

PRESENTATION OF CLINICAL PROOF OF CONCEPT IN LEAD PROGRAM

- **PYC is developing a drug candidate (known as VP-001) that addresses the underlying cause of a blinding eye disease of childhood called Retinitis Pigmentosa type 11 for which there are no treatments available**
- **PYC today announces that data from ongoing Phase 1/2 clinical trials of this drug candidate will be presented at international scientific conferences in May¹ highlighting that treatment with VP-001:**
 - **Is associated with statistically significant improvements in vision on a registrational endpoint²;**
 - **Has led to clinically meaningful gains in visual acuity³ and improved quality of life as reported by multiple patients enrolled in the ongoing clinical trials⁴; and**
 - **Is safe and well-tolerated with no treatment or procedure-related serious adverse events reported in any patient who has received the drug candidate to date**
- **The differentiation of this data set across both safety and efficacy dimensions⁵ highlights the utility of PYC's proprietary platform technology in the treatment of blinding eye diseases**
- **PYC will meet with the US Food and Drug Administration (FDA) on 6 June 2025 to align on the pathway to a New Drug Application for VP-001⁶**

PERTH, Australia and SAN FRANCISCO, California – 28 April 2025

PYC Therapeutics Limited (ASX:PYC) (**PYC** or the **Company**) is a precision medicine Company dedicated to changing the lives of patients with genetic diseases who have no treatment options available.

The Company currently has three clinical-stage drug development programs including a drug candidate (known as VP-001) that addresses the underlying cause of a blinding eye disease of childhood called Retinitis Pigmentosa type 11 (RP11). PYC today announces that VP-001 has demonstrated a favourable risk-benefit profile in ongoing open-label Phase

¹ Data from the ongoing clinical trials will be presented at the Foundation Fighting Blindness Retinal Therapeutics Innovation Summit on 2 May and at the Association for Research in Vision and Ophthalmology annual conference 4-8 May 2025

² As measured by Low Luminance Visual Acuity. See Figures 1 and 2 for more detail. Visual acuity assessment is an acceptable primary endpoint for a registrational trial in a blinding eye disease in the US, EU, UK and Japan.

³ See Figure 1 for more detail

⁴ Further details on these patient reported outcomes are available in the body of this announcement

⁵ See Figure 5 for more detail

⁶ Subject to the risks and uncertainties outlined in the Company's ASX disclosures of 17 February 2025

1/2 studies in patients with RP11 and that data supporting progression of the drug candidate into registrational trials will be presented at:

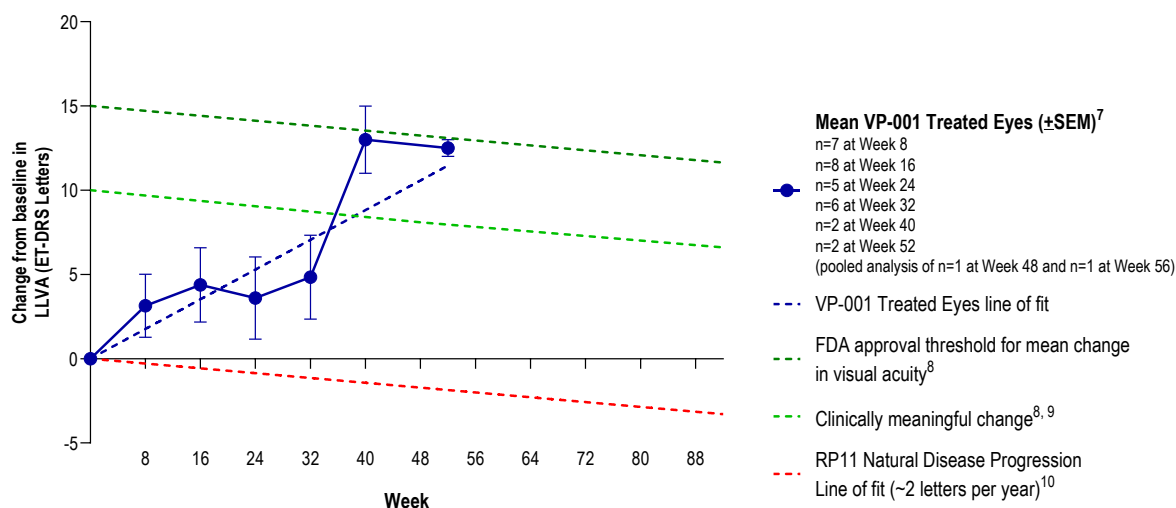
- The Foundation Fighting Blindness Retinal Therapeutics Innovation Summit in Salt Lake City, Utah on 2 May 2025; and
- The Association for Research in Vision and Ophthalmology (ARVO) Conference also in Salt Lake City, Utah on 4-8 May 2025.

