PYC Therapeutics

Life-changing science

Q3 Investor Update

30 August 2024

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Today's topics

- **Introduction to PYC**

- **Industry trends**
  - RNA therapies continue to feature as a major emerging therapeutic modality

- **PYC's progress**
  - PYC's RNA therapeutic pipeline is progressing well with all programs set to deliver a meaningful milestone in 2024[1]:
    - RP type 11 – human safety and efficacy data; **Deep dive today**
    - Optic Atrophy – human safety data;
    - Polycystic Kidney Disease – full pre-clinical data pack and regulatory submission to enable 'first in human' studies to commence; and
    - Phelan-McDermid Syndrome – nomination of a clinical candidate.

1. Based on management forecasts as at 21 August 2024 and subject to all of the risks outlined in the company's ASX filings

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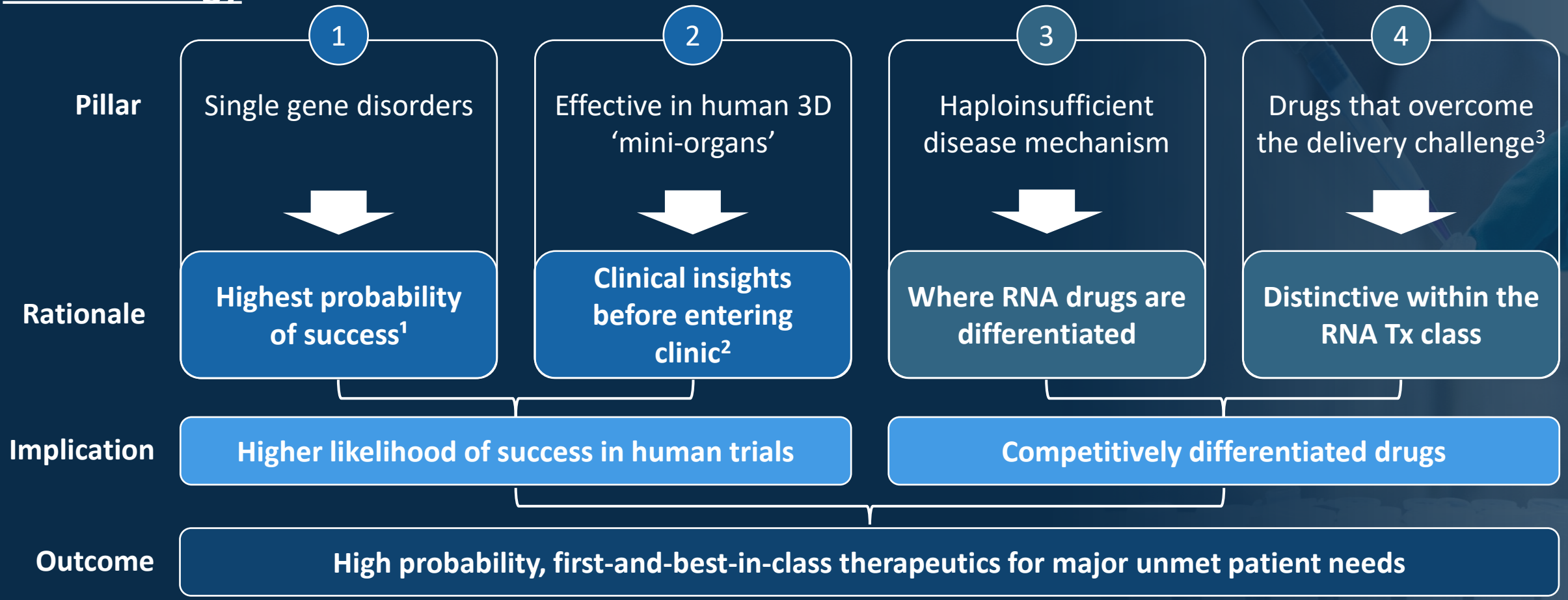
Introduction to PYC

PYC discovers and develops new drugs for patients who have severe diseases and no treatment options available.

