Developing Inhibitors of VEGF-C/VEGF-D

Circadian Technologies
(ASX:CIR, OTCQX:CKDXY)

Capital Raising Presentation – 6 October 2014

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Disclaimer

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Capital Raising Overview

Capital Raising Overview

Transformational A$17.4m capital raising completed to fund the Company through Q4 2017

- A$17.4m capital raising ("**Offer**") at A$0.175 per share comprising:
  - Placement of A$14 million to institutional and sophisticated investors in the US, Europe and Australia (**Placement**). The Placement to be conducted in two tranches:
    - Tranche 1: Placement of A$1.2m under the Company existing placement capacity under Listing Rule 7.1, and
    - Tranche 2: Conditional placement of A$12.8m subject to shareholder approval at the upcoming AGM on 18 November 2014
  - Fully underwritten 2 for 5 non-renounceable Rights Issue to raise A$3.4m available to existing eligible shareholders on the record date (**Rights Issue**)
- 1 free attaching option for every 2 shares subscribed for under the Offer
  - Exercisable at A$0.27 at any time before expiry on 25 November 2018
  - Placement options subject to shareholder approval at the upcoming AGM
  - ASX quotation of the options (subject to ASX approval)

Capital raising – Key Objectives

Accelerate development of lead compound OPT-302

- Scale-up & manufacturing of OPT-302 for clinical programs
- Complete US IND filing
- Initiate Phase 1 dose escalation trial in combination with Lucentis® in Wet Age-related Macular Degeneration (wet AMD) patients
- Advance OPT-302 through Phase 2a clinical studies in wet AMD
- Generate additional clinical and preclinical data to fully establish the profile of OPT-302 in wet AMD and potential additional indications

R&D and Business Development

- Complete data analysis of Phase 1 clinical program for VGX-100 in solid tumours
- Advance business development to accelerate licensing opportunities for VGX-100
- Improve balance sheet to provide a strong position for partnering opportunities

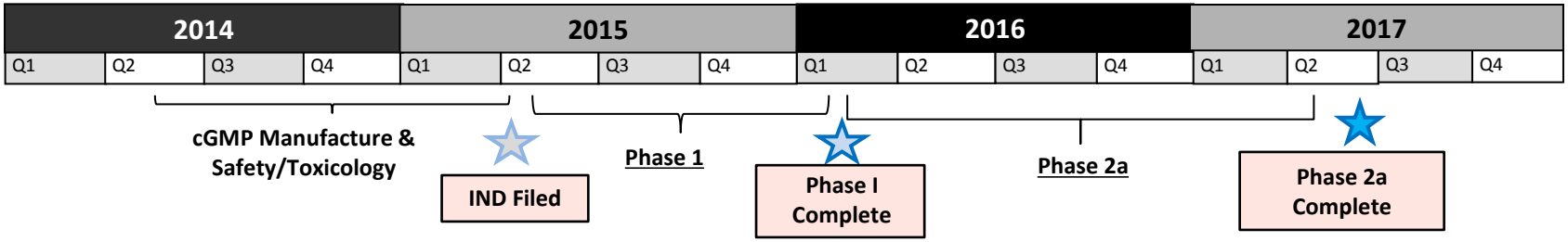
Timetable

Activity	Date*
Announcement of Offer and Appendix 3B lodged with ASX	Monday 6 October
Notice to shareholders regarding information required by Appendix 3B	Friday 10 October
'Ex' date	Monday 13 October
Record date for Rights Issue	7pm Wednesday15 October
Despatch of prospectus and personalised entitlement and acceptance forms	Friday 17 October
Settlement of Tranche 1 Placement shares	Friday 17 October
Rights Issue opens	Monday 20 October
Tranche 1 Placement shares allotment date	Monday 20 October
Rights Issue closes	Friday 31 October
Rights Issue shares and options quoted on a deferred settlement basis	Monday 3 November
Issue of shares and options under the Rights Issue and deferred settlement trading ends	Monday 10 November
Annual General Meeting (including the approval of the Placement)	Tuesday 18 November
Settlement of Tranche 2 Placement shares	Monday 24 November
Tranche 2 Placement share and options allotment date and Tranche 1 Placement options allotment date	Tuesday 25 November

**All dates are indicative only and subject to change. Circadian reserves the right to withdraw or vary the timetable without notice.*

Expenditure to Potential Value Accretion Points

Activity	July 1 2014 – July 1 2017
Cash Position	$6.8M[a]
Capital Raise	$17.4M[b]
Estimated R&D Rebate	$8.5M
Clinical Trials	$8.5M
Net Expenditure after Tax Rebate	$19.6M
Cash Position	$4.6M (At end Ph2a: $5.7M)



Expects to be funded through multiple meaningful clinical milestones

Dates provided in timeline are estimates.

a. At July 1 2014.

b. Assuming 100% of the funds raised under the conditional placement and Rights Issue, excludes the cost of the placement and Rights Issue and assumes no options are exercised and no further capital raising occurs.

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Company Overview

Investment Highlights

Leader in VEGF-C/-D and VEGFR-3 targeting compounds in Oncology and Ophthalmology

- Lead compound OPT-302 blocks VEGF-C and VEGF-D
- OPT-302 expected to enter Phase 1 clinical trial for wet age-related macular degeneration (AMD)
  - Phase 1 clinical trial expected to commence 2Q15
  - Results from Phase 1 clinical trial expected 1Q16
  - Results from Phase 2a clinical trial expected 2Q17
- VGX-100 Phase 1a/b study completed enrolment
  - Phase 2 ready asset poised for licensing/partnership
- Eli Lilly partnered compound IMC-3C5 to complete Phase 1 in solid tumours in 1H15
- Strong management team with substantial experience in developing drugs targeting the VEGF pathway, wet AMD and oncology
- Extensive worldwide intellectual property platform in respect of VEGF-C, VEGF-D and VEGFR-3*

* *Refer slide 29 for details on intellectual property*

Financials

CIR Key Statistics (A$)	
ASX Code	CIR
Share Price	$0.195
52 Week High / Low	$0.29 / $0.17
Ordinary Shares on Issue	48,633,015 (Post-Cap Raise: 148,086,221)
Market Capitalisation	~ 9.5m
Cash Holdings	~ 5.3m[a] (Post-Cap Raise: +A$17.4m)
Listed Investments (ASX: ANP, OIL)	~ 2m

a. *At Oct 1 2014.*

Top 5 Shareholders *(Pre-Cap Raise)*	
Investor	**% Interest**
BNP Paribas Noms	16.1%
Licentia Limited	6.5%
Ludwig Institute	6.4%
Baker Brothers Life Sciences	4.3%
Leon Serry	4.3%

