	Patient 2	Yes – patient was eligible for Part B study	2 (first dose was < 30 µg)
SAD	3 µg	Patient 3	No	n/a
SAD	10 µg	Patient 1	No	n/a
SAD	10 µg	Patient 2	No	n/a
SAD	10 µg	Patient 3	No	n/a
SAD	30 µg	Patient 1	Yes – patient was eligible for Part B study	3
SAD	30 µg	Patient 2	Yes – patient was eligible for Part B study	3
SAD	30 µg	Patient 3	No – patient not eligible for Part B study	1
SAD	75 µg	Patient 1	Yes – patient was eligible for Part B study	3
SAD	75 µg	Patient 2	Yes – patient was eligible for Part B study	3
SAD	75 µg	Patient 3	Yes – patient was eligible for Part B study	3
MAD	30 µg	Patient 1	Yes – patient enrolled in MAD study	3
MAD	30 µg	Patient 2	Yes – patient enrolled in MAD study	3
MAD	30 µg	Patient 3	Yes – patient enrolled in MAD study	3
MAD	75 µg	Patient 1	Yes – patient enrolled in MAD study	3
MAD	75 µg	Patient 2	Yes – patient enrolled in MAD study	3
MAD	75 µg	Patient 3	Yes – patient enrolled in MAD study	1

No treatment emergent-serious adverse events (TE-SAEs)

Safety outcomes	• No Treatment Emergent-Serious Adverse events observed in any subjects dosed with VP-001 to date
	  • Including subjects who received repeat doses of VP-001
	• Treatment-Emergent Adverse Events were mostly mild and/or procedure related
	  • 21/69 (30%) procedure related
	  • 24/69 (35%) non-ocular/systemic
	• Intraocular inflammation has generally not been observed
	  • One subject had rare AC cell (0.5+)
	  • No other reports of inflammation

A dose-dependent improvement in low-luminance visual acuity was observed in the first study of VP-001 for Retinitis Pigmentosa type 11



3µg treated eyes (n=3)
10µg treated eyes (n=2)[3]
30µg treated eyes (n=3)

30 µg identified as minimum dose of VP-001 with therapeutic potential in RP11

1. One patient in 30 µg cohort did not have LLVA assessed at week 12, the Week 16 data from this patient is used.
2. One patient in 30 µg cohort did not have LLVA assessed at Week 24, the Week 28 data from this patient is used.
3. Data not presented for one patient in the 10 µg cohort who had LLVA of 0 at baseline in treated eye.

Transition to therapeutically relevant repeat doses (subsequent data shown will reflect patients treated with multiple 30 or 75 µg doses)

Overview of *PLATYPUS*

Primary Outcome: **Safety & Tolerability**

Single Ascending Dose (SAD) study

- n = 3 patients per cohort
- Patients receive unilateral injection of VP-001
- Patients monitored on outcome measures

Cohort 1 (3 µg)

Cohort 2 (10 µg)

Cohort 3 (30 µg)

Cohort 4 (75 µg)

Minimum dose with therapeutic potential

SAD 'Part B' Extension study

Cohort 3 (30 µg)

Cohort 4 (75 µg)

Outcome measures

- Ocular and non-ocular adverse events (AEs)
- BCVA
- LLVA
- Microperimetry
- Perimetry
- FAF
- SD-OCT

Overview of *WALLABY*

Primary Outcome: **Safety & Tolerability**

Multiple Ascending Dose (MAD) study

Cohort 1 (30 µg)

Cohort 2 (75 µg)

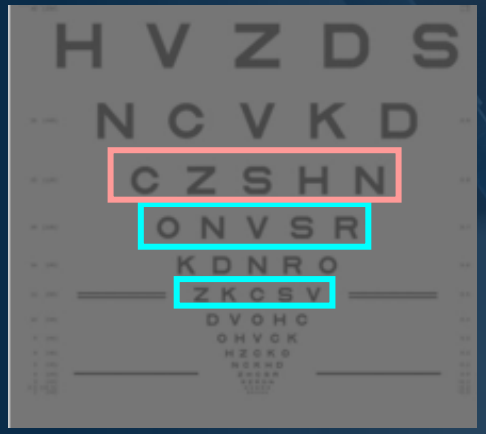
- n = 3 patients per cohort
- Patients receive unilateral VP-001 injection every 2 months
- Repeat injections of both 30 µg and 75 µg has already been confirmed safe and well-tolerated in the ongoing SAD 'Part B extension' study