The Company is specifically interested in the creation of precision therapies that address the underlying cause of diseases driven by a single genetic mutation.

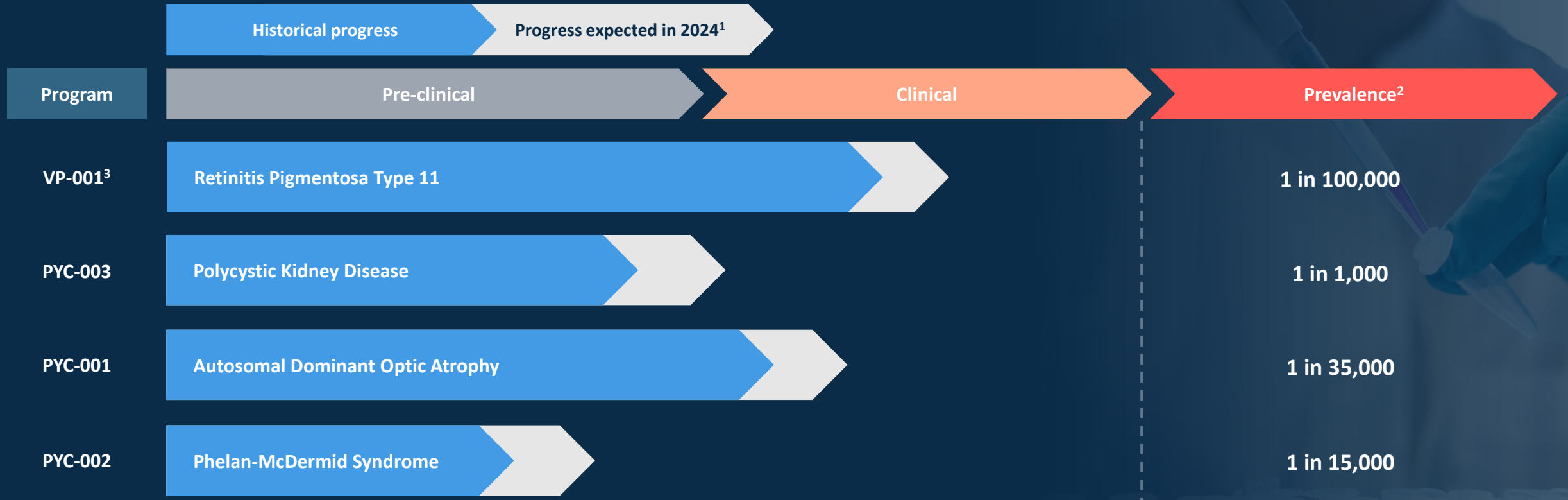
PYC has carefully selected the domain in which it operates

PYC's strategy



1. Advancing Human Genetics Research and Drug Discovery through Exome Sequencing of the UK Biobank. doi: 10.1101/2020.11.02.20222232
2. Endpoints News 4 May 2023 Roche doubles down on organoids, human model systems with new research institute
3. Refer ASX announcement 3 October 2022 for PYC OTS Poster Presentation

PYC has built a pipeline of first-in-class drug candidates with disease-modifying potential



1. Based on management's latest estimates accurate as at 4 July 2024 and subject to successful realisation of developmental milestones in each program as well as satisfaction of regulatory requirements and subject to all other risks customary to an early-clinical stage biotechnology company developing novel drug candidates
2. See references in Company presentation of 14 March 2024 for source material on prevalence by indication
3. PYC 96.2% ownership of VP-001 (3.8% ownership by Lions Eye Institute, Australia) and 100% ownership of all other pipeline programs

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Industry trends

PYC applies its RNA technology in the context of 'rare' single-gene disorders

"Across the genetics landscape, the winners will be those who prioritize the right conditions for treatment – and who have the capacity to carry through implementation"

"With some 6,000 so-called monogenic diseases, where a single gene is the cause, the potential applications are huge"[1]