CIR Price Performance

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Executive Management

Megan Baldwin, PhD. CEO & Managing Director

Dr Baldwin brings over 18 years of experience focussing on angiogenesis and therapeutic strategies for cancer and ophthalmic indications. Dr Baldwin joined Circadian in 2008 and since then has held various positions, including Head of Preclinical R&D and Chief Executive Officer of Opthea Pty Ltd. Prior to joining Circadian, she was employed at Genentech (now Roche), the world leader in the field of angiogenesis-based therapies for cancer and other diseases. Her experience included several years as a researcher in the group of leading angiogenesis expert Napoleone Ferrara, before moving to Genentech's commercial division and having responsibility for corporate competitive intelligence activities. In these roles, she developed extensive commercial and scientific knowledge in the field of anti-angiogenic and oncology drug development. Megan has a scientific background of more than 18 years, focused on angiogenesis and therapeutic strategies for cancer and ophthalmological indications. She holds a PhD in Medicine from the University of Melbourne, having conducted her doctoral studies at the Ludwig Institute for Cancer Research.

Michael Gerometta, PhD. Head of CMC & Development

Over 25 yrs experience in the biotechnology industry, most recently as COO of Q-Gen, the manufacturing facility of QIMR. Extensive experience working with CMO's overseas & locally in all facets of translational CMC from concept through to Phase 2. Guided manufacture of 4 biologics through to Phase ½ clinical trials, including oversight of two non-clinical programs as well as associated regulatory interactions.

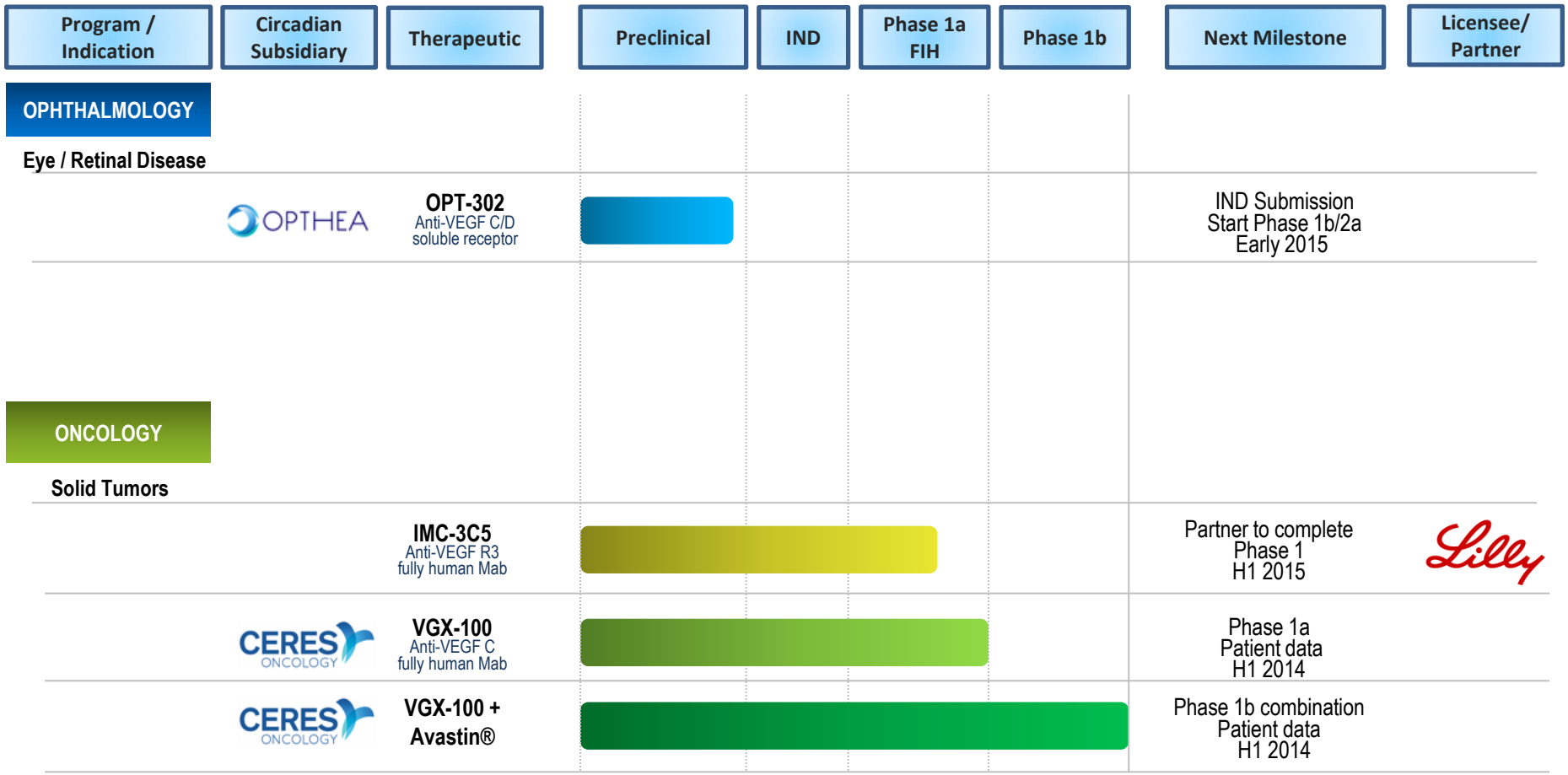
Ian Leitch, PhD. Senior Director Clinical Research

Over 15 years of research & management experience from drug discovery through clinical development in early stage and late biotech/pharma companies including global regulatory interactions spanning IND to NDA submissions. Has held senior clinical development roles at Amgen and Miravant in the US where he worked on cardiovascular programs and was Clinical Study Director for Ophthalmology, managing an international Ph3 clinical trial in wet AMD.

Richard Chadwick, PhD. Head of Intellectual Property

Qualified European and Australian patent attorney. Previously worked for five years in biotechnology group of FB Rice & Co and for 10 years in intellectual property roles in the United Kingdom. This included working as an in-house attorney at Dow Corning Limited and 5 years working as an in-house attorney at Unilever.