Improved vision after VP-001 treatment on two registrational endpoints with high impact for patients with RP11

1 Low-Luminance Visual Acuity (LLVA)

LLVA is a more sensitive marker of impaired central vision than BCVA and has been linked to higher experienced disability in Retinitis Pigmentosa[1-3]

IMPROVEMENT



Baseline

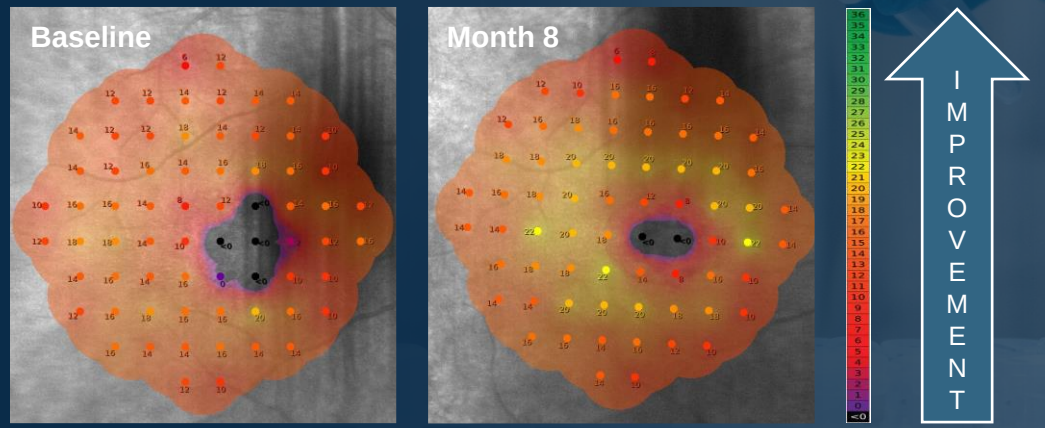
Week 16
(+4 letters in treated eye, n=8)[6]

Week 40
(+13 letters in treated eye, n=2)[6]

2 Microperimetry (MP)

Microperimetry correlates with LLVA and experienced disability in Retinitis Pigmentosa & can detect subtle defects in retinal sensitivity that precede changes in visual acuity[3-5]

Baseline → After VP-001 treatment[7]