Efficacy

RP11 patients enrolled in the Phase 1/2 studies who have received VP-001 have demonstrated clinically-meaningful and statistically significant improvements in vision in the treated eye (when compared to both the untreated 'fellow' eye and natural history studies of the disease course in patients with RP11) as assessed by multiple registrational endpoints including:

- Low Luminance Visual Acuity (LLVA) (See Figures 1, 2, 3 and 6); and
- Microperimetry (See Figures 4, 5 and 6)

Figure 1a. Mean change from baseline in LLVA in VP-001 treated eyes (dark blue lines) compared to untreated RP11 eyes (red dashed line) from PYC's ongoing Natural History Study (NHS)^{7,8,9,10}. The changes from baseline observed in patients who have passed 40 weeks of follow up from their first dose of VP-001 have surpassed the 10-letter improvement considered to be clinically meaningful (equating to the ability to read two additional lines on the Early Treatment Diabetic Retinopathy Study (ET-DRS) visual acuity assessment chart).



⁷ 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 ≥ 30 mcg VP-001, with LLVA >0 at baseline who do not have a confirmed mutation in a second RP gene. All data available as of 22 April 2025.

⁸ 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

⁹ Idefenone 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 Idefenone in patients with Leber hereditary optic neuropathy: The LEROS nonrandomized controlled trial, Cell Reports Medicine. doi: 10.1016/j.xcrm.2024.101437

¹⁰ Line of fit of data collected from RP11 patients enrolled in PYC's Natural History Study followed for at least 52 weeks

The increase in visual acuity observed following treatment with VP-001 has reached statistical significance when compared to both the untreated fellow eye ($p < 0.002$) (See Figure 2) and the natural history of RP11 disease progression ($p < 0.0001$) (See Figure 3).

Figure 1b. Illustration of the magnitude of visual acuity improvement observed in Figure 1a from a standardised baseline (every 5 letters of improved visual acuity gained by patients equates to the ability to read an additional line on the ET-DRS eye chart)

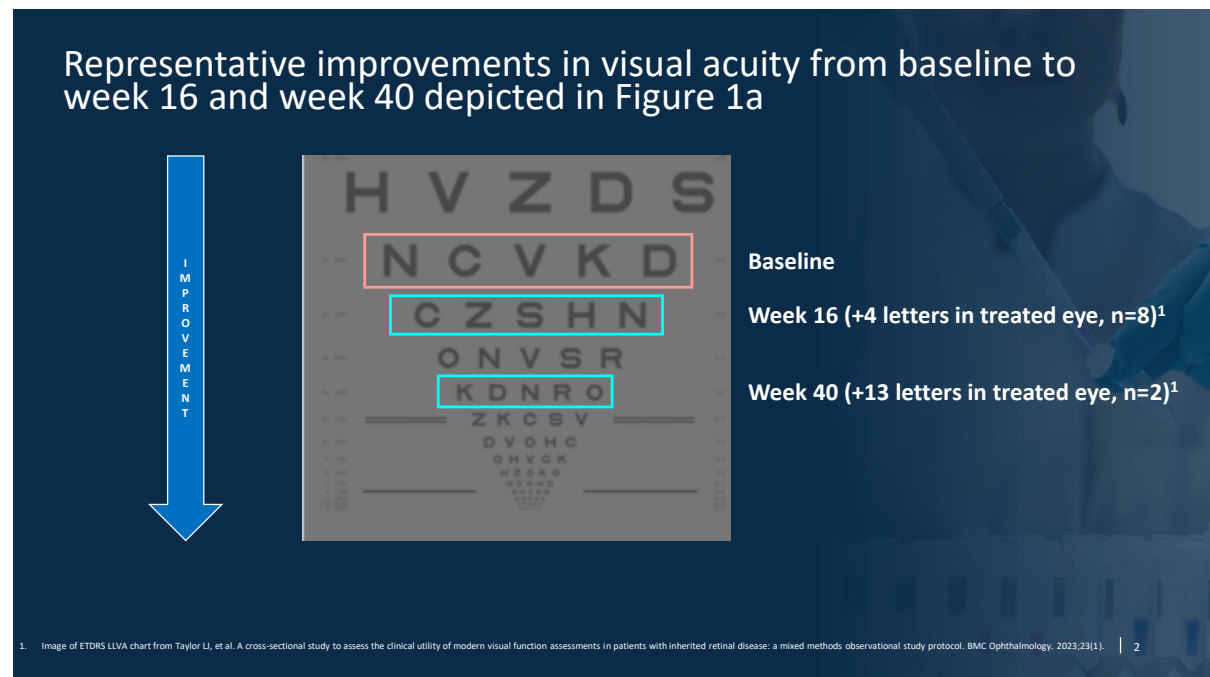
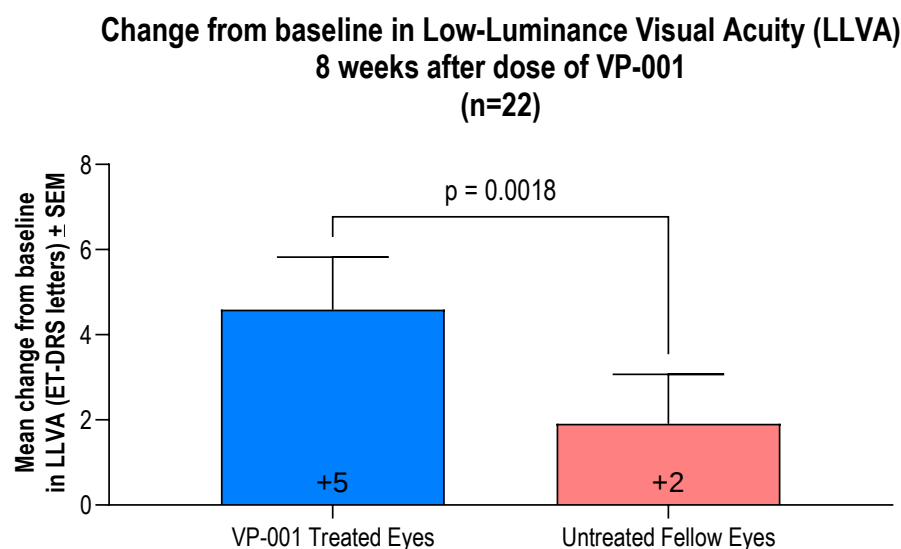