Therapeutic Product Development Pipeline



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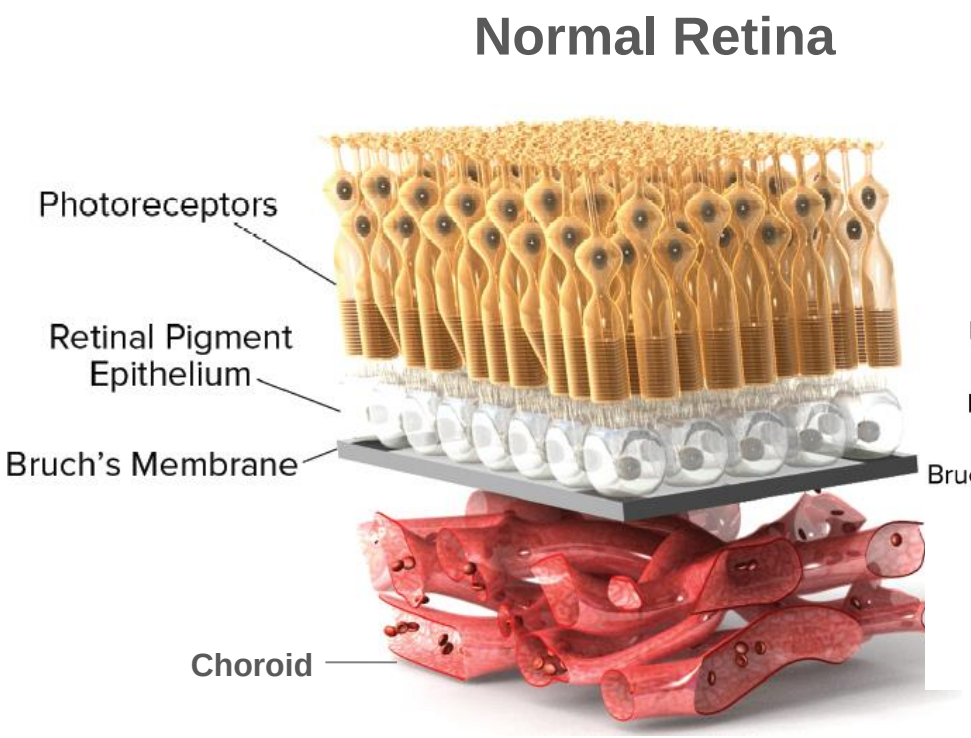
Lead Program

OPT-302 for Wet Age-related Macular Degeneration

- The VEGF pathway is a well validated target in wet AMD
  - Annual global market for drugs targeting VEGF-A in wet AMD is in excess of $US5bn
- Impressive preclinical data provides strong positioning for OPT-302
  - Animal data as single-agent equal to existing products – Lucentis® & Eylea®
  - Data demonstrates improved efficacy in combination with approved products
  - Preclinical data with OPT-302 in combination with Eylea® demonstrates comparable activity to Fovista® (OPHT lead compound) when used in combination in the same animal model
- Extensive worldwide intellectual property platform in respect of VEGF-C, VEGF-D and VEGFR-3
- Demonstration of safety & efficacy of OPT-302 in Phase 1 and 2 trials is expected to provide a substantial uplift in valuation
- Average valuation of ophthalmology listed companies in Phase 2 development for products targeting wet AMD is >$US400mn market cap

The normal retina and ‘Wet’ (neovascular) AMD



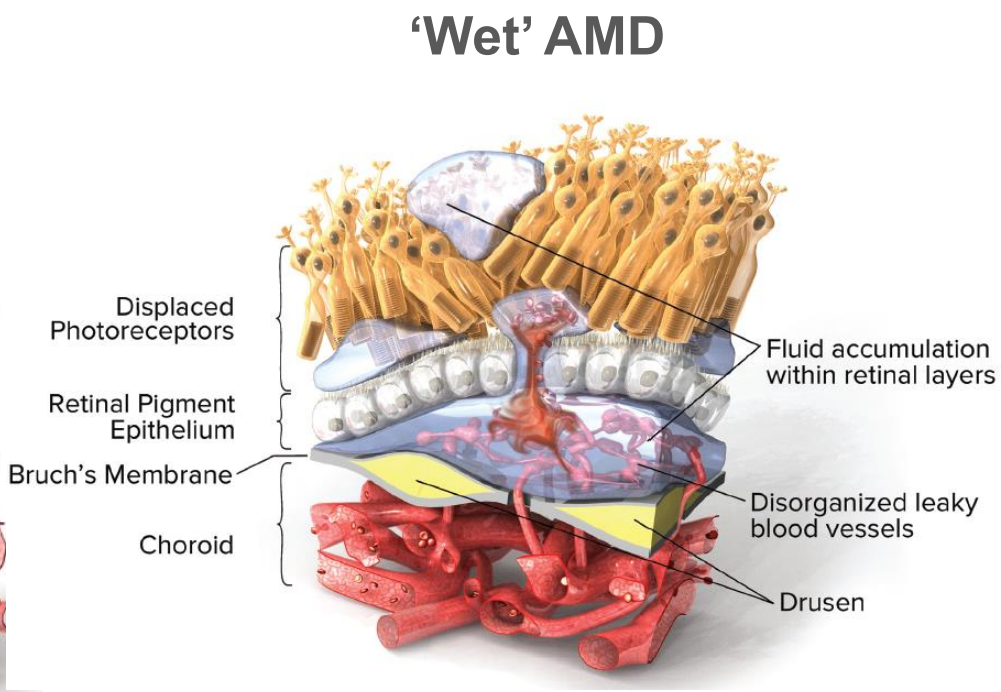


Figure: The Angiogenesis Foundation

Wet (neovascular) AMD

Photo: The Angiogenesis Foundation

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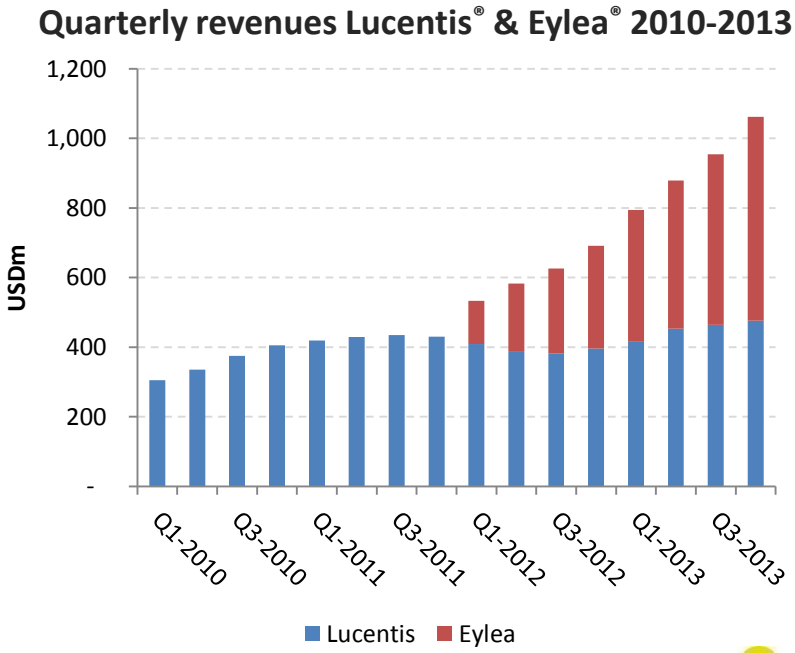
Wet AMD is a major commercial opportunity