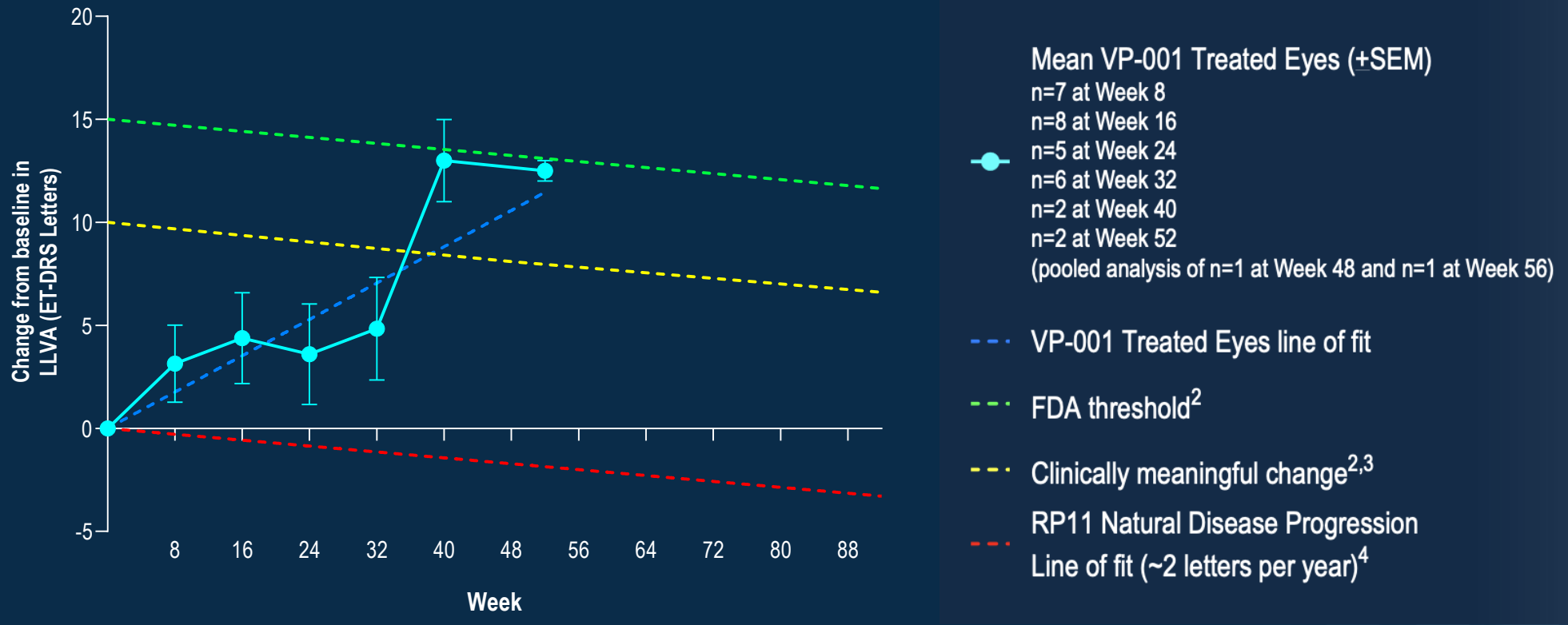


IMPROVEMENT

1. Low Luminance Visual Acuity and Low Luminance Deficit in Choroideremia and RPGR-Associated Retinitis Pigmentosa. (Wood et. al, 2021) doi:10.1167/tvst.10.2.28
2. Endpoints for clinical trials in ophthalmology (Schmetterer et. al, 2023) doi: 10.1016/j.preteyeres.2022.101160
3. Karuntu JS, Nguyen X-T-A, Boon CJF. Mesopic microperimetry is correlated with vision-related quality of life in patients with retinitis pigmentosa. Investigative Ophthalmology & Visual Science. 2023;64(8):4639-.
4. Clinical Perspectives and Trends: Microperimetry as a Trial Endpoint in Retinal Disease (Yang and Dunbar, 2021) doi: 10.1159/000515148
5. Clinical applications of microperimetry in RPGR-related retinitis pigmentosa: a review (Buckley et. al, 2021) doi: 10.1111/aos.14816
6. Image of EDTRS LLVA chart from Taylor LJ, et al. A cross-sectional study to assess the clinical utility of modern visual function assessments in patients with inherited retinal disease: a mixed methods observational study protocol. BMC Ophthalmology. 2023;23(1).
7. Representative depiction of microperimetry – RP11 patients treated with VP-001 have improved retinal sensitivity on multiple endpoints within microperimetry

RP11 patients treated with VP-001 have shown improvements in low-luminance visual acuity within 12 months

VP-001 treated eyes[1] show improvement in LLVA compared to the disease progression observed in the Natural History Study (NHS) of patients with RP11[2,3]