1. Endpoints News 15 May 2023 Gene Editing Technology's $50 Billion Market Opportunity

Rare disease is becoming more attractive for drug developers

"Keeney cited regulators' growing willingness to consider surrogate endpoints for rare diseases as bolstering the larger business model for developing these drugs"[1]

1. FierceBiotech 5 March 2024 After tough rightsizing, Biogen looks to newer rare diseases to broaden lens

“RNA is now leading the market with stellar clinical results and outstanding long-term potential[1]”

1. Stifel Biopharma Market Update 12 August 2024

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PYC's pipeline progress and RP11 deep dive

The focus of today's discussion is the immediate future in RP11

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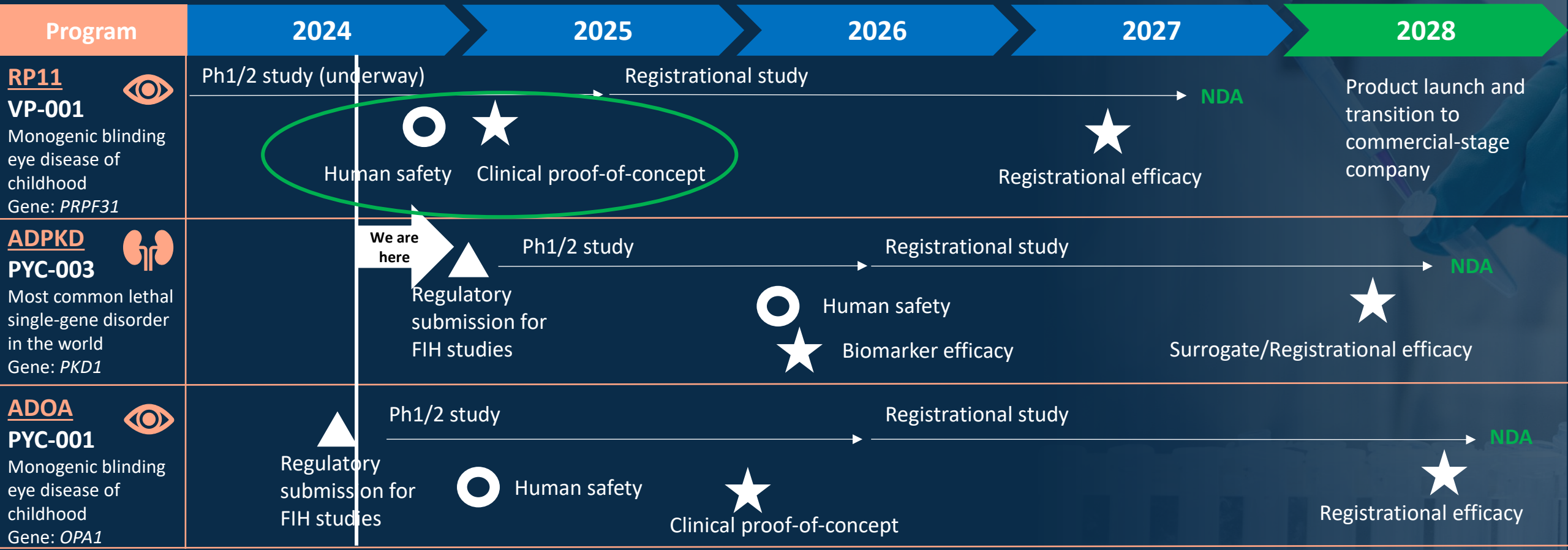
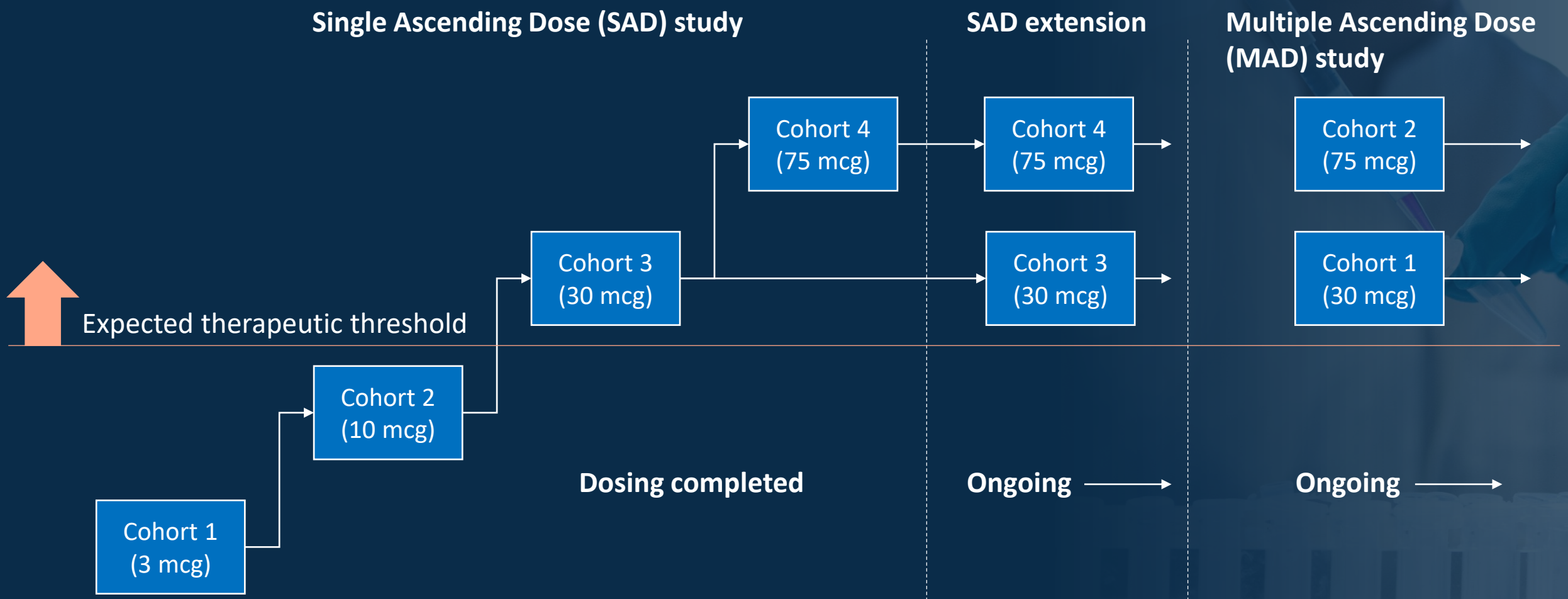
PYC's path to market is staged with human data read-outs for first-in-class drugs with disease-modifying potential[1]



