



Life-changing
science

April Investor Update

April 2021

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Who's on today's call

PYC US Development and Corporate Hub

Sahm Nasser, Chief Executive Officer US 



Extensive experience in commercial drug development with Merck, incl. product leadership, investor relations and business development. Consultant with McKinsey & Co prior to Merck.

Dr Glenn Noronha, Chief Development Officer 



Over 20 years leading drug development programs in ophthalmology, oncology, CNS and GI; 6 retina programs spanning candidate nomination through clinical development and approval. Previous C-suite & leadership roles at BridgeBio, Clearside and Alcon

Kaggen Ausma, Chief Business Officer 



Previous roles in McKinsey & Co across Strategy, Commercial, VC and PE, and public market finance with CLSA Asia-Pacific

PYC Australia Discovery Hub

Professor Sue Fletcher, Chief Scientific Officer 



Leading global expert and pioneer in RNA therapeutics. Co-inventor of Exondys-51, Vyondys-53, and Amondys-45, commercialised by Sarepta. Prof. Fletcher leads PYC's discovery team and is the co-inventor of VP-001

Dr Rohan Hockings, Chief Executive Officer Australia 



Experience across both clinical and commercial roles including Private Equity, Commercial Law, and Strategy, prior to joining PYC

PYC's focus is exploiting our distinctive PPMO technology

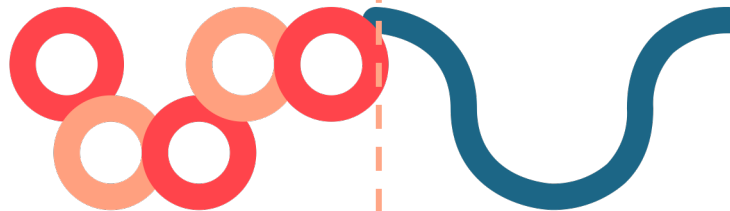
Cell Penetrating Peptide

Naturally-derived

Sequence diversity

Screened upfront for efficacy and safety

Enable preferential delivery to target tissues and cells



PMO (Phosphorodiamidate Morpholino Oligomer)

Latest generation ASO, neutral (uncharged)