1 LLVA

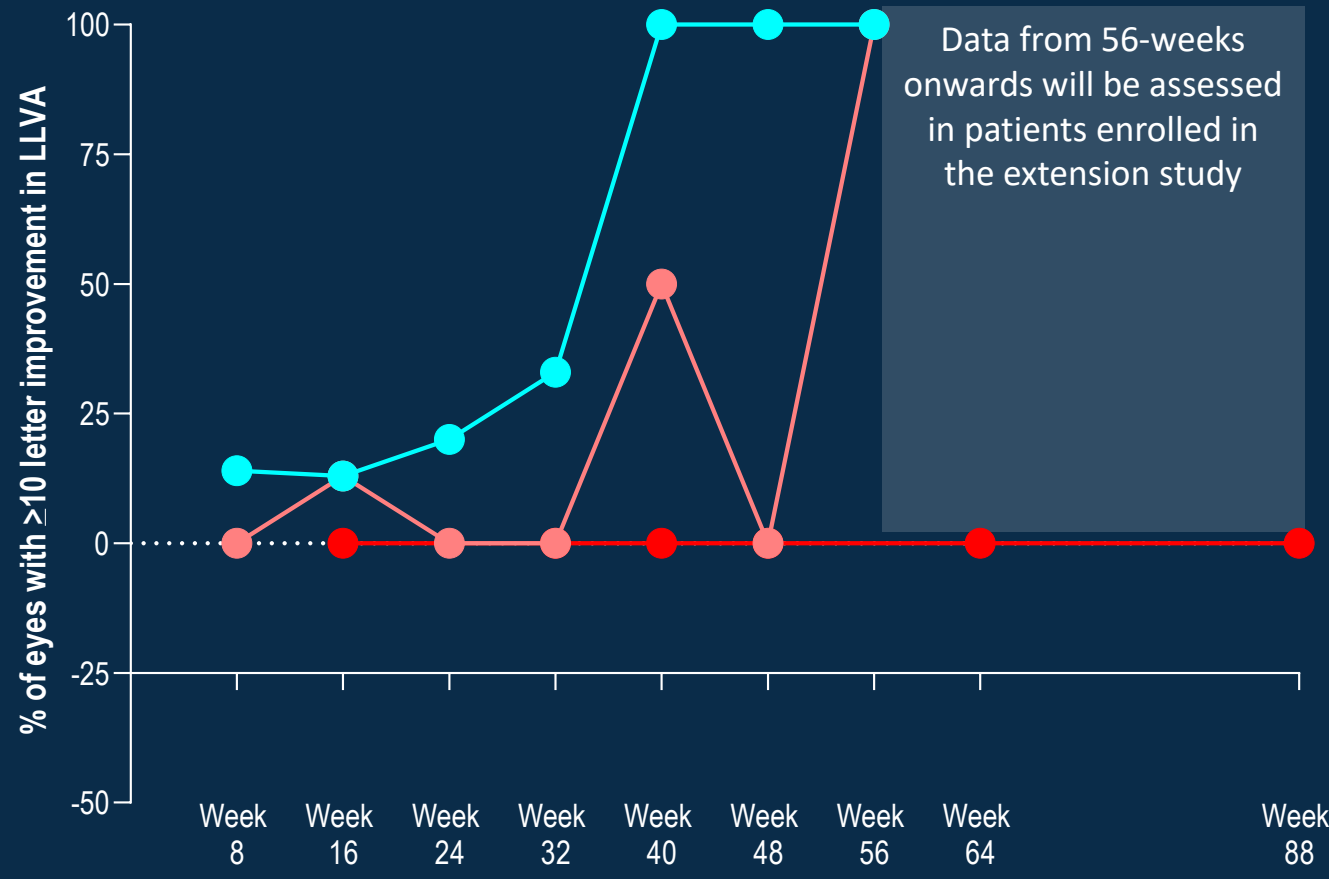
Luxturna treated eyes showed +8.1 letters at Month 12[5] (BCVA)