"Few people are aware that macular degeneration is an incurable eye disease and that it is the leading cause of blindness for those aged 55 and older in the United States" …
American Macular Degeneration Foundation

- Estimated >$US5B p.a. market opportunity in wet AMD in US alone
- Increasing with aging population

- Only two targeted therapies approved for wet AMD
- Both target VEGF-A
  - Roche/Novartis: **Lucentis®**
  - Regeneron/Bayer: **Eylea®**
  - Roche/Genentech: Avastin® (off-label)
  - Lucentis® and Eylea® tracking to >$5B



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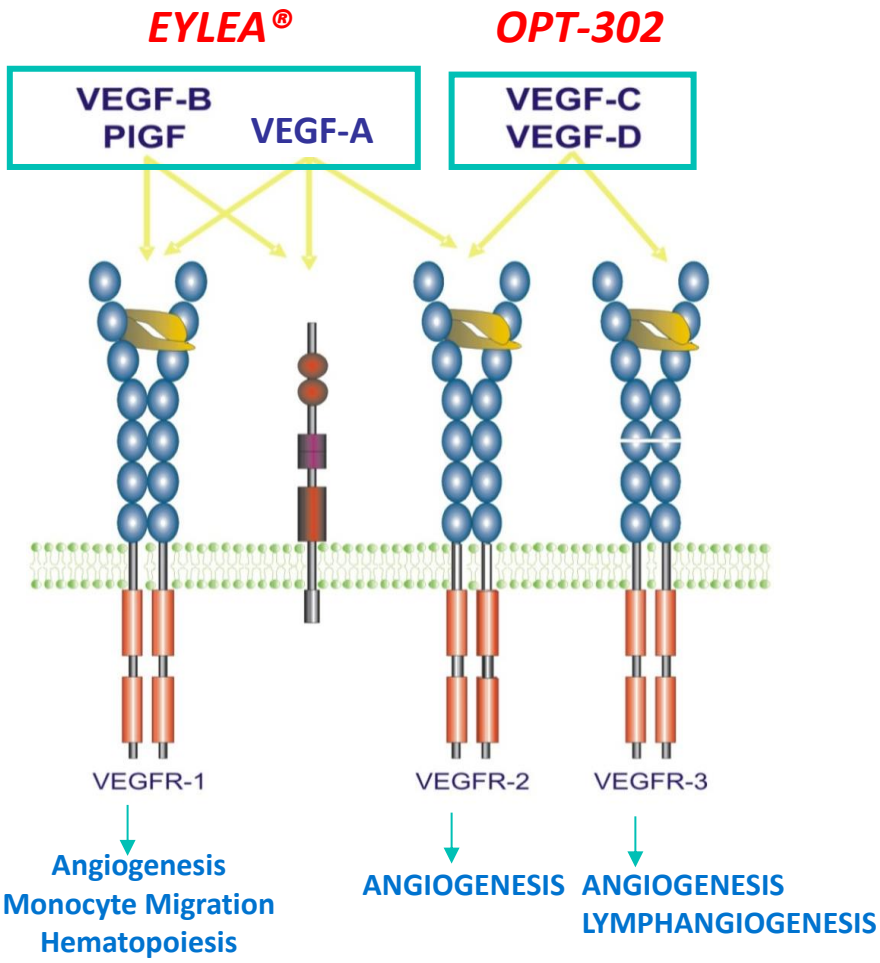
VEGF-C & -D stimulate blood vessel growth and vessel leakage through VEGF-receptors

EYLEA® + OPT-302 administration potently and selectively blocks all members of the VEGF family



- The VEGF family is the key driver of angiogenesis
- Existing therapies target VEGF-A but not VEGF-C or VEGF-D
- VEGF-C and VEGF-D stimulate angiogenesis via overlapping & distinct pathways to VEGF-A
- Combined VEGF-A/VEGF-C inhibition has the potential to improve patient response by **more complete** blockade of angiogenesis & vascular leakage

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The opportunity for OPT-302: An unmet medical need remains despite anti-VEGF-A therapy

Existing therapies for wet AMD target VEGF-A but not VEGF-C

Long term single-agent anti-VEGF-A therapy (Lucentis®/Eylea®)
- Suboptimal visual outcome:

- **Only one-third of patients recover driving vision***
- **One-sixth progress to registered blindness***
- **>50% patients do not achieve a significant gain in vision**

OBJECTIVE:

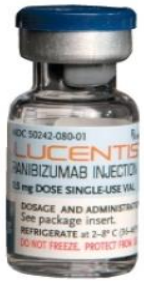
OPT-302 combined with existing agents for wet AMD results in:

Complete blockade of the main pathway driving blood vessel growth

** Ambati. IOVS. 52(5), 2011.*

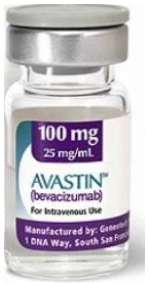
More complete blockade of the VEGF/VEGFR pathway is clinically more effective than anti-VEGF-A therapy

MACUGEN® PEGAPTANIB SODIUM INJECTION



Wet AMD

- Improved efficacy of Lucentis® that blocks all isoforms of VEGF-A compared to Macugen® that selectively blocks the VEGF-A_{165} isoform



Gastric Cancer

- Cyramza® (neutralising VEGFR-2 that blocks VEGF-A, VEGF-C and VEGF-D) is more effective than Avastin® (selective VEGF-A inhibitor) in gastric cancer