Precision and flexibility

Safer profile

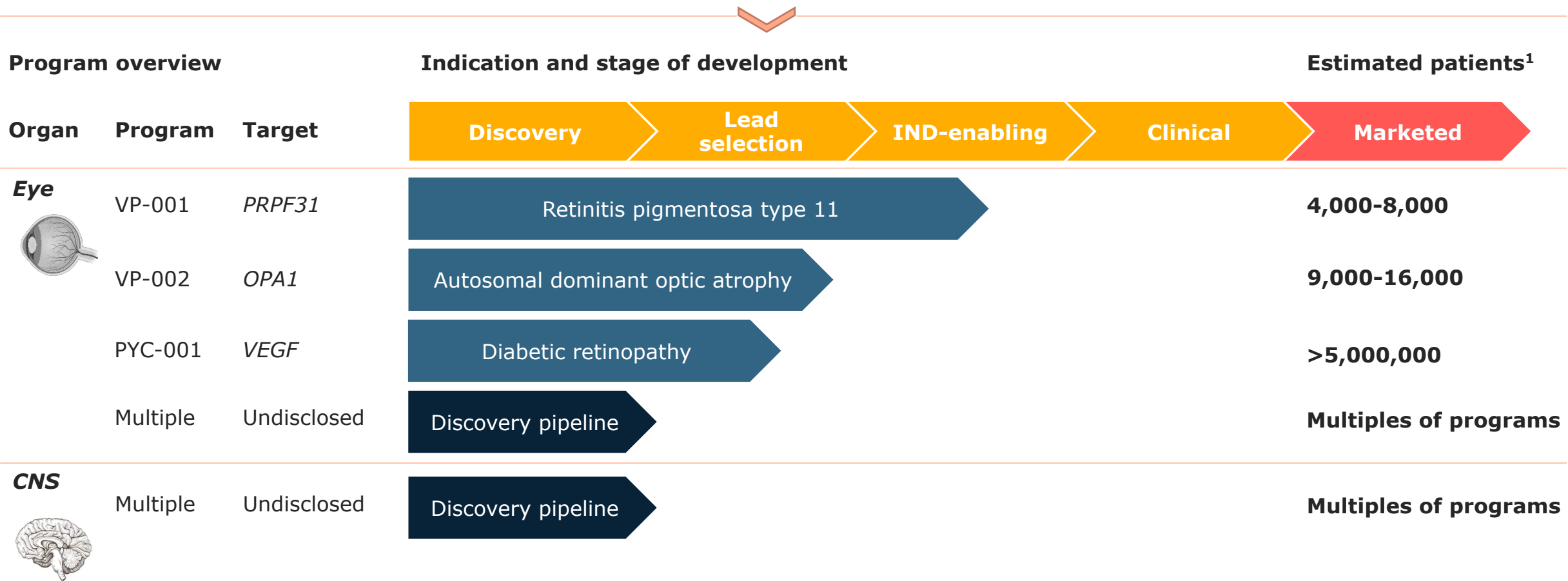
Durable profile

Flexible and precise RNA therapeutic molecule with potential for broader therapeutic window, longer duration of effect and application to a range of tissue and cell types

PYC is applying our technology to create life-changing treatments, with an initial focus on diseases of the eye



PYC is a multi-asset drug development company



PYC has 100% ownership of PYC-001 and 90% ownership of VP-001 and VP-002 (10% ownership by Lions Eye Institute, Australia)

¹ See ASX announcement 'Technical Presentation - October 2020' dated 9 October 2020; National Eye Institute (US) prevalence estimates for Diabetic Retinopathy ; see Nasca A, et al. 'Not only dominant, not only optic atrophy: expanding the clinical spectrum associated with OPA1 mutations.' *Orphanet J Rare Dis.* 2017 May 12;12(1):89

PYC has pushed our technology further than ever before in 2020



Demonstrated the effectiveness of PYC's lead program, VP-001, in gold-standard pre-clinical models for Retinitis pigmentosa type 11



Expanded PYC's drug pipeline to 3 development candidates, demonstrating the scalability of PYC's PPMO platform across high value indications



Executed a \$41M capital raise to set the foundation for development across multiple candidates and build out US operations to enable near and medium term objectives



Initiated build of PYC's US-base with the appointment of Sahm Nasser as PYC US CEO

2021 is a pivotal year for PYC as we progress multiple candidates towards clinical development

Execute



- VP-001 through large animal studies in mid-2021 paving the way for IND submission in first half of 2022
- VP-002 for ADOA proof-of-concept and preclinical efficacy readouts
- PYC-001 for DR to proof-of-concept readouts

Establish



- Establish US management team
- Build US preclinical and clinical development capabilities
- Appoint US based and industry experienced Board Directors
- Engage with US capital markets and drive corporate development

Expand



- Expand Ocular pipeline towards additional development programs
- Showcase distinctive delivery of PPMO into the Central Nervous System (CNS)
- Identify first CNS development program for important neurodegenerative disease