Figure 2. Comparison of mean change from baseline in VP-001 treated eyes (+5 letters) with untreated fellow eyes (+2 letters) at 8-weeks¹¹ following each dose of VP-001 as assessed by LLVA.

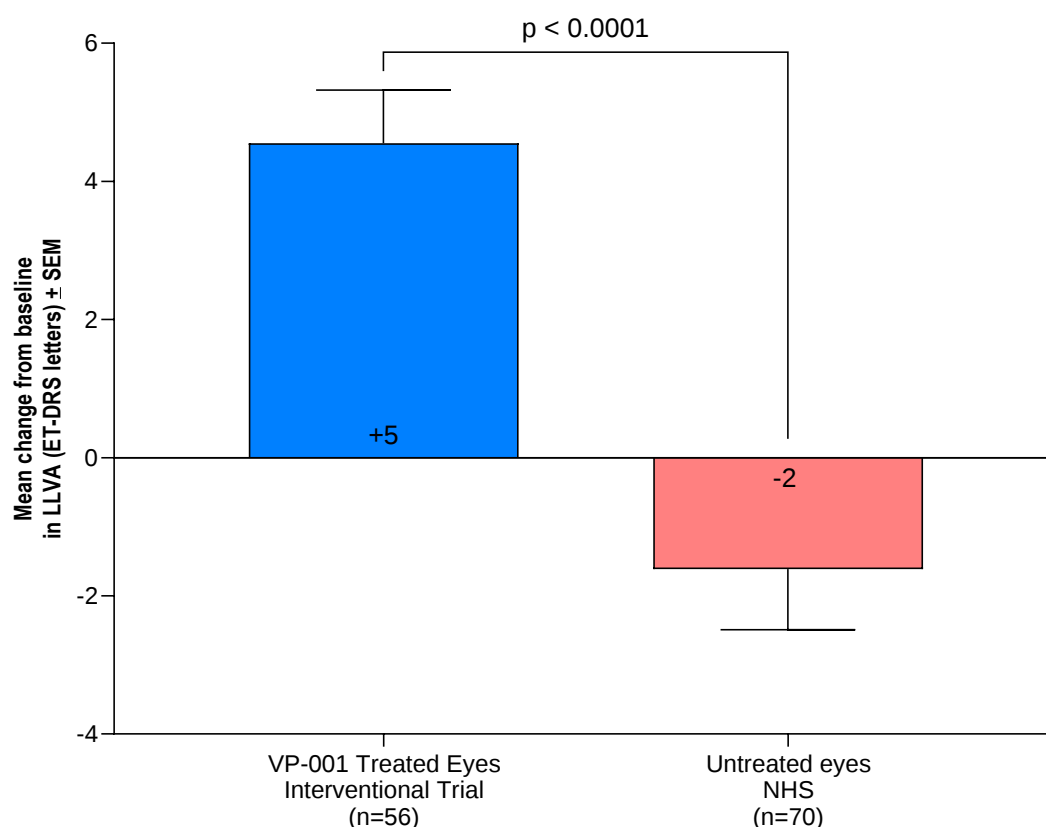


¹¹ All patient cohorts receiving ≥ 30 mcg of VP-001 as first dose. Analysis of the treated eye of patients enrolled in interventional trial who have received multiple doses of ≥ 30 mcg VP-001, with LLVA > 0 at baseline who do not have a confirmed mutation in a second RP gene. All data available as of 22 April 2025. One patient did not have LLVA assessed at 8 weeks after first dose of VP-001. The Week 12 data for this patient is used. P-value represents two-sided paired-test comparing change from baseline in treated eye to untreated eye (n=22 pairs)

The improvement in visual acuity in the untreated fellow eye has been observed in other ophthalmology trials involving the treatment of a single eye with an effective therapeutic¹². The natural history of RP11 disease progression is considered the more appropriate comparative benchmark for evaluating the impact of VP-001 (See Figure 3).