1. Based on management forecasts as at 4 May 2024 and subject to all of the risks outlined in the company's ASX filings

PYC's RP11 program is progressing through two concurrent multiple dose studies



1. See ASX announcements of 10 July and 23 July 2024

Objectives

- Introduce the relevant efficacy endpoints in the SAD and MAD studies
- State the results observed to date
- Provide context on why these are relevant and what we are looking for in the ongoing repeat dose studies[1]

1. Based on management forecasts as at 21 August 2024 and subject to all of the risks outlined in the company's ASX filings

PYC's Retinitis Pigmentosa Type 11 program has the potential to be the first approved therapy in this indication[1]

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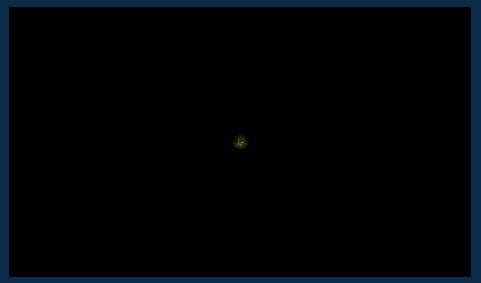
Degenerative sight of an RP11 patient

6 YEARS OLD

26 YEARS OLD

46 YEARS OLD



Retinitis Pigmentosa (RP)[2,3]