We are making good progress towards our critical 2021 deliverables

Execute



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Expand

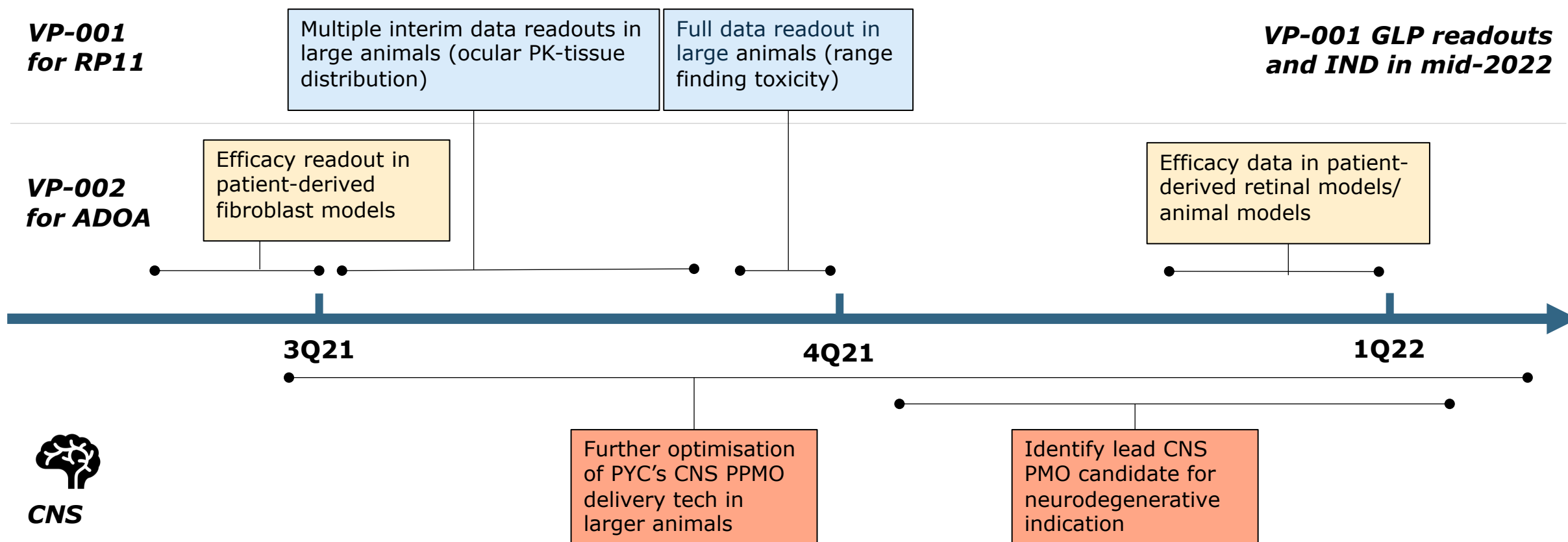


- ☐ Expand Ocular pipeline towards additional development programs
- ☒ Showcase distinctive delivery of PPMO into the Central Nervous System (CNS)
- ☐ Identify first CNS development program for important neurodegenerative disease

We are looking forward to numerous critical value inflection points throughout 2021

VP-001 for Retinitis pigmentosa type 11

VP-002 for Autosomal Dominant Optic Atrophy



Ocular

- **Proof of concept data for PYC-001** for Diabetic Retinopathy in 2021
- Anticipate **development of further ocular drug candidates** leveraging the de-risked ocular PPMO platform



VP-001 for the treatment of Retinitis pigmentosa type 11

Matthew, living with RP11

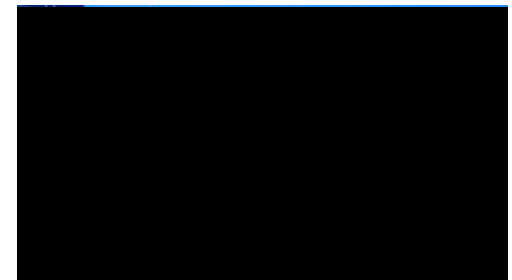
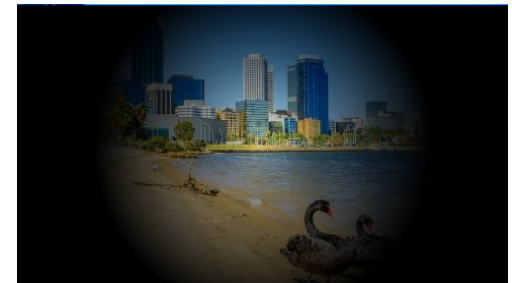
VP-001 for Retinitis pigmentosa type 11

Retinitis pigmentosa (RP) is a genetic, blinding eye disease

- Retinitis pigmentosa type 11 (RP11) is a form of RP caused by mutation in the *PRPF31* gene
 - **Severe, progressive blinding eye disease**
 - Onset between the ages of 10 and 20
 - Patients experience manifestations of rod cone dystrophy including night blindness progression to tunnel vision losing peripheral vision
 - Progressive loss of visual function and functional vision eventually leading to blindness between 40-50 years of age
- There is **no treatment for patients with RP11**