Figure 3. Comparison of mean change from baseline in VP-001 treated eyes (+5 letters) with untreated eyes (-2 letters) from the Natural History Studies in patients with RP11 as assessed by LLVA across all timepoints available in both studies¹³.

Change from baseline in Low-Luminance Visual Acuity (LLVA) in RP11 eyes treated with VP-001 compared to untreated eyes from PYC's natural history study (NHS)



In addition to the improvements in functional vision assessed by LLVA, patients treated with 30 micrograms or more of VP-001 also have improved visual function as measured by microperimetry (See Figures 4, 5, 6, 7, 8 and 9). These improvements compare favourably with other precision therapies for different forms of inherited retinal disease (See Figure 5).

¹² See, for example Hanhart, J., Tiosano, L., Averbukh, E. et al. Fellow eye effect of unilateral intravitreal bevacizumab injection in eyes with diabetic macular edema. Eye 28, 646–653 (2014). <https://doi.org/10.1038/eye.2014.94>

¹³ P-value represents two-sided unpaired t-test comparing mean change from baseline in treated eyes to untreated eyes in the natural history study across all timepoints

Figure 4. Microperimetry results demonstrating enhanced retinal sensitivity in an RP11 patient eye treated with VP-001¹⁴

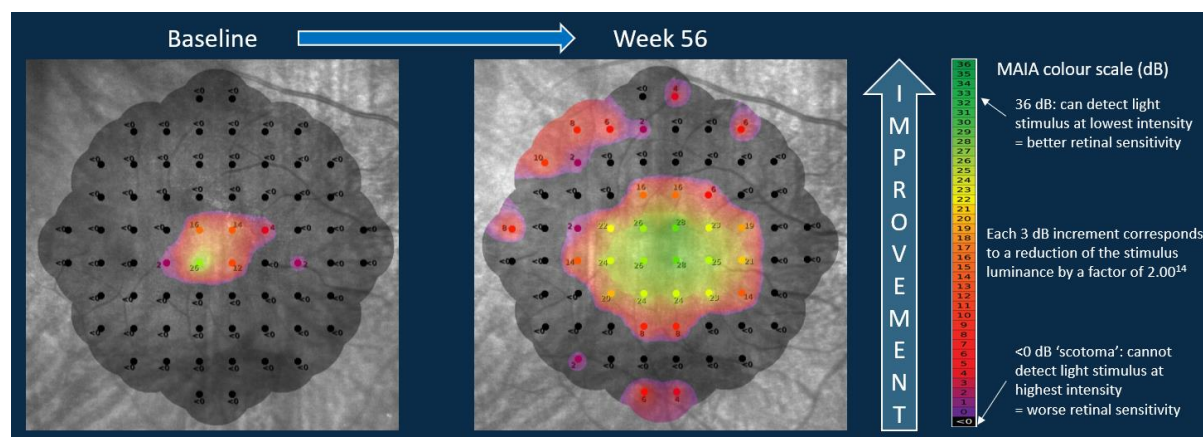
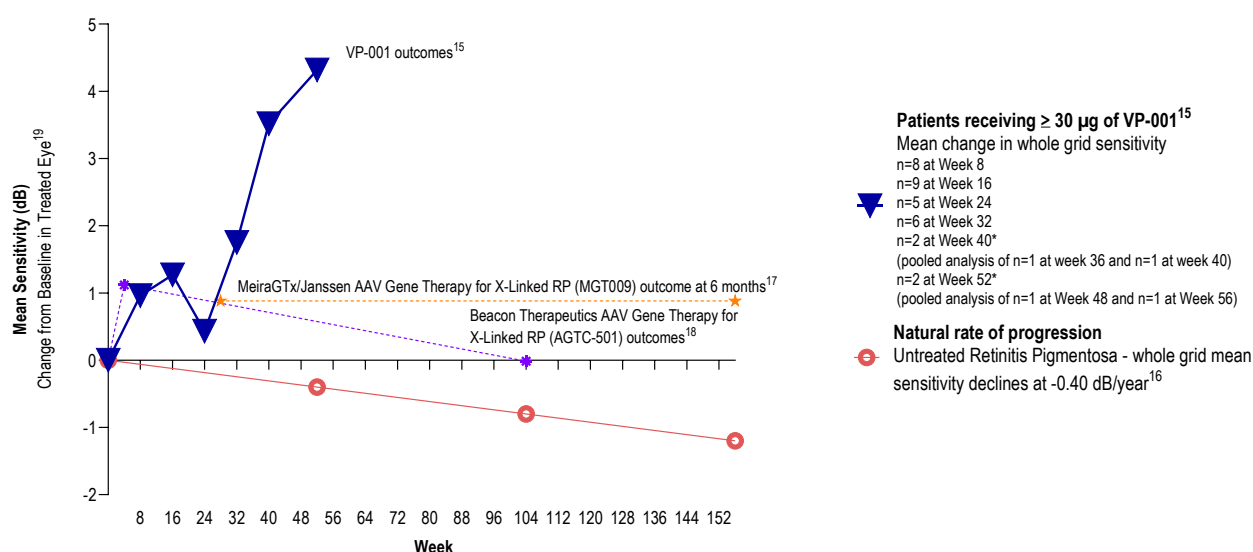