- A severe and progressive blinding eye disease that begins in childhood
- Affects 1 in every 3,500 people (RP11 accounts for ~3% of RP)
- Patients experience night blindness followed by tunnel vision and ultimately legal blindness
- There are no treatments available for patients with RP type 11 nor are there any in clinical development

1. Subject to the risks and uncertainties described in the Company's ASX disclosures of 14 March 2024
2. Daiger S et al. 'Genes and Mutations Causing Autosomal Dominant Retinitis Pigmentosa' Cold Spring Harb. Perspect. Med. 5 (2014)
3. Ellingford J et al. 'Molecular findings from 537 individuals with inherited retinal disease' J Med Genet 53, 761-776 (2016)

What is microperimetry and why are we interested in it as an endpoint in the RP11 trials?

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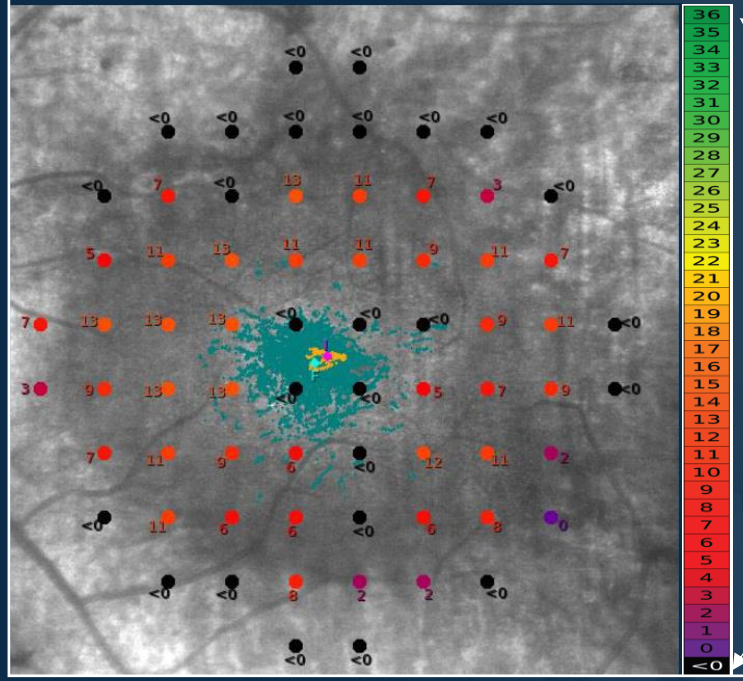
Microperimetry has been used extensively to characterise functional vision in a wide range of retinal conditions, often detecting subtle defects in retinal sensitivity that precede visual acuity loss and tracking disease progression over relatively short periods of time[1,2]

The Retinitis Pigmentosa field has consolidated around microperimetry as a critical endpoint in human trials[1,2]

- Microperimetry (MP) is distinguished from conventional visual field assessment by its ability to display and track a live fundus image during an examination, whilst adjusting for fixational eye movements.
- This provides assurance that threshold sensitivity values correspond to specific retinal locations.
- Diseases affecting the macula can result in unstable and/or eccentric fixation, making MP an attractive tool in their assessment.
- Additionally, characteristics of fixation may change during disease progression and MP devices are able to quantify and track these changes.

Example microperimetry image



MAIA colour scale (dB)

36 dB: can detect light stimulus at lowest intensity = better retinal sensitivity

Each 1 dB increment corresponds to a reduction of the stimulus luminance by a factor of 1.26[3]

<0 dB 'scotoma': cannot detect light stimulus at highest intensity = worse retinal sensitivity

1. Clinical Perspectives and Trends: Microperimetry as a Trial Endpoint in Retinal Disease (Yang and Dunbar, 2021) doi: 10.1159/000515148
2. Clinical applications of microperimetry in RPGR-related retinitis pigmentosa: a review (Buckley et. al, 2021) doi: 10.1111/aos.14816
3. Section 2.1.1 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

How do we monitor progression using microperimetry over time?