1. All patient cohorts receiving ≥ 30 mcg of VP-001 as first dose. Analysis of the treated eye of patients enrolled in interventional trial who have received multiple doses of VP-001, with LLVA >0 at baseline who do not have a confirmed mutation in a second RP gene.
2. A >10 letter change in visual acuity is considered clinically meaningful and ≥15 letter change has become a standard outcome measure in clinical trials – See Roy W. Beck MD et al. (2007) Visual acuity as an outcome measure in clinical trials of retinal diseases, Ophthalmology. doi: 10.1016/j.ophtha.2007.06.047
3. Idebenone was approved by the EMA using a clinically relevant benefit definition of ≥10 letter gain of visual acuity for patients with on-chart visual acuity at baseline – see Definition of outcome measures Yu-Wai-Man et al. (2024) Therapeutic benefit of idebenone in patients with Leber hereditary optic neuropathy: The LEROS nonrandomized controlled trial, Cell Reports Medicine. doi: 10.1016/j.xcrm.2024.101437
4. Line of fit of data collected from RP11 patients enrolled in PYC's Natural History Study followed for at least 52 weeks
5. Russell S, Bennett J, Wellman JA, et al. Efficacy and safety of voretigene neparvovec (AAV2-hRPE65v2) in patients with RPE65 mediated inherited retinal dystrophy: a randomised, controlled, open-label, phase 3 trial. Lancet 2017; 390: 849–60.

A greater proportion of RP11 eyes treated with VP-001 show improvement in LLVA compared to untreated eyes

RP11 patients treated with VP-001 have shown improvements in LLVA relative to untreated RP11 Natural History Study subjects

1 LLVA



VP-001 Treated Eyes Interventional Trial[2]

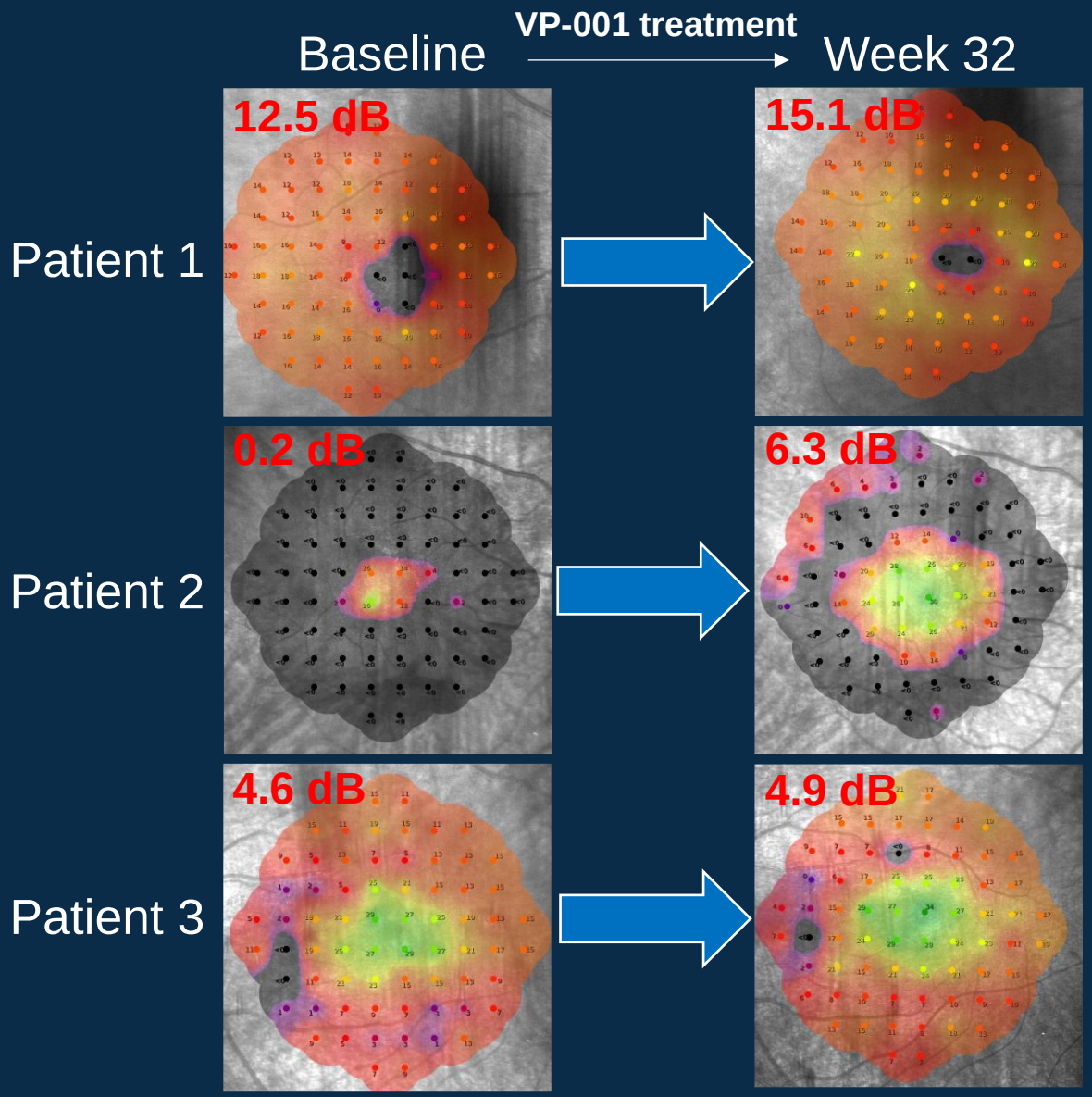
Untreated Eyes Interventional Trial[2]