Figure 5. Mean change from baseline in retinal sensitivity in VP-001 treated eyes as assessed by microperimetry^{15,16,17,18,19}. A 3dB improvement in sensitivity on microperimetry equates to a 2-fold enhancement of the ability of the retina to detect light²⁰.



¹⁴ Section 2.1.1.1 from Pfau et. al. Fundus controlled perimetry (microperimetry): Application as outcome measure in clinical trials in Progress in Retinal and Eye Research. Volume 82, May 2021, 100907

¹⁵ All patient cohorts receiving $\geq 30 \text{ mcg}$ 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 who do not have a confirmed mutation in a second RP gene. All data available as of 22 April 2025.

¹⁶ Iftikhar M, Kherani S, Kaur R, Lemus M, Nefalar A, Usmani B, et al. Progression of Retinitis Pigmentosa as Measured on Microperimetry: The PREP-1 Study. Ophthalmol Retina. 2018;2(5):502-7.

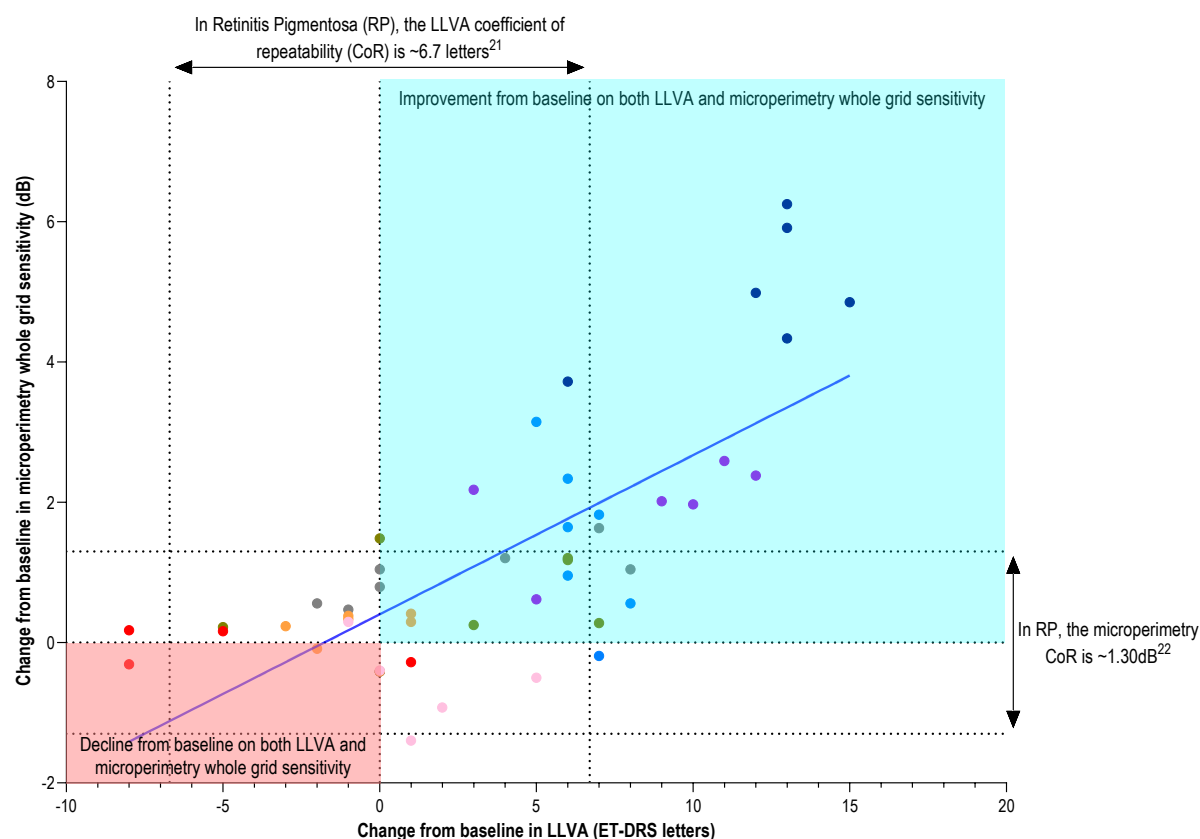
¹⁷ Ph1/2 AAV5-RPGR (Botaretigene Sparaparvovec) Gene Therapy Trial in RPGR-associated X-linked Retinitis Pigmentosa (XLRP) – Michaelides, ARVO 2022