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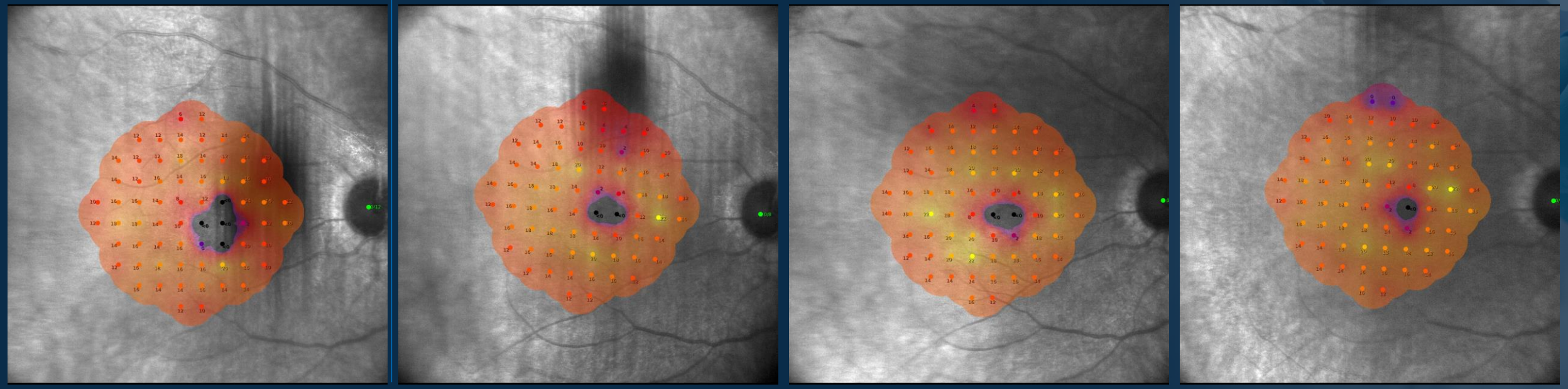
Post single 30 µg treatment with PYC's drug candidate

Baseline | **Week 4** | **Week 8** | **Week 16**



Multiple patients in PYC's ongoing Single Ascending Dose study have improved visual function after a single dose of PYC's investigational drug candidate for a progressive and irreversible blinding eye disease, including:

- Enhanced whole grid retinal sensitivity;
- Enhanced sensitivity of functional transition points; and
- A decreased number of scotomas[1].

1. See ASX announcements of 5 August and 12 August 2024

How can microperimetry be used as a registrational endpoint?

The FDA has issued guidance on the use of microperimetry as a registrational endpoint[1-3]

1) Continuous outcomes (slopes)
   Clinically relevant difference in slope of mean sensitivity of a pre-defined area*
   (i.e., a slope analysis showing a progressive separation between treatment and control groups over time)

2) Binary outcomes (proportion with change)
   At least 5 pre-defined grid points with a mean improvement of $\geq$ 7dB improvement maintained for at least 2 timepoint (i.e., the percentage (%) of eyes in which the mean of all pre-specified points changed by $\geq$ 7 dB)

