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Investor Update

Dr Jeremy Levin, Executive Chairman

17 December 2025

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Our intention:

Opthea is relaunching, using all the assets and knowledge we have in VEGF-C/D, to target Lymphangioleiomyomatosis (LAM) – a rare disorder with major unmet medical need, which fits the biology of OPT-302

Agenda

- CURRENT STATUS
- STRATEGIC REVIEW
- OUTCOME OF REVIEW
- WHY LYMPHANGIOLEIOMYOMATOSIS (LAM)
- REINSTATEMENT OF QUOTATION ON ASX
- CONCLUSION AND Q&A

Current status:

Strong IP, experienced team and cash reserves

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Drug development | Local operations | Local ASX listing | Global outlook

STRONG IP

Patents
- Global portfolio of IP that could extend protection to 2046

OPT-302 package
- Registration ready-data
- Manufacturing data
- Non-clinical and clinical package
- Known safety profile

AN EXPERIENCED TEAM

Board
- Jeremy Levin (Chair)
- Kathy Connell
- Lawrence Gozlan
- Hamish George (Joint CoSec)
- Stephanie Vipond (Joint CoSec)

Management
- Jeremy Levin (Exec Chair)
- Stuart Mudge (COO)
- Mike Gerometta (CTO)[1]
- Hamish George (CFO)

CASH RESERVES

Cash
- A$37.6m[2]
- Significant runway

Tax credit
- A$10.8m R&D Tax incentive received

Fiscal discipline
- Committed to disciplined capital management and transparent investor communication

1. Chief Technical Officer, responsible for CMC and other related technical aspects.
2. Pro-forma cash balance representing A$26.8M as at 30 Sept plus A$10.8M R&D Tax Incentive rebate received 06 October 2025.

A disciplined strategic review:

Prioritised feasibility, shareholder value and ROI

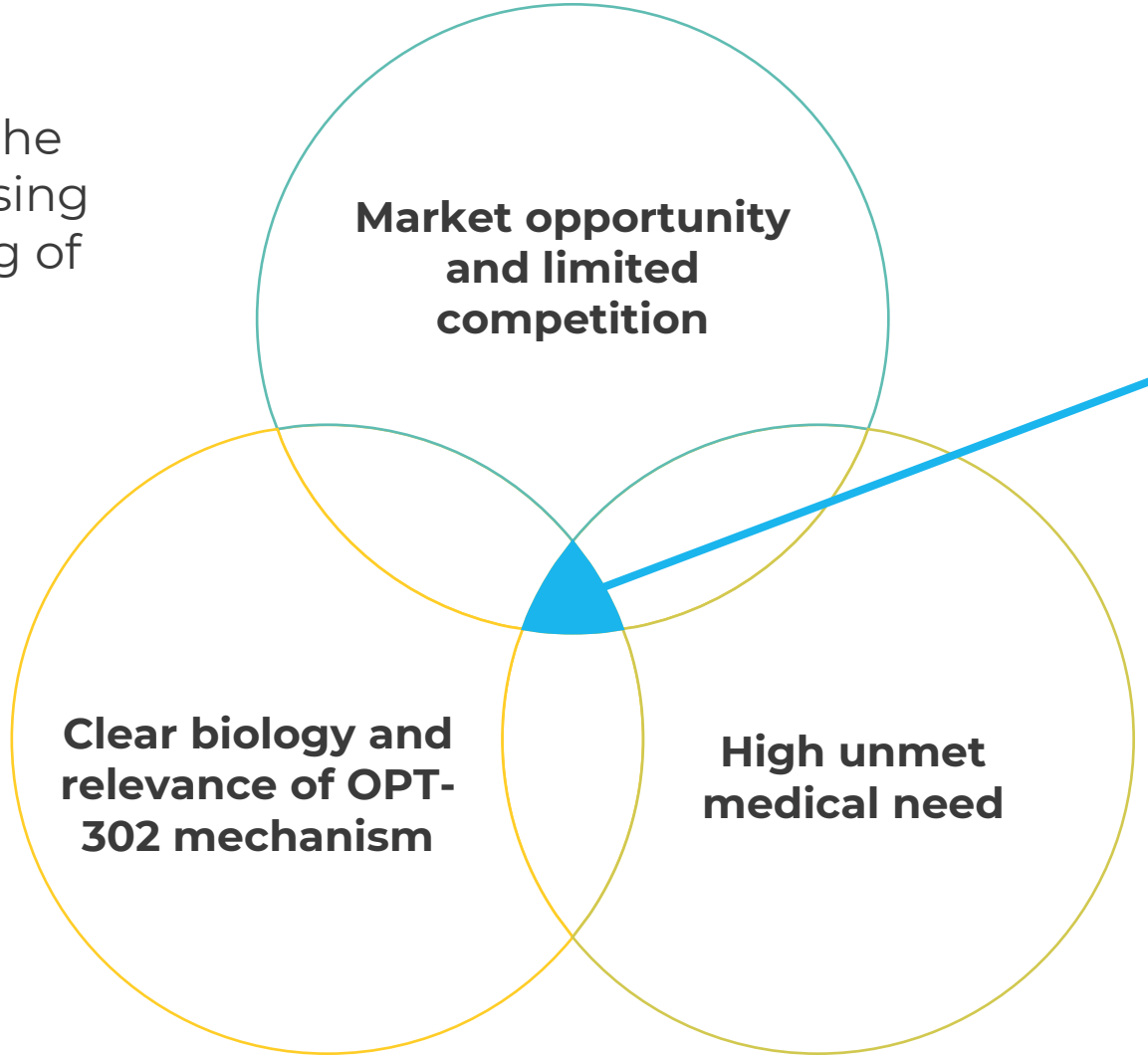
The Board explored several strategic and value creating options for Opthea and the underlying shareholder capital