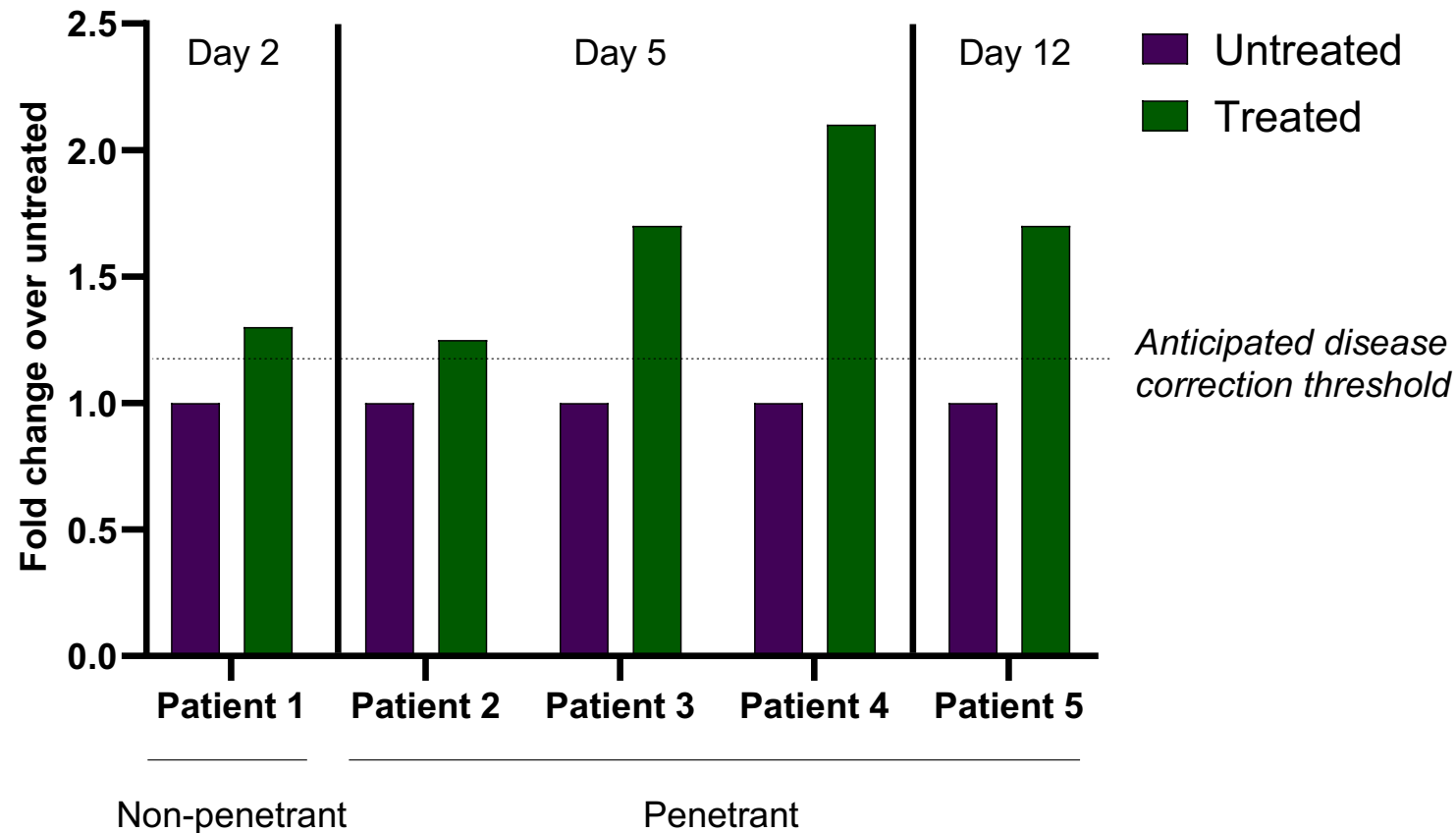
By tackling the molecular issue, VP-001 has the potential to be transformational to patients

- **4,000-8,000** patients in the western world
- Unmet need with no other drugs in clinical development; VP-001 has the potential to be first in class and best in class for the treatment of RP11



VP-001's core goal is to increase levels of PRPF31 protein

PRPF31 protein levels, RPE, 5 μ M treatment, (n=1 per patient)



Increasing PRPF31 levels has improved function in the gold-standard pre-clinical models