Untreated Eyes NHS[2]

Timepoint	N of eyes in interventional trial	N of eyes in NHS
Week 8	7	
Week 16	8	10
Week 24	5	
Week 32	6	6
Week 40	2	2
Week 48	1	6
Week 56	1	
Week 64		6
Week 88		4

1. A ≥10 letter change in visual acuity is considered clinically meaningful and ≥15 letter change has become a standard outcome measure in clinical trials – See Roy W. Beck MD et al. (2007) Visual acuity as an outcome measure in clinical trials of retinal diseases, Ophthalmology. doi: 10.1016/j.ophtha.2007.06.047
2. All patient cohorts receiving ≥ 30 mcg of VP-001 as first dose. Analysis of the treated eye of patients enrolled in interventional trial who meet the proposed registrational trial eligibility criteria.

Microperimetry improvements have been observed in VP-001 treated eyes



7 loci improved by ≥7dB

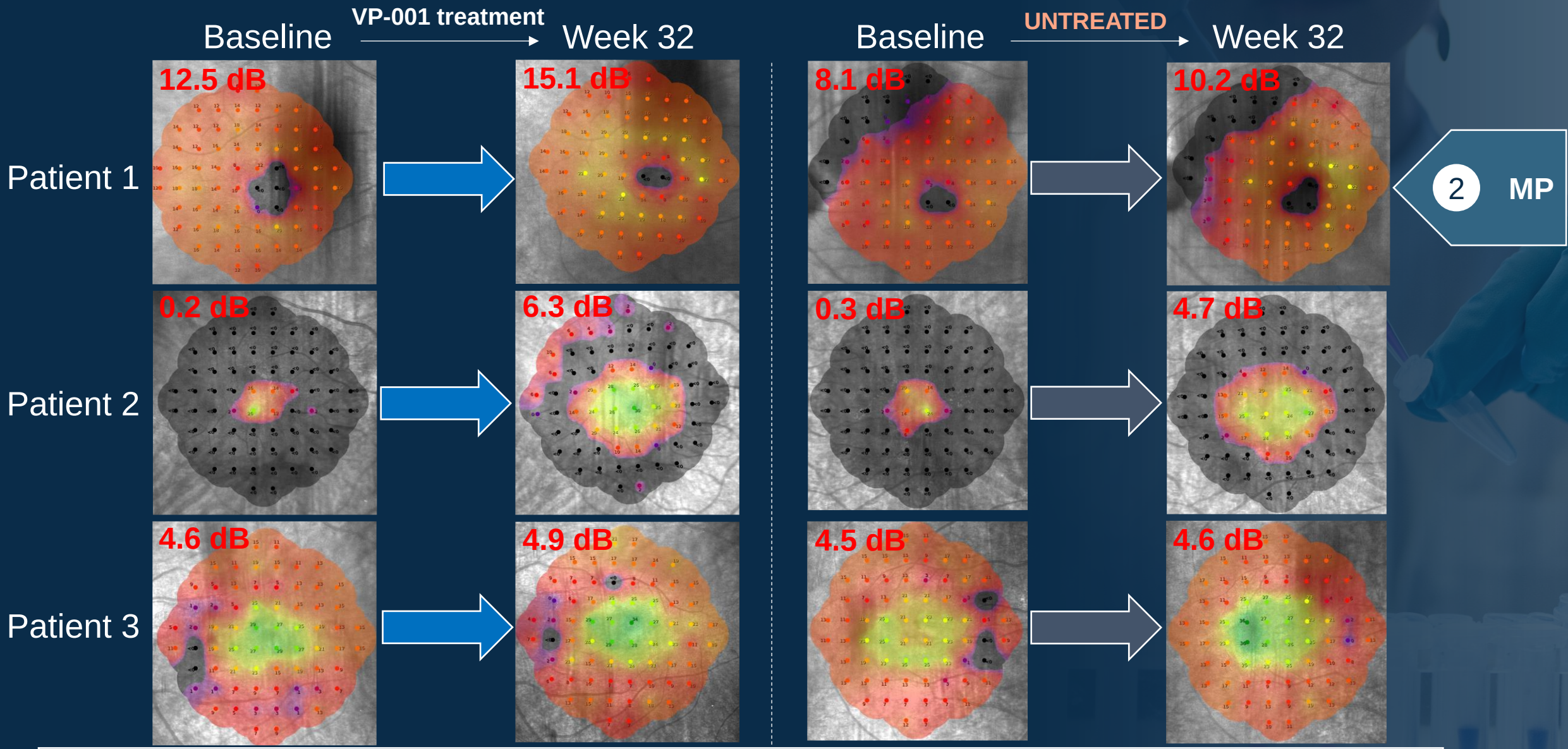
23 loci improved by ≥7dB

12 loci improved by ≥7dB

Mean macular sensitivity (dB) in red

2 MP

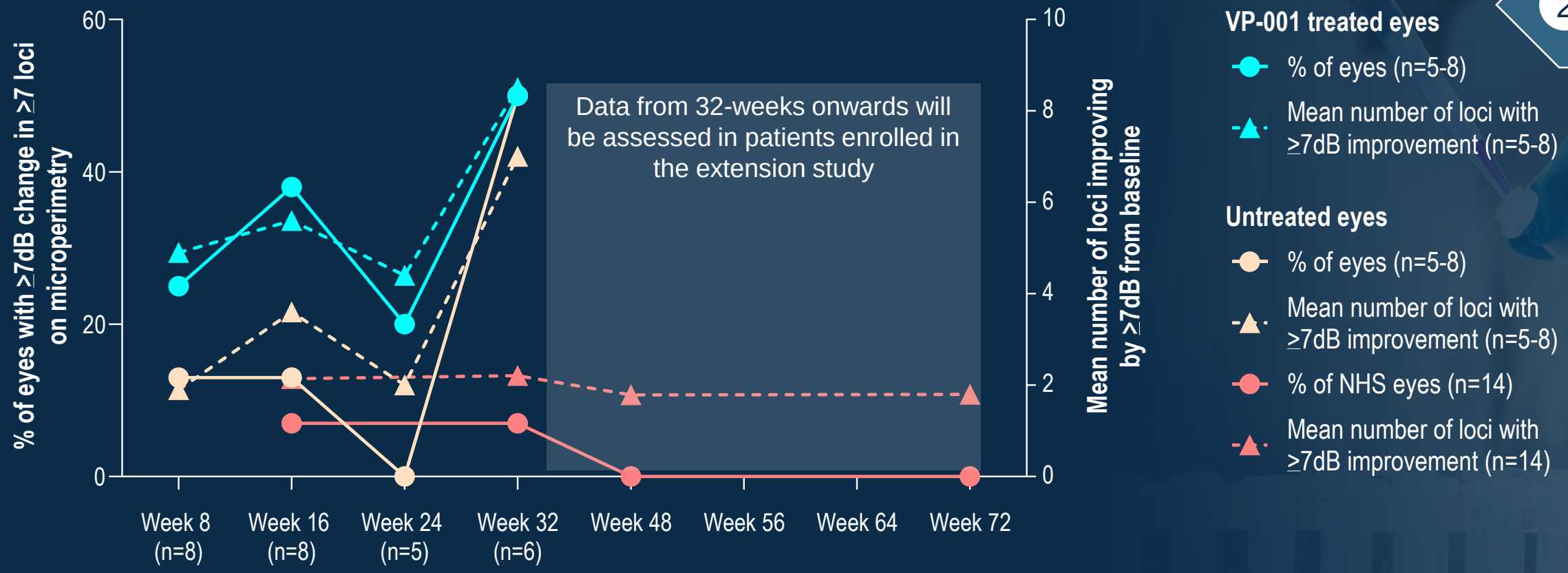
Bilateral improvements in retinal sensitivity following unilateral injection