¹⁸ Analysis of centrally dosed patients who received a dose that was deemed to be 'tolerated' (mean of n=7 patients receiving $2.24 \times 10^{11} \text{ vg/eye}$ and n=7 patients receiving $6.8 \times 10^{11} \text{ vg/eye}$) – see Yang P, et al. Subretinal Gene Therapy Drug AGTC-501 for XLRP Phase 1/2 Multicenter Study (HORIZON): 24-Month Safety and Efficacy Results. Am J Ophthalmol. 2025 Mar;271:268-285. doi: 10.1016/j.ajo.2024.11.021

¹⁹ Microperimetry under mesopic or scotopic conditions

²⁰ Section 2.1.1.1 from Pfau et. al. Fundus controlled perimetry (microperimetry): Application as outcome measure in clinical trials in Progress in Retinal and Eye Research. Volume 82, May 2021, 100907

Figure 6. Change from baseline in LLVA and microperimetry mean whole grid sensitivity in RP11 eyes treated with VP-001^{21,22,23}



Patient Impact

Two patients who have enrolled in the clinical trials of VP-001 were invited by their Principal Investigator to give feedback in relation to their lived experience following treatment with the drug candidate. A third patient voluntarily shared their experience following treatment with their Principal Investigator. Highlights from the feedback provided by each of the three patients is included below:

Patient 1

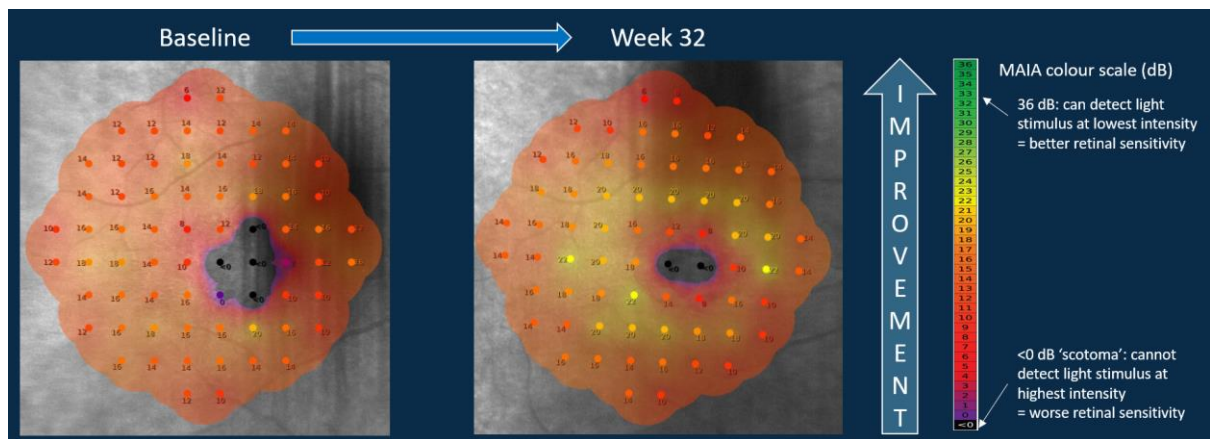
"I noticed I could actually see the white lid of the [coffee] cup. When I only had my left eye open (my non-treated eye), the cup disappeared. When I only had my right eye open (my treated eye), the cup appeared. It is a moment I'll always remember. It is the first moment, since being diagnosed as a college student, that I felt like it was possible that I may be able to see even as I get older. Even as my kids grow up."