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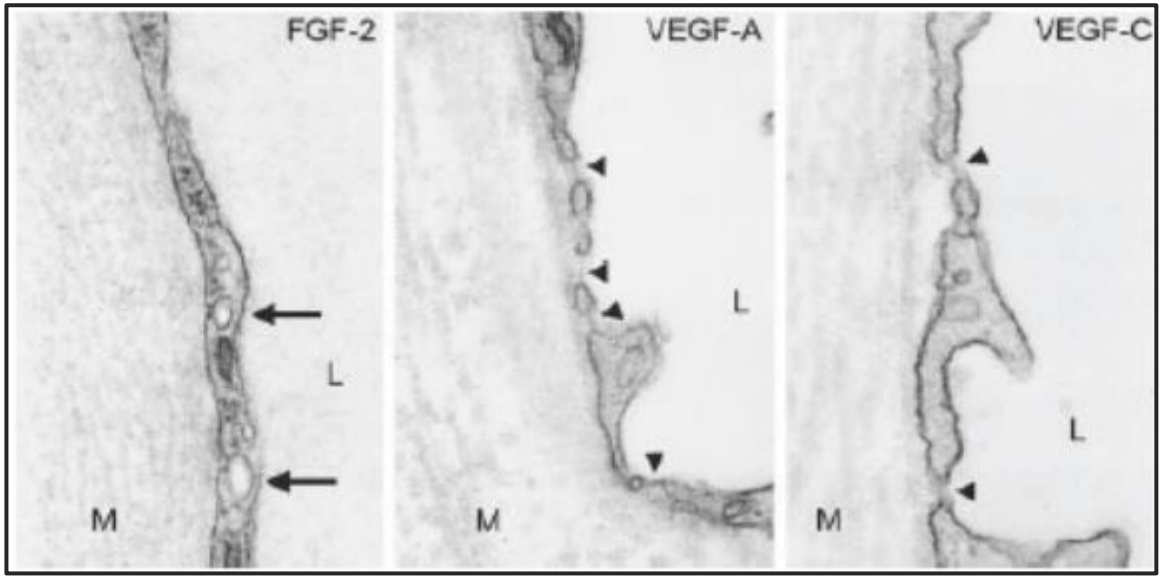
VEGF-C Induces Vascular Permeability - Suggests Contribution to Retinal Edema

Cao et al,. Circ Res., 2004



- Persistent retinal vascular leakage in patients 'sub-responsive' to Lucentis®/Eylea®
- CATT trial indicated that after 12 months of Lucentis®:
  - Administered monthly, ~50% of patients have fluid by OCT
  - Administered by PRN, ~71% have persistent fluid
- VEGF-C is a potent inducer of vascular leakage that is not blocked by existing therapies

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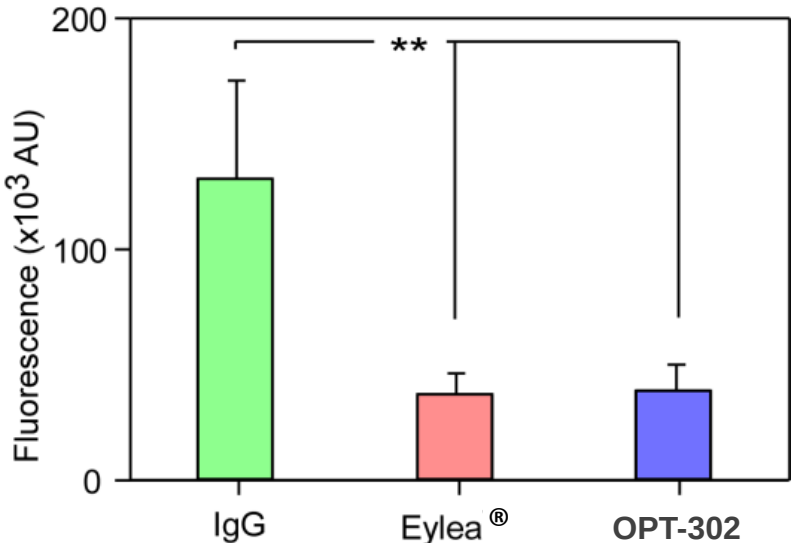
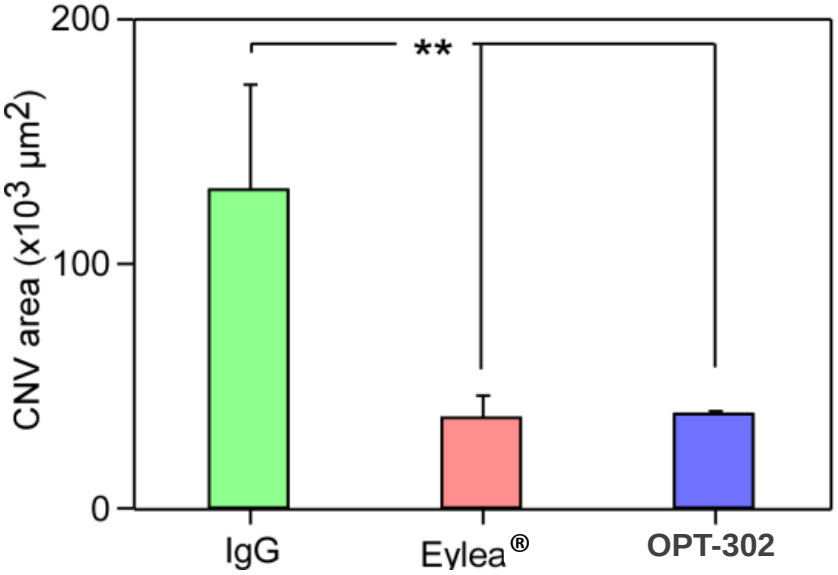
Comparable activity of OPT-302 & Eylea® in mouse AMD

Reduction of vascular leakage in mouse CNV model



Reduction of CNV lesion area in mouse CNV model



Lashkari et al , 2013 ARVO Annual Meeting, 4999-A0128.
Schepens Eye Research Institute, Department of Opthamology, Harvard Medical School
(CNV: choroidal neovascularisation)

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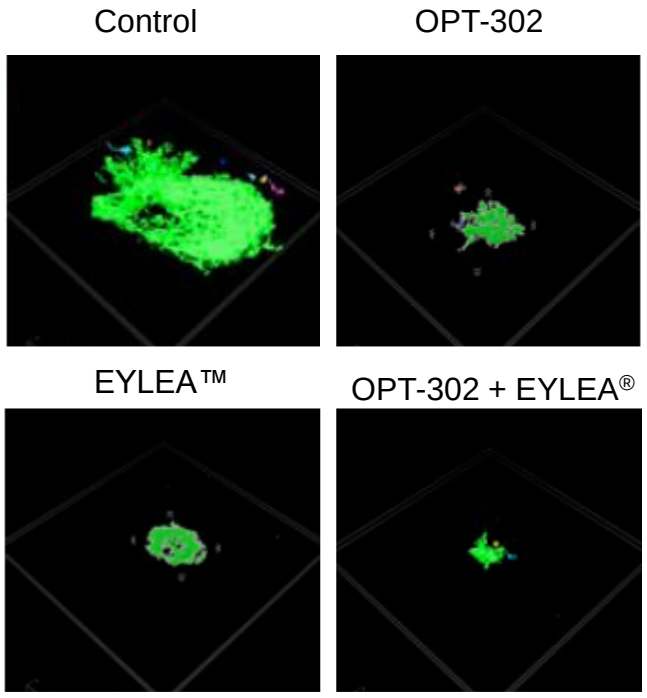
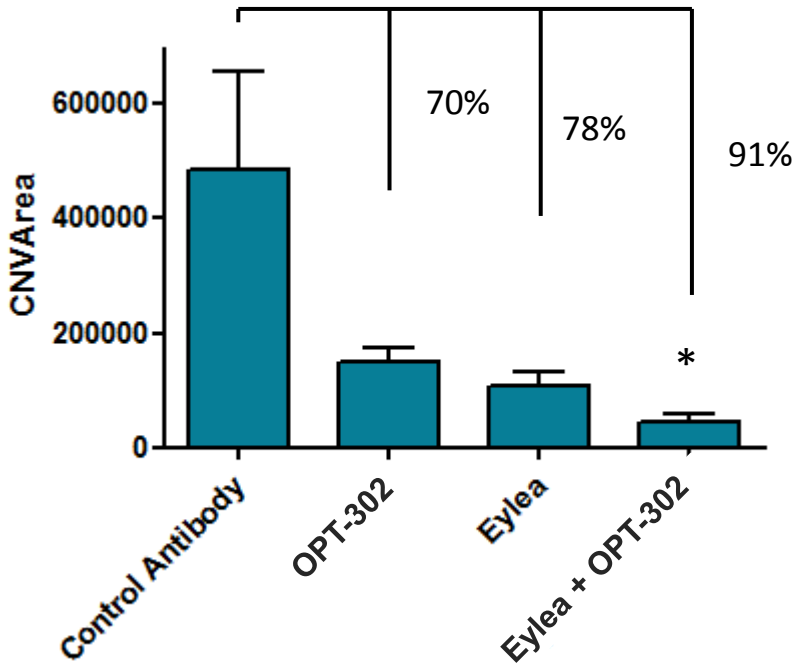
Significant additive activity of OPT-302 & Eylea® in mouse AMD