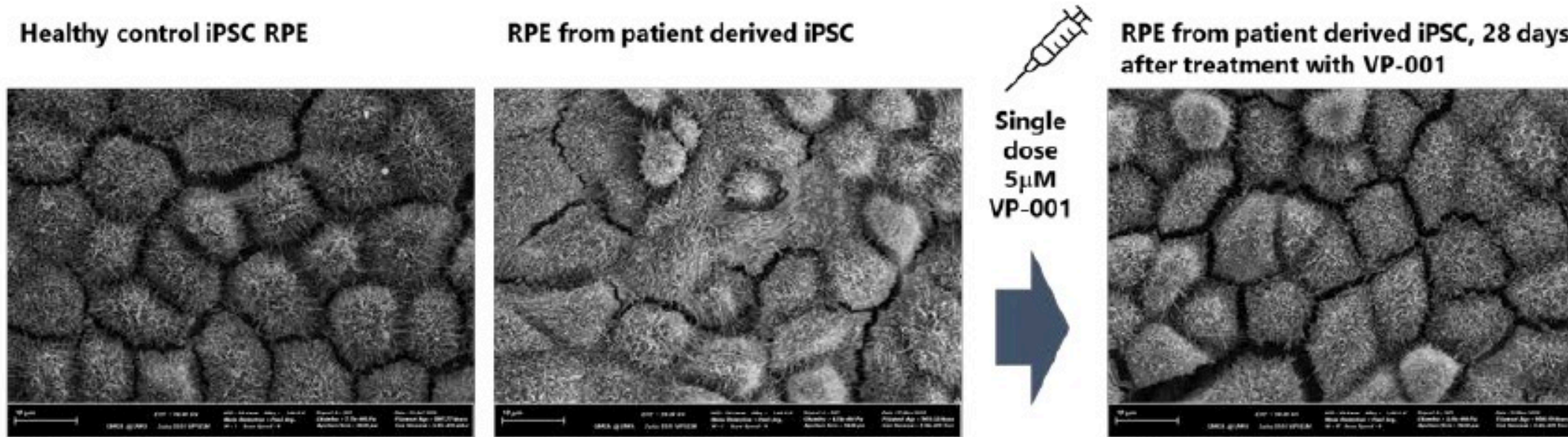


Figure 1. Scanning electron microscopy of retinal pigment epithelium cells derived from control and patient iPSC. Images selected as representative of full data set.

These results demonstrate VP-001's ability to correct the structural deficiency in patient derived retinal cells that is one of the key causes of vision loss in RP11 patients¹

¹ Buskin A. Disrupted alternative splicing for genes implicated in splicing and ciliogenesis causes PRPF31 retinitis pigmentosa. Nat Commun. 2018 Oct 12;9(1):4234.

2021's key milestones for VP-001 centre on large animal studies

Rabbit pharmacokinetics [PK] and tissue distribution

Rabbit Dose-range finding [DRF] toxicity study

Non-human primates [NHPs] DRF toxicity study

GLP animal toxicity studies

Formal regulatory (FDA) engagement

Timeline

3Q21

Following an intravitreal injection of VP-001:

- Understand ocular tolerability in a large eye
- Confirm low to no systemic levels,
- Obtain a detailed understanding of the ocular biodistribution in a large eye, and
- In part, inform dosing

3Q21

In a dose descending tox evaluation obtain data to:

- Understand at what dose toxicity may be observed, and
- Inform through these early data what might be the highest safe dose in rabbits

Late 3Q21

In a dose descending tox evaluation obtain data to:

- Understand at what dose toxicity is observed, and
- Inform through these early data what might be the highest safe dose in NHPs

Initiate in late 2021

Under GLP conditions:

- Evaluate toxicity data at more than one dose to support the FIH clinical study planned for 2H22
- Obtain acute and Chronic tox information, and
- Inform doses for the FIH clinical trial

Late 2021

Informs our development planning including the:

- Early regulatory strategy, and confirms path for
- GLP tox studies,
- FIH clinical trials, and
- CMC efforts to support clinical studies

Impact of the milestone

VP-001 Probability of success

Increasing probability of approval for VP-001



VP-002 for the treatment of Autosomal dominant optic atrophy

Elina, living with ADOA

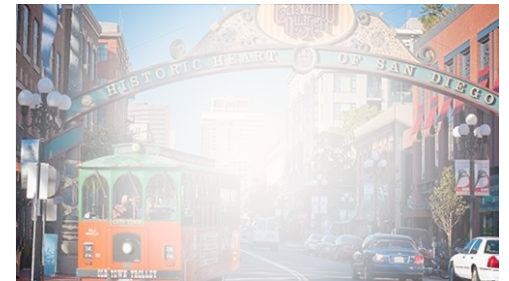
VP-002 for Autosomal dominant optic atrophy

Autosomal dominant optic atrophy (ADOA) is a genetic, blinding eye disease

- ADOA-*OPA1* is a form of RP caused by mutation in the *OPA1* gene
 - **Severe, progressive blinding eye disease**
 - Onset between the ages of 5 and 20
 - Primarily affects central vision
 - Leads to blindness between 40-50 years of age
- There is **no treatment for patients with ADOA**