The phenomenon of **improved visual acuity in untreated contralateral eyes** has been observed in several prior clinical trials and **may be attributed to factors such as visual cortex activation, brain plasticity**, or vector shedding into the contralateral eye (Mol Ther. 2024 Dec 4;32(12):4185-4207. doi: 10.1016/j.ymthe.2024.10.017)

Clinically meaningful improvements in microperimetry have been observed in RP11 patients treated with VP-001[1]

There is a high degree of confidence that it is likely attributable to a genuine treatment effect rather than random chance[2]



2 MP

1. All patient cohorts receiving ≥ 30 mcg of VP-001 as first dose. Analysis of treated and untreated eyes of patients enrolled in interventional trial who meet the proposed registrational eligibility criteria. Data not included if patient fixation was 'unstable' in either eye (n=1 patient not included at Week 16 and Week 48 as fixation stability was unstable in untreated eye). Week 56 data from interventional trial not included as n=1.
2. This threshold ensures that the probability of observing an improvement of ≥7 dB in at least 7 unspecified loci out of the total 68 due to random variability alone is limited to 5% - see Yaghy A, et al. Addressing Multiplicity in Retinal Sensitivity Analysis: An Alternative Approach to Assessing Gene Therapy Efficacy in Inherited Retinal Diseases. Transl Vis Sci Technol. 2025 Mar 3;14(3):25. doi: 10.1167/tvst.14.3.25. PMID: 40146151; PMCID: PMC11954535.

Multiple RP11 patients have reported improved vision and quality of life after treatment with VP-001

- *"For the first time, I've seen airplanes in the sky- it was amazing! When we travel to the national parks and stay in our camper van, now I can get around at dusk by myself in unfamiliar places like new campgrounds. My visual field has widened – I see things in my environment I never was able to see."*

- *"My central vision was clearer… there was less haze. I was amazed!"*
- *"It was actually so clear that my existing eyeglass prescription was too strong for my treated eye thus making things a little distorted. I had an eye exam and got a new lens."*
- *"I honestly think the treatment helps quicker than the decline occurs."*

- *"I had become accustomed to finding my Starbuck's cup by feel… when I only had my left eye open (my non-treated eye), the cup disappeared. When I had only my right eye open (my treated eye), the cup appeared. It is a moment I'll always remember. It is the first moment since being diagnosed, that I felt like it was possible I may be able to see even as I get older… even as my kids grow up."*
- *"The other change is harder to describe. When walking down the hallways at work, there is simply more clarity in a wider range of my right eye. On my right side, I have more breathing room. I can see more."*

1. Comments reflect patient reported outcomes following treatment with VP-001 in an open-label study (meaning they may be subject to a 'placebo-effect' or bias) and communicated to the treating clinician (Principal Investigator) and relayed voluntarily to PYC

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