Combined inhibition of VEGF-A (Eylea®), VEGF-C and VEGF-D (OPT-302) is more effective than inhibition of VEGF-A alone





** Pairwise comparison: OPT-302 vs Eylea + OPT-302 (p<0.02)*
Eylea vs Eylea + OPT-302 (p<0.05)

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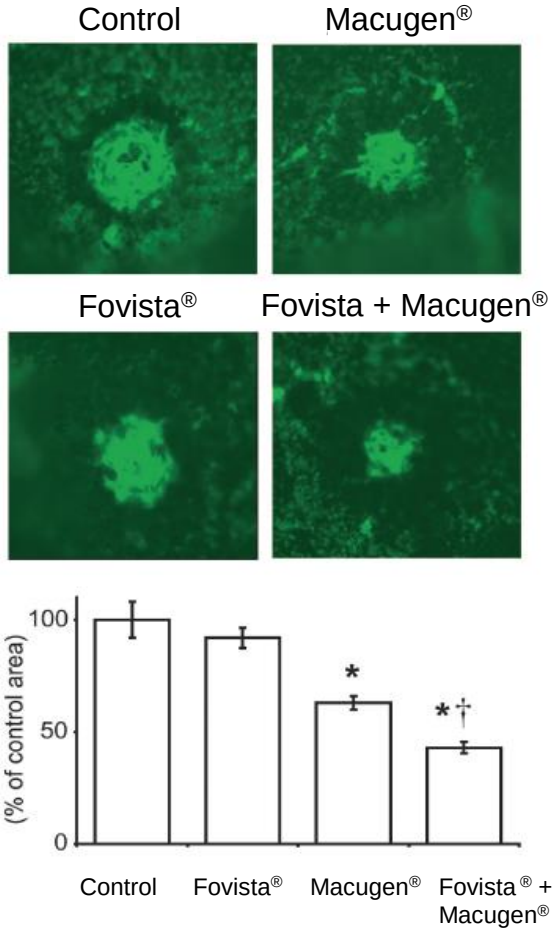
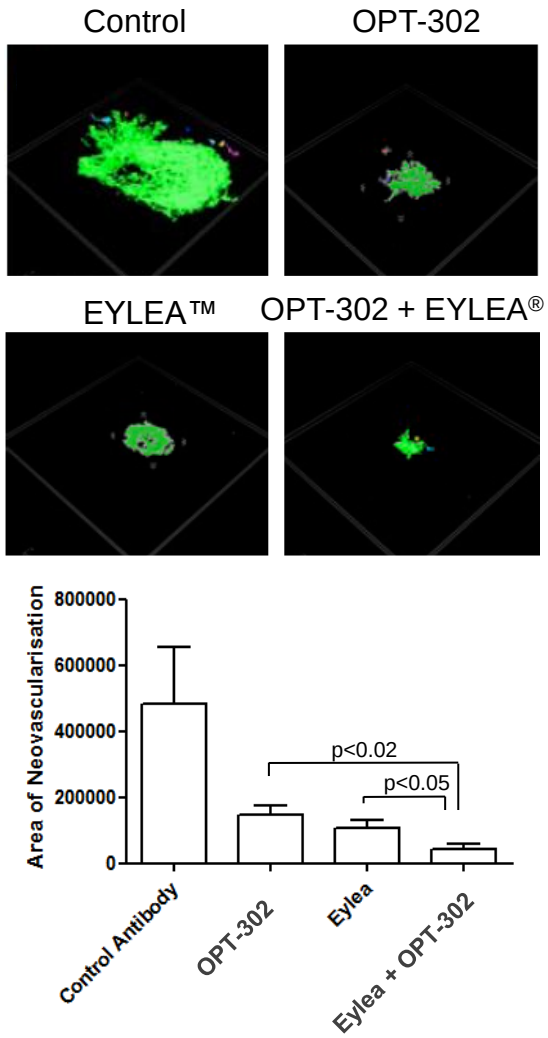
Ophthotech and Opthea:

Distinct approaches for Wet AMD combination therapy





"Macugen®" – targets VEGF-A_{165} isoform
"Fovista®" – aptamer targeting PDGF-b
Jo et al., Am.J.Pathol., 168(6), 2036-2053, 2006.