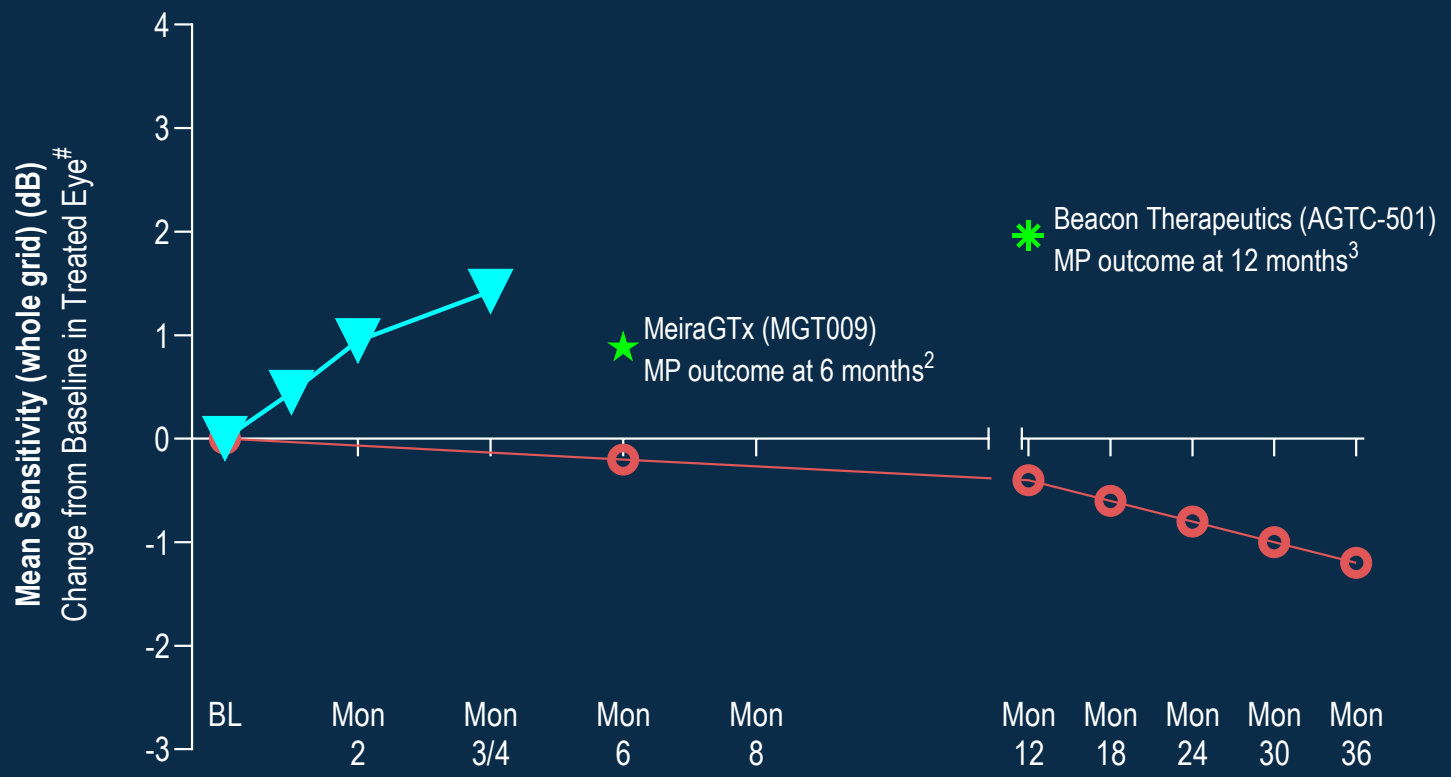
*This may be the entire retinal sensitivity grid or pre-defined points

1. Yang Y, Dunbar H. Clinical Perspectives and Trends: Microperimetry as a Trial Endpoint in Retinal Disease. Ophthalmologica. 2021;244(5):418-450. doi: 10.1159/000515148. Epub 2021 Feb 10.
2. Birch DG, et al. Overcoming the Challenges to Clinical Development of X-Linked Retinitis Pigmentosa Therapies: Proceedings of an Expert Panel. Transl Vis Sci Technol. 2023;12(6):5.
3. Foundation Fighting Blindness – Clinical Consortium

What do the results from the SAD show?

Improved retinal function following treatment with VP-001

Retinal sensitivity as assessed by microperimetry (MP) in SAD cohort 3 and 4 patients over time



Microperimetry under mesopic or scotopic conditions
Patient 2 of clinically relevant dose cohort 1 (SAD cohort 3) did not have microperimetry assessment at Month 2.
Patient 3 of clinically relevant dose cohort 1 (SAD cohort 3) did not have a microperimetry assessment at Month 2, 3 or 4.