OPTION	RETURN OF CAPITAL	ACQUISITION OF ASSETS OR MERGER	REPURPOSE OPT-302 ASSETS AND EVALUATE OTHER VEGF ASSETS
ASSESSMENT	✗ Minimal ROI	– Medium ROI	✓ ROI potential if successful
	✗ IP written off	✗ Long lead time	✓ Shorter lead times
	✗ Value leaking	✗ Asset risk	✓ Asset well understood
	✗ Upside forfeited	✗ Shareholder dilution	✓ No near-term shareholder dilution
	✓ Execution	– Execution	✓ Ability to leverage existing body of data towards another disease mediated by VEGF C/D

Outcome of review:

Targeting high need indications for Opthea's portfolio with path to commercial viability

Identifying the most promising re-purposing of OPT-302

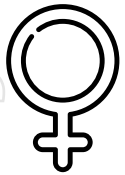


Lymphangioleiomyomatosis (LAM)

This rare, chronic lung disease affecting women of reproductive age with high unmet need meets all the criteria for the promising re-purposing of OPT-302

About LAM:

A rare disease with significant unmet needs affecting young women



3-8 women in every one million worldwide[1, 2]

Genetic condition

Not caused by lifestyle choices

35

Average age of diagnosis

- Abnormal smooth-muscle–like cells (“LAM”) cells infiltrate lungs and lymph channels
- LAM cells overproduce VEGF-C and VEGF-D, driving abnormal lymphatics and fluid problems[2]
- Multiple cysts form throughout the lung[3], trapping air, destroying tissue and creating air leaks
- Over time this leads to a steady loss of breathing capacity, incapacitation and reduced lifespan
- mTOR inhibitors can stabilise disease on treatment, but do not cure LAM and progression often returns off therapy
- Patients may face progressive lung loss and lymphatic complications, with tolerability limits. Creating the need for an add-on biologic targeting complementary biology

No existing cure

1. Prevalence is reported as 3.4-7.8 cases per million women but newer Northern Europe data suggest 20.9–26.04 per million adult women, consistent with underdiagnosis.
2. Issaka, R. B., et al. (2009). See Appendix for full citation.
3. LAM can also be present elsewhere in the body including the kidneys for 40% of women with LAM. **Source:** Living with LAM.