Figure 7. Microperimetry outcomes at baseline and week 32 for this patient

²¹ Scatter plot showing change from baseline in Low-Luminance Visual Acuity (LLVA) on the x-axis against change from baseline in retinal sensitivity (microperimetry whole grid) for all patients who received 30 mcg or more of VP-001 (as their first dose) and who meet the proposed registrational trial eligibility criteria. All data available as at 22 April 2025 (n=49 pairs of data where LLVA and microperimetry both are available for the treated eye across n=8 patients, colour coded by patient). Line shows Pearson correlation $r = 0.73$, $p < 0.0001$.

²² Wood LJ, Jolly JK, Josan AS, Buckley TMW, MacLaren RE. Low Luminance Visual Acuity and Low Luminance Deficit in Choroideremia and RPGR-Associated Retinitis Pigmentosa. *Transl Vis Sci Technol.* 2021 Feb 5;10(2):28. doi: 10.1167/tvst.10.2.28. PMID: 34003913; PMCID: PMC7900861.

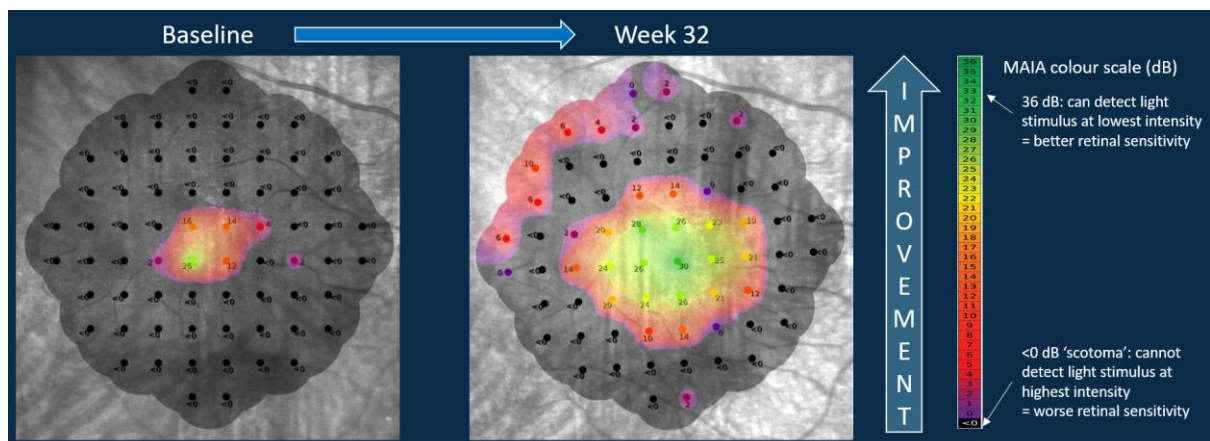
²³ Buckley, T.M.W., Jolly, J.K., Menghini, M., Wood, L.J., Nanda, A. and MacLaren, R.E. (2020), Test-retest repeatability of microperimetry in patients with retinitis pigmentosa caused by mutations in RPGR. *Clin Experiment Ophthalmol*, 48: 714-715. <https://doi.org/10.1111/ceo.13753>



Patient 2

"My central vision was clearer... there was less haze. 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. After the 2nd injection of Phase B, I could see really well! I was amazed!!!... The treated eye was leaps and bounds better than my untreated eye. I honestly think the treatment helps quicker than the decline occurs, if that makes sense. This is the first treatment for my mutation and to know it works yet I'm unable to obtain it on a regular basis fills me with sadness. My untreated eye is falling behind and I can only hope by the time VP-001 is readily available, I still have enough useful vision left to be able to treat positively."