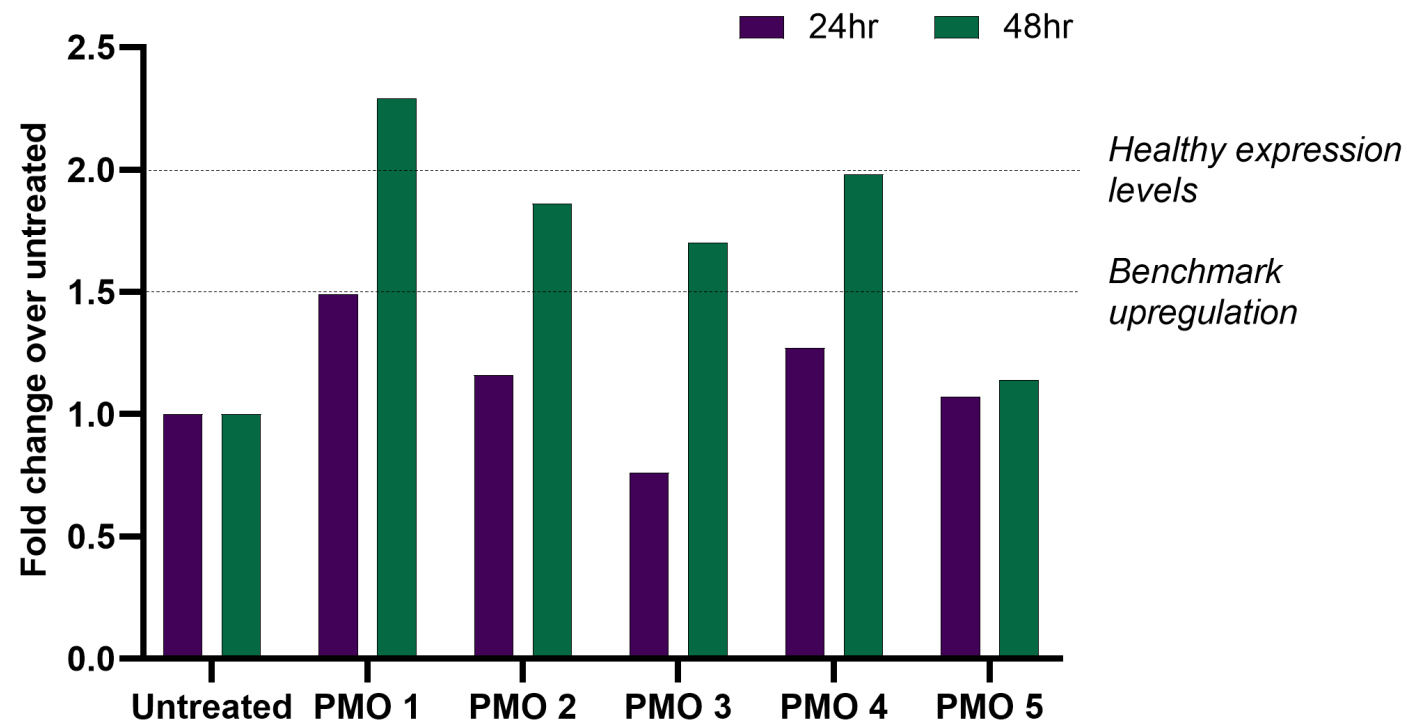
VP-002 has the potential to be transformational to patients

- **9,000-16,000** patients in the western world
- Unmet need with no other drugs in clinical development



VP-002 is targeted at increasing levels of OPA1 protein

Change in OPA1 protein levels, 50 μ M PMO treatment, patient fibroblasts



For upregulation benchmark see poster 'Antisense oligonucleotide mediated increase of OPA1 expression using TANGO technology for treatment of autosomal dominant optic atrophy' Fig.6 at https://www.stoketherapeutics.com/wp-content/uploads/ASGCT2020_final.pdf

See ASX announcement 12 October 2020



Life-changing
science

Expansion into Central Nervous
System diseases

Neurological disease is a substantial and increasing global burden

#1 cause of disability globally

#2 cause of death globally

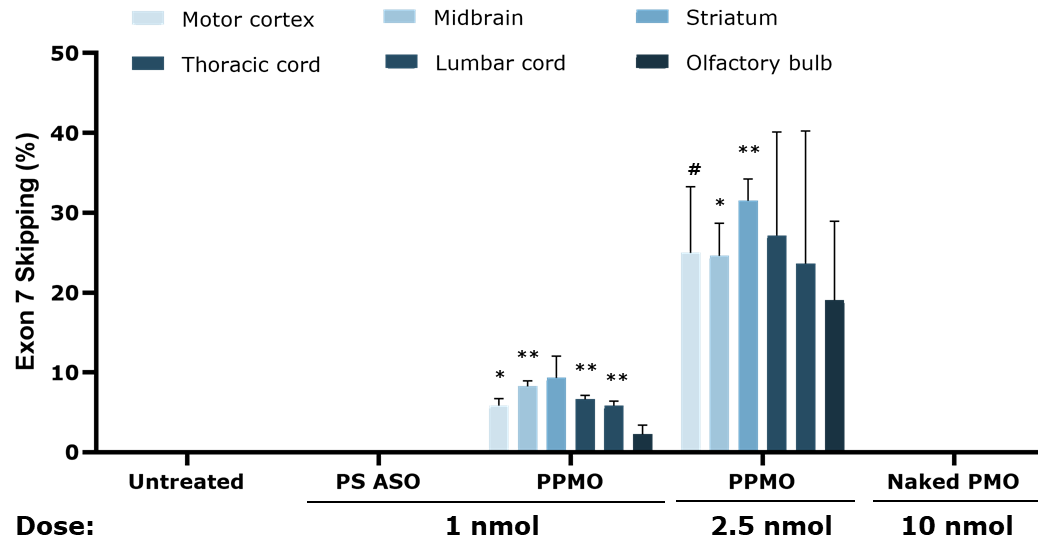
Neurodegenerative diseases affect over 52 million people globally and are responsible for over 2.5 million deaths annually