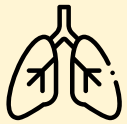
LAM market and commercial logic:

Concentrated rare-disease pathway with limited disease-modifying therapy

Prevalence reported as 3.4–7.8 cases per million adult women; but newer data suggests **20.9–26.04 per million**, consistent with underdiagnosis[1]

Patients are concentrated and managed by a **finite specialty footprint,** with ~70 global LAM clinics[3]

Current disease-modifying therapy is **not curative**: in the pivotal randomised trial[2], sirolimus stabilised lung function on treatment, but decline resumed after discontinuation



Standardised patient identification for a rare lung disease: ATS/JRS guidelines recommend using serum VEGF-D with an 800 pg/mL threshold to support

Commercial reality: orphan-drug **pricing spans a wide, well-established range** with orphan treatment annual costs range up to $500,000 per treated patient[4]

1. Updated Prevalence of Lymphangioleiomyomatosis in Europe. See Appendix for full citation.
2. Lynn et al (2011) Efficacy and Safety of Sirolimus in Lymphangioleiomyomatosis, The New England Journal Of Medicine. See Appendix for full citation.
3. The LAM Foundation.
4. Launch Price and Access Report: Drug Approvals from 2022–2024 (Final Report). See Appendix for full citation.

Existing patient journey:

Current limitations and unmet clinical needs

Current patient journey

EARLY SYMPTOMS

- Non-specific: breathlessness in exertion, cough, fatigue
- Chest pain, lung collapse and/or coughing up blood

MISDIAGNOSIS

- Often mistaken for asthma, emphysema and bronchitis, or chronic obstructive lung disease

DIAGNOSIS

- CT-scans
- Spirometry
- Blood tests – elevated VEGF-D is a strong indicator of LAM[1]

DETERIORATION

- Quality of life falls as daily activities become harder
- Hospital visitations increase

DISEASE MANAGEMENT

- Rapamycin[2] can stabilise some patients, but not all
- True disease control and restoration remains unmet

LUNG TRANSPLANT OR INCAPACITATION

- Quality of life and lifespan are significantly impacted without a double lung transplant

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1. ATS/JRA guidelines recommend using serum VEGF-D with an 800 pg/mL threshold to support diagnosis.
2. Drugs derived from rapamycin are not curative but are capable of slowing the destructive progress of LAM in some patients.

Scientific rationale:

Targeting VEGF-C/D pathway in LAM

"Lock and key" system

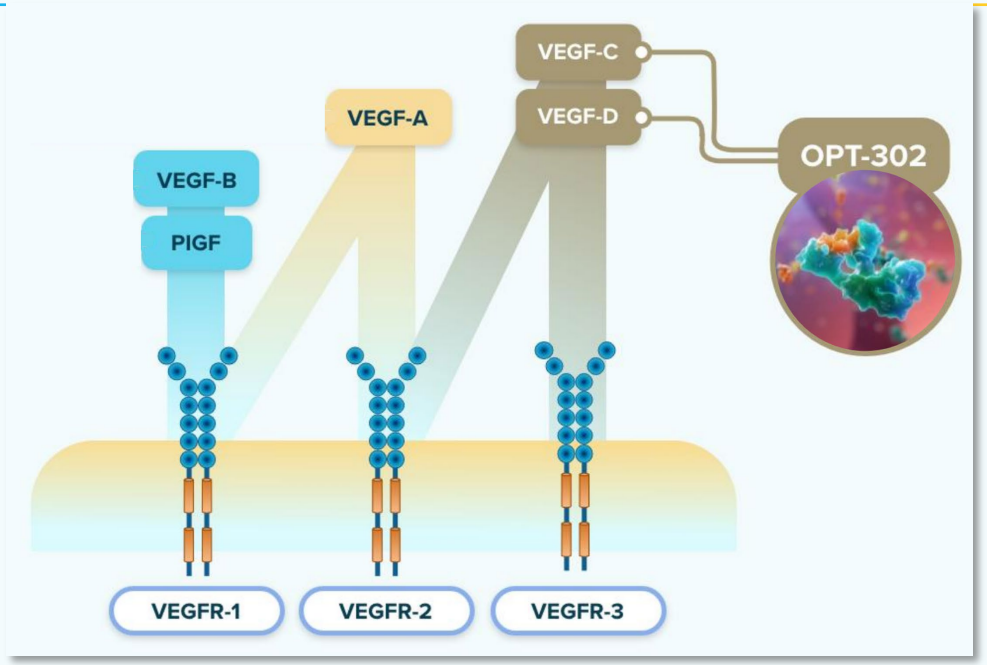
VEGF-C and VEGF-D are growth signals that tell lymphatic vessels to grow and become more permeable.

VEGFR-3 is the receptor on lymphatic cells that receives these signals.