Figure 8. Microperimetry outcomes at baseline and week 32 for this patient

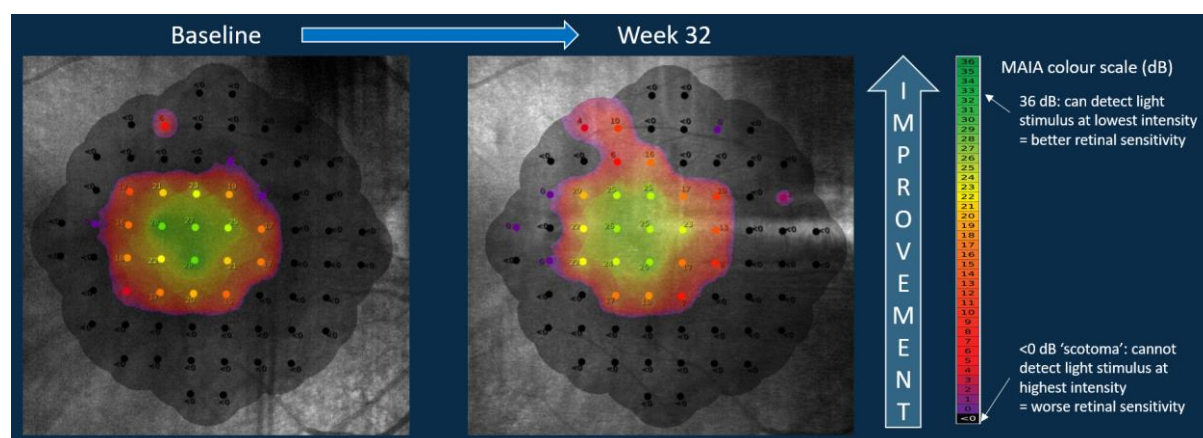


Patient 3

The third patient feedback was provided voluntarily by the Principal Investigator relaying the patient's experience:

"She now sees airplanes in the sky (never had before), stars at night, animals/creatures along the road and on their hikes frequently. She got up to walk out from her most recent visit here and forgot her cane because she just doesn't need it as much anymore. The stories go on."

Figure 9. Microperimetry outcomes at baseline and week 32 for this patient



PYC's Chief of Research and Development, Dr. Sri Mudumba, commented on the data: *"We are particularly encouraged by the strong alignment between the biological mechanism of action and the observed clinical benefit. This translational effect is further supported by the positive feedback from patients treated with VP-001, many of whom have reported meaningful improvements in daily visual function."*

Safety/Tolerability

There have been no reported treatment-related or procedure-related serious adverse events in any patient who has received VP-001 to date. This safety/tolerability profile differentiates PYC's proprietary RNA technology from other precision medicine modalities used to treat blinding eye diseases and creates optionality for the Company to expand the use of its platform technology into other areas of major unmet need within ophthalmology.

Presentation Materials

Copies of the presentation materials for both the Foundation Fighting Blindness Retinal Therapeutics Innovation Summit and ARVO conference will be made available on the Company's website.

Next steps

PYC will meet with the FDA on 6 June 2025 to align on a registrational study design for VP-001 in RP11. The objective of the planned registrational studies is to support a New Drug Application for VP-001 which, if successful, will mark the first approved treatment option for patients with this blinding eye disease of childhood. VP-001 has received multiple FDA special designations intended to accelerate and support the path to approval (including Fast Track Designation, Orphan Drug Designation, and Rare Pediatric Disease Designation)^{6,24}.

About PYC Therapeutics

PYC Therapeutics (ASX: PYC) is a clinical-stage biotechnology company creating a new generation of RNA therapies to change the lives of patients with genetic diseases. The Company utilises its proprietary drug delivery platform to enhance the potency of precision

²⁴ Refer ASX Announcements 2 August 2023, 21 October 2024 and 24 May 2024

medicines within the rapidly growing and commercially proven RNA therapeutic class. PYC's drug development programs target monogenic diseases – **the indications with the highest likelihood of success in clinical development**²⁵.

For more information, visit pyctx.com, or follow us on LinkedIn and Twitter.

Forward looking statements

Any forward-looking statements in this ASX announcement have been prepared on the basis of a number of assumptions which may prove incorrect and the current intentions, plans, expectations, and beliefs about future events are subject to risks, uncertainties and other factors, many of which are outside the Company's control. Important factors that could cause actual results to differ materially from assumptions or expectations expressed or implied in this ASX announcement include known and unknown risks. Because actual results could differ materially to assumptions made and the Company's current intentions, plans, expectations, and beliefs about the future, you are urged to view all forward-looking statements contained in this ASX announcement with caution. The Company undertakes no obligation to publicly update any forward-looking statement whether as a result of new information, future events or otherwise.

This ASX announcement should not be relied on as a recommendation or forecast by the Company. Nothing in this ASX announcement should be construed as either an offer to sell or a solicitation of an offer to buy or sell shares in any jurisdiction.

This ASX announcement was approved and authorised for release by the Board of PYC Therapeutics Limited

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²⁵ Advancing Human Genetics Research and Drug Discovery through Exome Sequencing of the UK Biobank <https://doi.org/10.1101/2020.11.02.20222232>