There is a clear need for better treatments

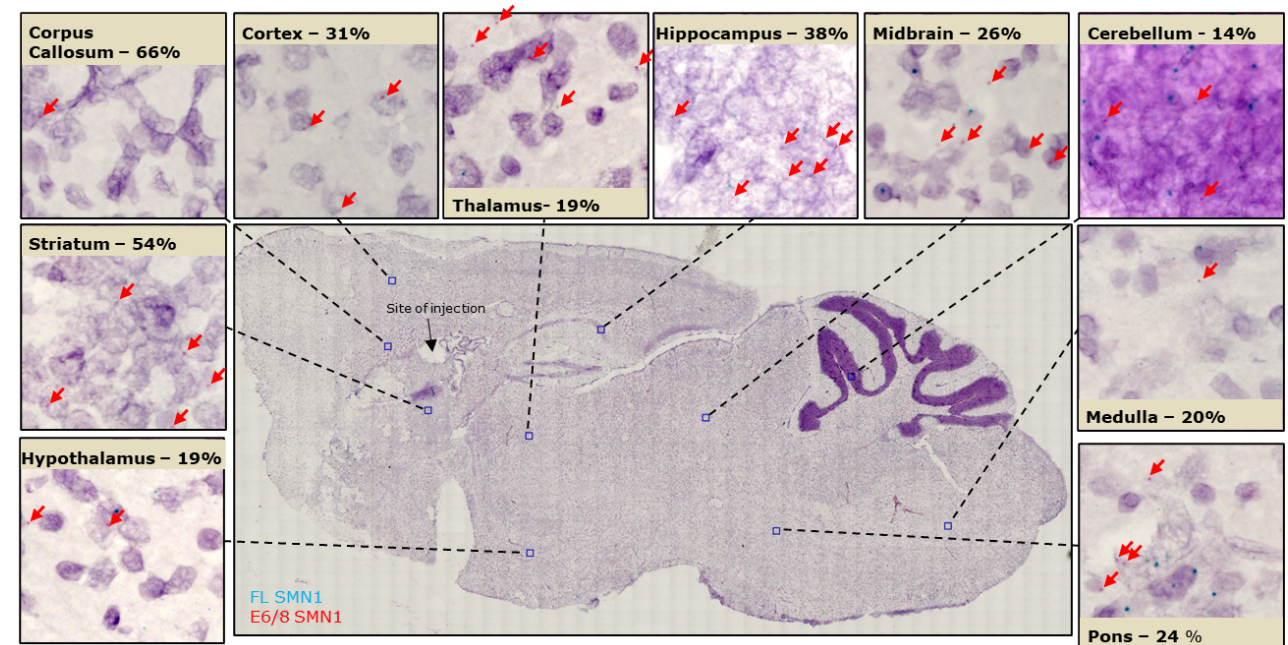
- **Solve delivery to right part of the brain at safe dose levels**
- **Solve delivery to the right cells in the brain**
- **Have a clear safety profile for multiple dosing**
- **Medicines that intervene at the genetic level**
Genetic factors are central to the causes of neurodegenerative disease; both as a direct cause in inherited disease and as critical modifiers in complex, sporadic diseases

Initial results show great promise for PPMO in the CNS

PMO delivery to the brain, *Smn* exon 7 skipping, Day 5 post single I.C.V. injection in mice¹



PMO distribution in the brain, *Smn* exon 7 skipping, Day 5 post single I.C.V. injection in mice²