When VEGF-C or VEGF-D bind to VEGFR-3, the lymphatic system gets a strong "expand and remodel" message. In LAM, this leads to abnormal, dilated, and leaky lymphatic vessels.

The problem[1]

In LAM, excess VEGF-D (and VEGF-C) activates VEGFR-3 on lymphatic vessels, driving abnormal, leaky lymphatics in the lungs and accelerating disease progression.



The mechanism

By trapping VEGF-C/D with OPT-302 before they activate VEGFR-3, we aim to dampen the lymphatic signaling that fuels LAM, aiming to stabilise lung function and slow disease progression.

1. Issaka, R. B., et al. (2009). See Appendix for full citation.

Why OPT-302:

A VEGF-C/D “trap” suited to LAM[1, 2]

Fitting the Mechanism of Action with the underlying pathology

OPT-302 a VEGF-C/D “trap” designed to bind and sequester VEGF-C and VEGF-D, preventing activation of VEGFR-3–mediated lymphatic signaling

What is de-risked

- Target biology and mechanism are well characterised in lymphatic biology.
- OPT-302 has an established molecular mechanism and data informing manufacturability and safety monitoring.

What still must be proven

- Optimal route and exposure target including lung/lymphatic distribution.
- Chronic dosing safety/tolerability at LAM-relevant exposures (including immunogenicity risk management).
- Clear clinical benefit in LAM with a regulatory-aligned endpoint strategy.

Why it fits LAM

- Targets the VEGF-C/D → VEGFR-3 axis implicated in lymphatic remodeling/leakage and lymphatic manifestations in LAM.
- Intended to complement current therapy mTOR inhibition:
  - mTOR inhibitors address LAM cell growth
  - OPT-302 is positioned to address the lymphatic biology.

1. Jackson TL. (2023), See Appendix for full citation.
2. McCormack FX (2016). See Appendix for full citation.

Delivery paths:

Evaluating optimal delivery for efficacy and safety

Pathways under consideration

Inhaled	Exploring a nebulised formulation of OPT-302 for direct delivery to the lung and thoracic lymphatics
Intravenous	Would provide broad access to lymphatic vessels throughout the body, but may increase the risk of systemic side effects
Subcutaneous	Allows gradual systemic absorption and may reach lymphatic vessels throughout the body, but may offer limited direct access to lung lymphatics

The final delivery path for OPT-302 will be determined by data from large-animal models and early human studies.

Regulatory strategy:

Will seek orphan designation when appropriate

Orphan drug designation may unlock

Market exclusivity	Orphan designation would grant 7-10 years of market exclusivity post-approval, across jurisdictions (US, EU, Japan & Australia) reducing competitive risk and supporting premium pricing
Regulatory incentives	Opportunity for accelerated regulator review timelines, reduced or waived filing fees, and potential tax credits to lower development costs and shorten time to market
Pricing power	Orphan drugs often command high per-patient pricing (up to $500,000 per treated patient annually[1]) due to rarity and unmet need, which can transform a small patient base into meaningful revenue.

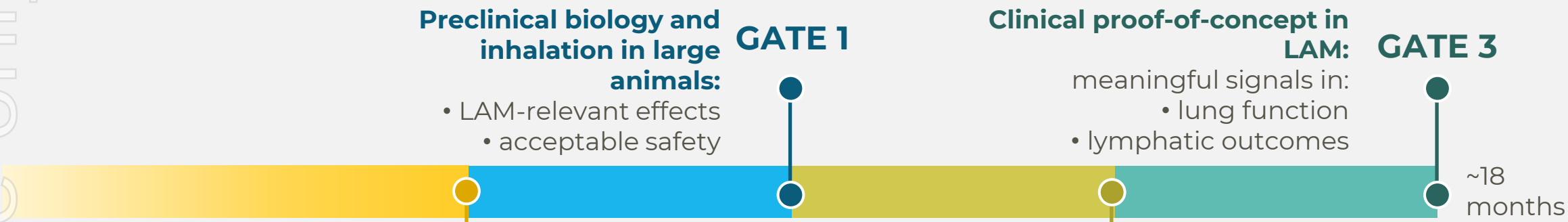
✓ **Competitive protection** ✓ **Lower development costs**
✓ **Reduced time to market** ✓ **Premium pricing power**
✓ **Addressing a critical, long-neglected need in women's health**

1. Launch Price and Access Report: Drug Approvals from 2022–2024 (Final Report). See Appendix for full citation.

Stage-gated plan:

Rigorous data-driven milestones and stop criteria

Pre-defined stop criteria at each gate



Build strong relationships with LAM Foundations globally

Funded via existing cash reserves

Continued operations in Australia, leverage R&D tax credits

LAM organisations:

A family of networks and resources for individuals with LAM across the globe

Opthea will build on the substantial work completed and ongoing with the global LAM foundations, clinics and communities, establishing long-term partnerships

THE LAM FOUNDATION
A BREATH OF HOPE

Living with LAM
www.livingwithlam.org

Foundation for Women's Health

Lung Foundation Australia

~70 global LAM clinics, patient data bases, biospecimen repository, focused International LAM research conference & LAMposium

ATS

TSC Alliance®

...and more

Reinstatement on ASX:

Rebuilding market confidence through transparency

Opthea plans to seek reinstatement of its securities on the ASX in the first half of calendar year 2026[1]

- Strategic review completed.
- In this presentation, Opthea has communicated the outcome of that strategic review and its intentions in respect of its operations and plans.
- Opthea therefore intends to re-engage with ASX with a view to making adequate market disclosure to ASX's satisfaction sufficient for ASX to permit reinstatement of Opthea's securities to quotation on ASX.

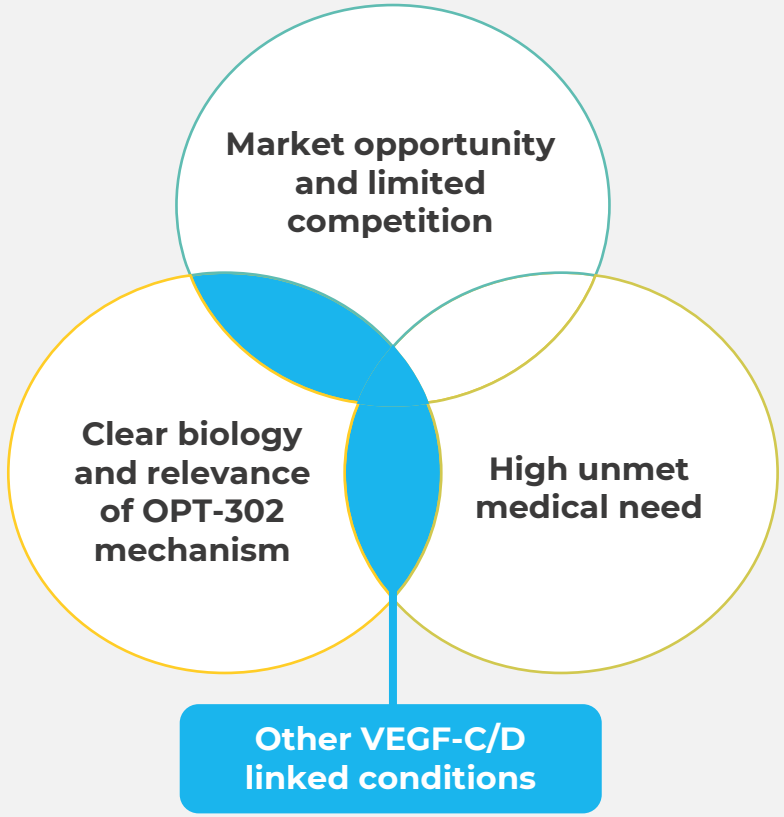
1. Opthea plans to seek re-instatement of its securities to quotation on ASX without a public offer.

Conclusion:

Focused execution to unlock value in rare disease affecting women

- Clearly defined problem in women's health with unmet need and suboptimal treatment options
- OPT-302 has been through substantial clinical testing – the remaining focus is to determine its effect on a specific lung disease
- Specialist LAM centres, registries and patient groups are well developed, which supports efficient studies and rapid learning from early data
- Rare diseases come with market protection and attractive pricing
- A convincing result could justify a family of programs in related lymphatic or VEGF-C/D–linked conditions

The family of future opportunity



Q&A

Appendix:

Full citations

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- McCormack FX. et al (2011) *Efficacy and Safety of Sirolimus in Lymphangioleiomyomatosis*, The New England Journal Of Medicine Vol 364 No 17.: Efficacy and Safety of Sirolimus in Lymphangioleiomyomatosis | New England Journal of Medicine