1. 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.
2. Ph1/2 AAV5-RPGR (Botaretigene Sparoparvovec) Gene Therapy Trial in RPGR-associated X-linked Retinitis Pigmentosa (XLRP) – Michaelides, ARVO 2022
3. Subretinal gene therapy AGTC-501 for X-linked retinitis pigmentosa in the Phase 1/2 Horizon study: Post-hoc analysis of microperimetry results in the high dose groups – Birch, ARVO 2024

What have other companies seen in Phase 1/2 trials in other forms of Retinitis Pigmentosa?

	PYC Therapeutics VP-001	MeiraGTx – J&J MGT009	Beacon Therapeutics AGTC-501
Disease (*causative gene*)	Retinitis Pigmentosa (*PRPF31*)	X-linked Retinitis Pigmentosa (*RPGR*)	
Efficacy in patient-derived retinal organoids	Yes	Yes[2]	n/a
Efficacy in patients supporting pivotal trial	Early data[1]	Yes	Yes
Mean retinal sensitivity change from baseline in treated eye (microperimetry)#	1.42 (Month 3/4)*	0.88 (Month 6)[3]**	1.96 (Month 12)[4]^
Route of administration	Intravitreal	Subretinal	Subretinal
Serious adverse events observed	No	Yes[3]	Yes[5]
Able to be repeat dosed	Yes	No	No
Status	Multiple dose studies underway	Acquired by J&J after completion of a Phase 1/2 trial[6]	Pivotal trial underway[7]

Microperimetry under mesopic or scotopic conditions
*Pooled analysis of the Month 4 results from SAD cohort 3 and Month 3 results from SAD cohort 4
**Pooled analysis of low and intermediate dose cohorts
^Analysis of centrally dosed patients who met Phase 3 sensitivity criteria from the high dose cohort

1. See ASX announcements of 5 and 12 August 2024
2. AAV-RPGR Gene Therapy for RPGR-Associated X-Linked Retinitis Pigmentosa (XLRP): Human retinal organoid vector efficacy data poster presentation - P. Sladen et al., ARVO 2024
3. Ph1/2 AAV5-RPGR (Botaretigene Sparoparvovec) Gene Therapy Trial in RPGR-associated X-linked Retinitis Pigmentosa (XLRP) – Michaelides, ARVO 2022
4. Subretinal gene therapy AGTC-501 for X-linked retinitis pigmentosa in the Phase 1/2 Horizon study: Post-hoc analysis of microperimetry results in the high dose groups – Birch, ARVO 2024
5. Subretinal AGTC-501 Gene Therapy for XLRP: 12-Month Interim Safety & Efficacy Results of the Phase 2 SKYLINE Trial – Penessi, 2024
6. FierceBiotech 21 December 2023 MeiraGTx gifts remaining gene therapy rights to J&J for up to $415M
7. FierceBiotech 3 July 2024 Beacon attracts $170M series B to push eye disease gene therapy through late-stage trial

What other endpoints might we consider for the registrational study?

Microperimetry correlates with Low Luminance Visual Acuity (LLVA) and experienced disability in Retinitis Pigmentosa

- Patients with Retinitis Pigmentosa show a more pronounced visual acuity deficit at low luminance[1]
- Lower luminance deficit correlates with microperimetry retinal sensitivity in RP[2]
- Lower visual acuity in low luminance has been linked to higher experienced disability in clinically advanced Retinitis Pigmentosa patients[3]
- Previous trials in Retinitis Pigmentosa have established a correlation between improvements in central retinal sensitivity and LLVA[4]

1. Alexander KR, Derlacki DJ, Fishman GA, et al. Acuity-luminance and foveal increment threshold functions in retinitis pigmentosa. Investig Ophthalmol Vis Sci. 1991;32:1446–1454.
2. Wood LJ, et al. 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.
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. Lam BL, Pennesi ME, Kay CN, Panda S, Gow JA, Zhao G, et al. Assessment of Visual Function with Cotoretigene Toliparvovec in X-Linked Retinitis Pigmentosa in the Randomized XIRIUS Phase 2/3 Study. Ophthalmology. 2024.

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Q&A