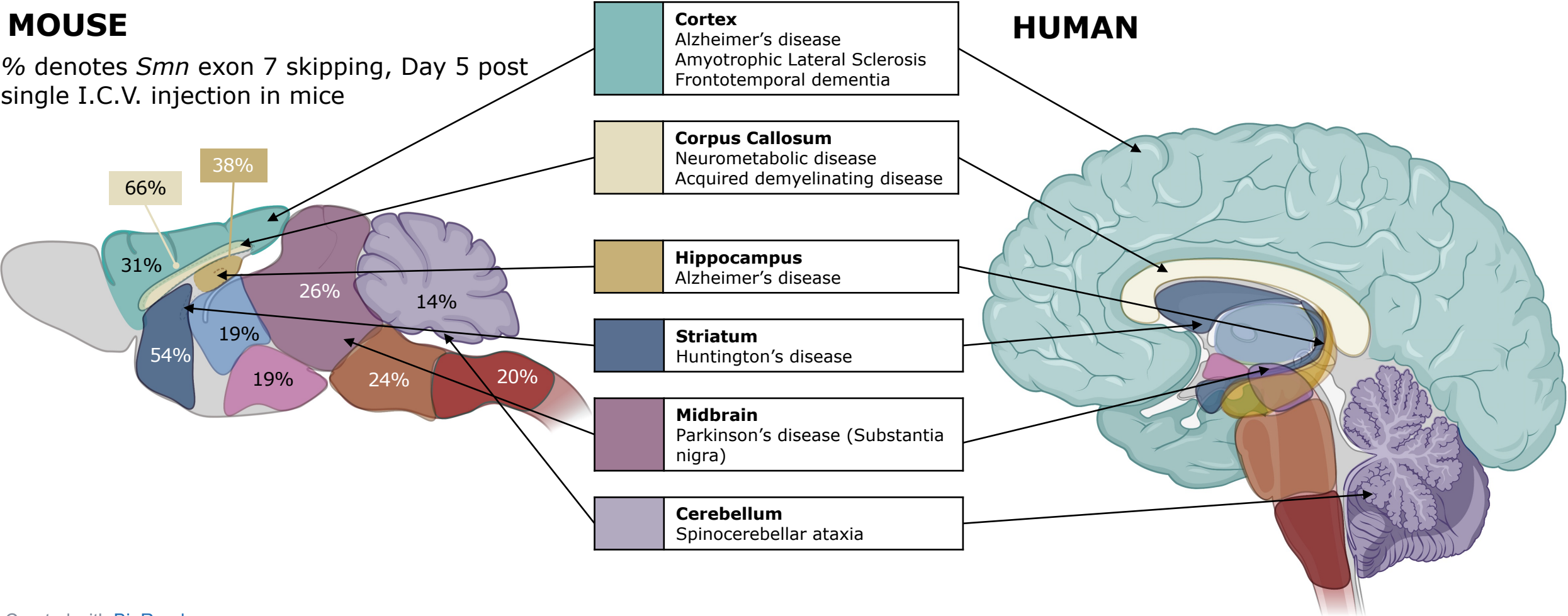


¹ n=2 for all groups except PYC PPMO 1nmol group where n=3. Statistical significant calculated compared to control as unpaired two-way t-test, #: $p \leq 0.1$; *: $p \leq 0.05$; **: $p \leq 0.01$
² RNA in situ hybridization (ISH:Bascope) signals detected using full length *Smn* (blue dots) and E6/8 *Smn* (red dots)-specific probes in PYC CPP-PMO (SMN1) treated mouse brain section. All sections were counterstained with hematoxylin. Brain regions were identified, magnified and the exon 7 skipped (E6/8) transcripts were shown as red punctate dots indicated by red arrows. The percentage of *Smn* transcripts that were exon 7 skipped, E6/8 was determined by random sampling and the averages were indicated next to the brain region.

... and this indicates we can access regions of the brain that matter in neurodegenerative diseases

MOUSE

% denotes *Smn* exon 7 skipping, Day 5 post single I.C.V. injection in mice



2H 2021

Refine our CNS delivery platform

- Determine cell level delivery
- Optimise our CPP selection for our target brain region and cell type

Focused discovery effort in neurodegeneration

- Select target pathway
- Progress a potential candidate to early proof of concept of target engagement and mechanism of action

2021 will be a transformative year for PYC Therapeutics



- Furthest a PYC Therapeutic has ever advanced in preclinical development—testing VP-001 in larger animals ahead of IND submission
- Multiple ocular assets running in parallel with key catalysts throughout 2021
- Expansion into the CNS, a highly attractive new therapeutic area with significant unmet patient needs
- Execution of a new operating model across Australia and the US to ensure access to critical expertise and partners to unlock the full potential of PYC's science