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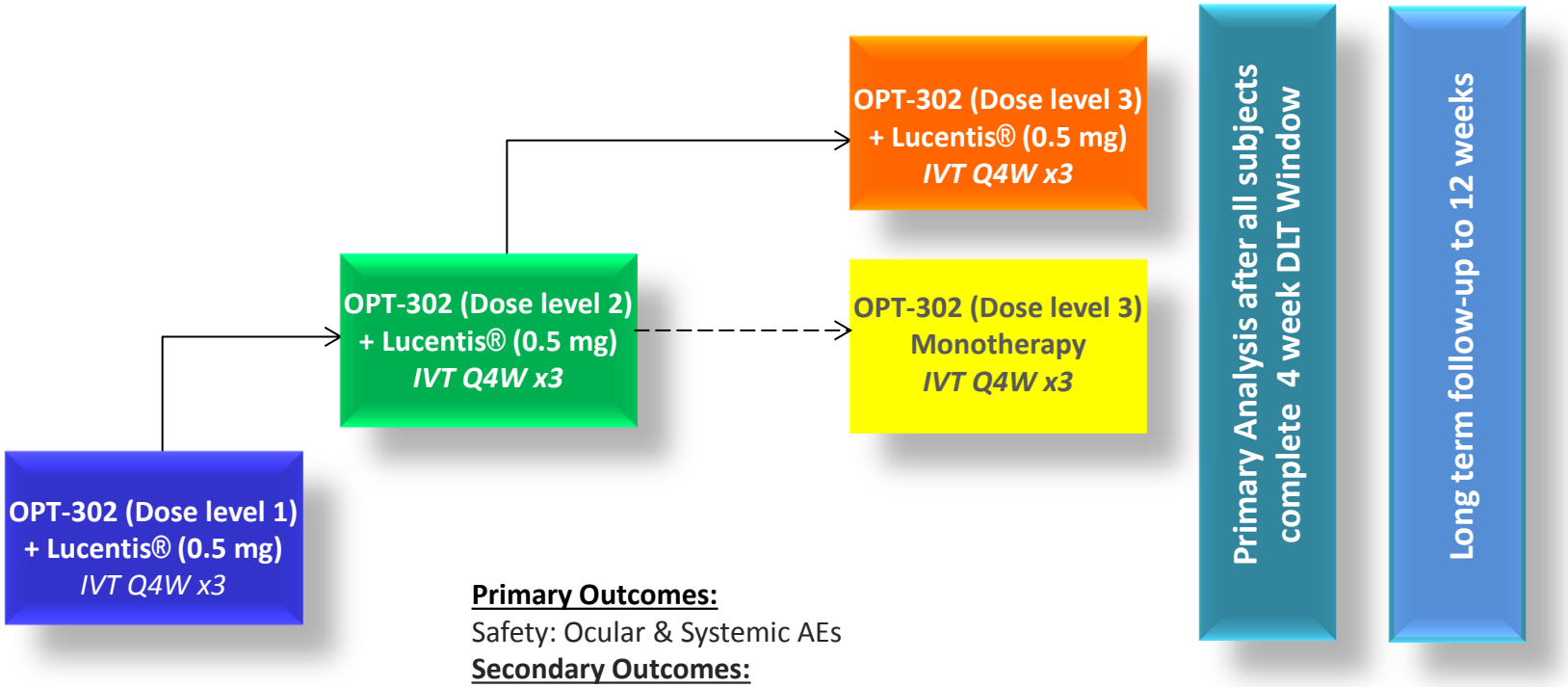
OPT-302 Phase 1: Multiple Dose Combination & Monotherapy Study of Safety, PK & Efficacy



Primary Outcomes:

Safety: Ocular & Systemic AEs

Secondary Outcomes:

Mean change from baseline in:

- visual acuity
- central retinal thickness
- CNV area

Pharmacokinetics

Anti-Drug antibody formation

Biomarkers

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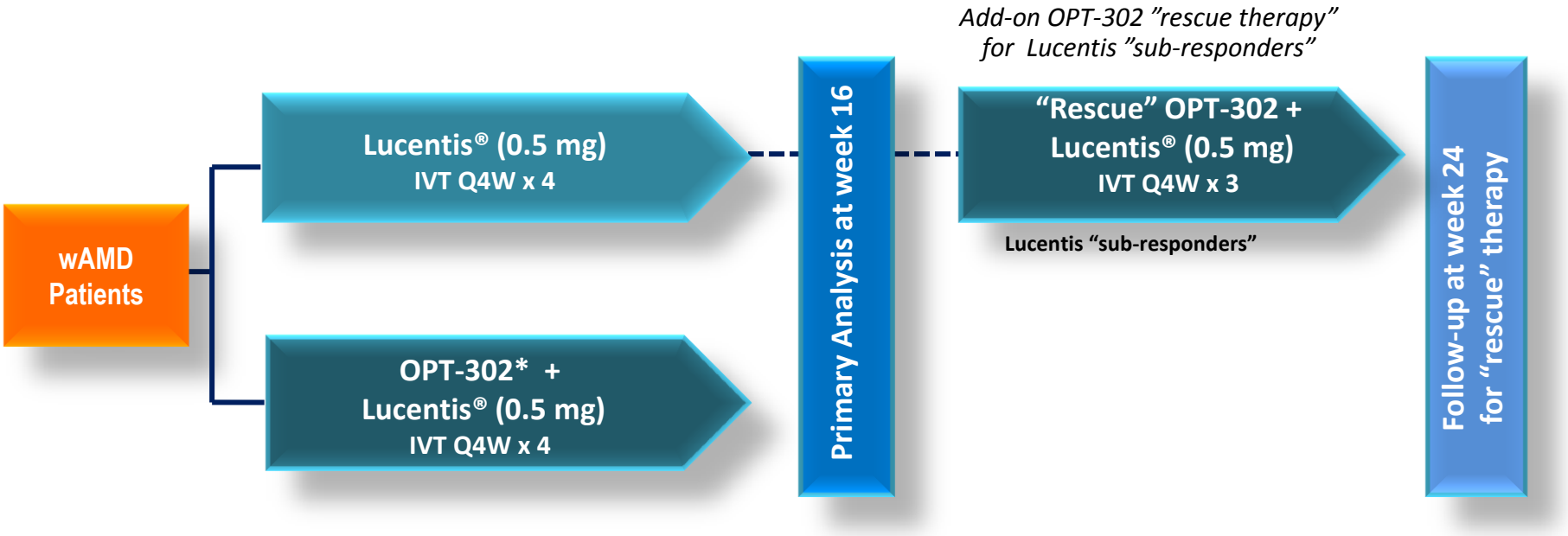
Phase 2a Efficacy Study:
OPT-302 Combination versus anti-VEGF-A Monotherapy
(including extension sub-study of OPT-302 'Rescue' therapy for a-VEGF-A "sub-responders")



Key Endpoints:

Mean change from baseline in:

- visual acuity
- central retinal thickness & fluid
- CNV area

Safety: Ocular & Systemic AEs

Pharmacokinetics

Anti-Drug antibody formation

Biomarkers

** Dose level to be determined from Phase 1*

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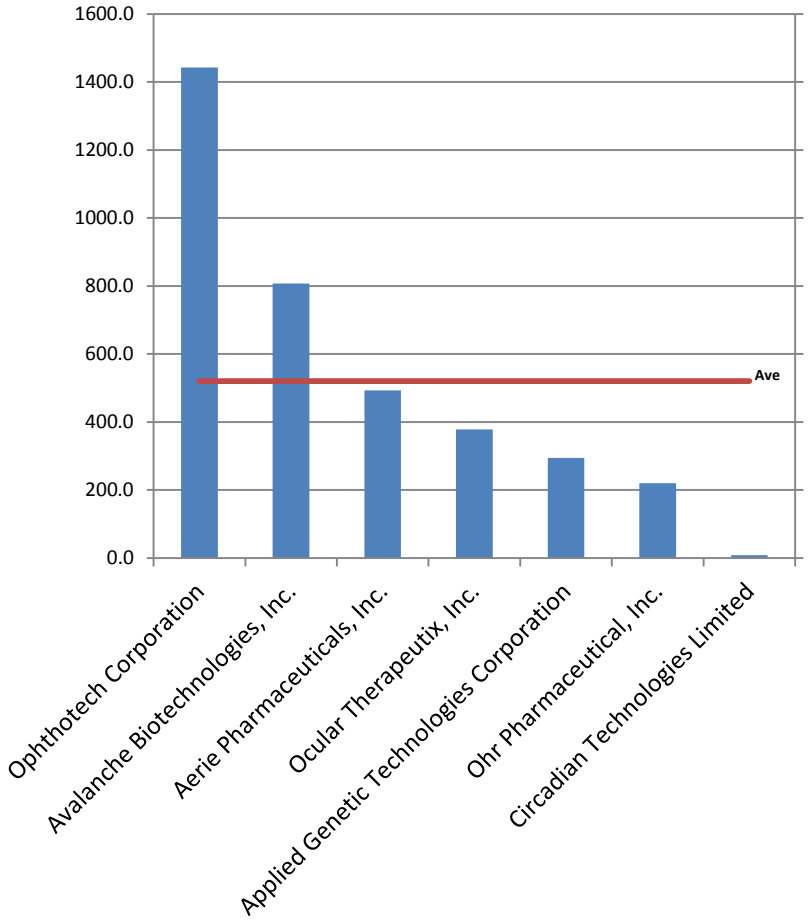
Listed Ophthalmology Companies in Phase 1-3

Company	Market Capitalisation (A$m)[a]	Stage of Development
Ophthotech Corporation	1442.8	Phase 3
Avalanche Biotechnologies, Inc.	807.7	Phase 1/2
Aerie Pharmaceuticals, Inc.	492.7	Phase 3
Ocular Therapeutix, Inc.	378.3	Phase 2/3
Applied Genetic Technologies Corporation	294.3	Phase 1/2
Ohr Pharmaceutical, Inc.	219.6	Phase 2
Circadian Technologies Limited	9.5	Phase 1 Start 1H15
Average	**520.6**	



a. Sept 15 2014, assumes A$1 = US$1.08

Ophthotech: Capital Raising and IPO *Case Study*

Potentially significant implications for Circadian valuation

- Developing Fovista® (a-PDGF-b aptamer) in combination with a-VEGF-A therapy
  - Similar approach as Circadian/Opthea to combine with existing a-VEGF-A therapies
- Published preclinical data 2006
- Fovista ® is not active as a single-agent in wet AMD; OPT-302 highly active as a single-agent in preclinical model

Ophthotech Valuation Progression ($US)

- Series A: $36M (2007)
  - on basis of preclinical data
- Series B: $30M (Dec 2009)
- Completion of Phase 2b announced Oct 2012
- IPO (Sept 2013)
  - 7.6M shares @ $22 per share
  - Raised $167.2M
  - Trading at $35 - $48 per share
  - Current Mkt Cap >$1.3Bn

OPT-302: Intellectual Property

Summary covering sVEGFR-3 IP for Eye Disease

Composition of Matter	Term
Covering sVEGFR-3 (incl. OPT-302) • Granted Patents: Europe, Japan, Canada, Australia • Case allowed in US Sept 2014 – Grant Expected Jan 2015	 2022 ~2026
Covering OPT-302 • Recently filed new specific composition of matter PCT international patent application	~2034
"Use" Patent	
US Patent granted covering generic use of sVEGFR-3 capable of binding VEGF-C to inhibit blood vessels in mammal having disease characterised by expression of VEGFR-3 in blood vessels	2023
Patent Term Extension/Exclusivity	
+5 years under patent term extension OPT-302 entitled to data exclusivity (DE) and market exclusivity (ME) in many jurisdictions, e.g.: • US (12 years DE for biologics) • Europe (10 years made up of 8 years DE + 2 years ME) • Japan (up to 8 years *de facto* DE) • South Korea (5 years DE) • Canada (up to 8 years made up of 6 years DE + 2 years ME) • Australia (5 years DE)	

Summary

Leader in VEGF-C/D and VEGFR-3 targeting compounds in Oncology and Ophthalmology

- Lead compound OPT-302 is a fully owned and highly valuable asset
  - Phase 1 clinical trial for wet age-related macular degeneration (AMD) 2Q15
  - Program expected to be funded through meaningful Phase 1 and 2A clinical milestones to Q4 2017
- Two oncology assets in clinical development
  - VGX-100 Phase 2 ready asset poised for licensing/partnership
  - Eli Lilly partnered IMC-3C5 to complete Phase 1 in solid tumours in 1H15
- Funding progresses ophthalmology program to value-adding milestones, accelerates licensing opportunities for VGX-100 and strengthens CIR balance sheet
- Clinical and business development news-flow over next 24 months
- Strong management team with substantial experience in developing drugs targeting the VEGF pathway, wet AMD and oncology
- Extensive worldwide intellectual property platform in respect of VEGF-C, VEGF-D and VEGFR-3

Key Risk Factors

- OPT-302 is in preclinical development and product commercialisation resulting in product sales and revenues are likely to be years away.
- Scale-up of OPT-302 manufacture to support clinical studies is underway but not complete. As such, there is a risk that scale-up may present technical difficulties.
- OPT-302 is yet to complete requisite preclinical safety/toxicology studies to support IND filing to the FDA for initiation of clinical studies at US sites. There is a risk that OPT-302 does not demonstrate an acceptable safety profile in preclinical studies to support initiation of clinical studies.
- OPT-302 may fail to demonstrate a safety profile or sufficient evidence of therapeutic efficacy in Phase 1 or 2 clinical studies to support its ongoing clinical development.
- Circadian may not obtain regulatory approvals required to initiate clinical studies under an IND and clinical start may be delayed if the FDA requests additional studies be conducted in addition to those that are currently planned.
- As Circadian currently has no material revenues, it may need to raise further capital in the future, which may dilute existing shareholders.
- Circadian value may be impacted if its intellectual property is not able to be adequately protected or is subject to challenge by a third party.
- Circadian value may be impacted by competitive or alternative products or technologies.

** This is not an exhaustive list of risks. There may be other risks associated with an investment in Circadian.*