OPT-302:
a VEGF-C/VEGF-D 'Trap' for wet AMD

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Circadian Technologies
(ASX:CIR, OTCQX:CKDXY)

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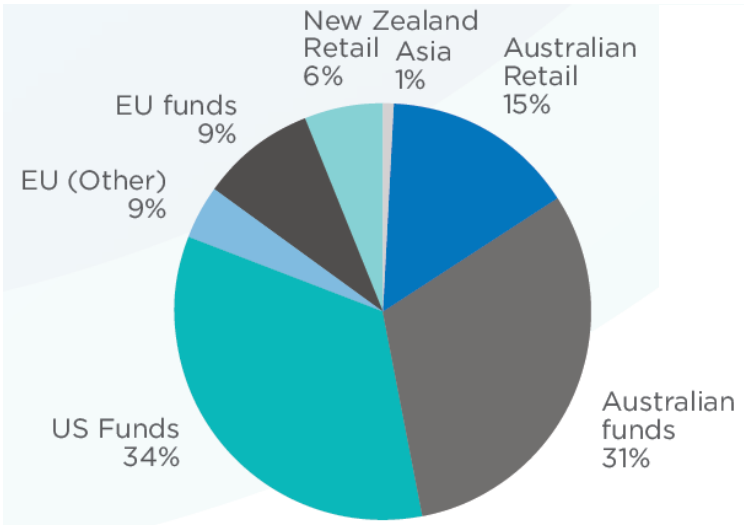
Opthea Pty Ltd

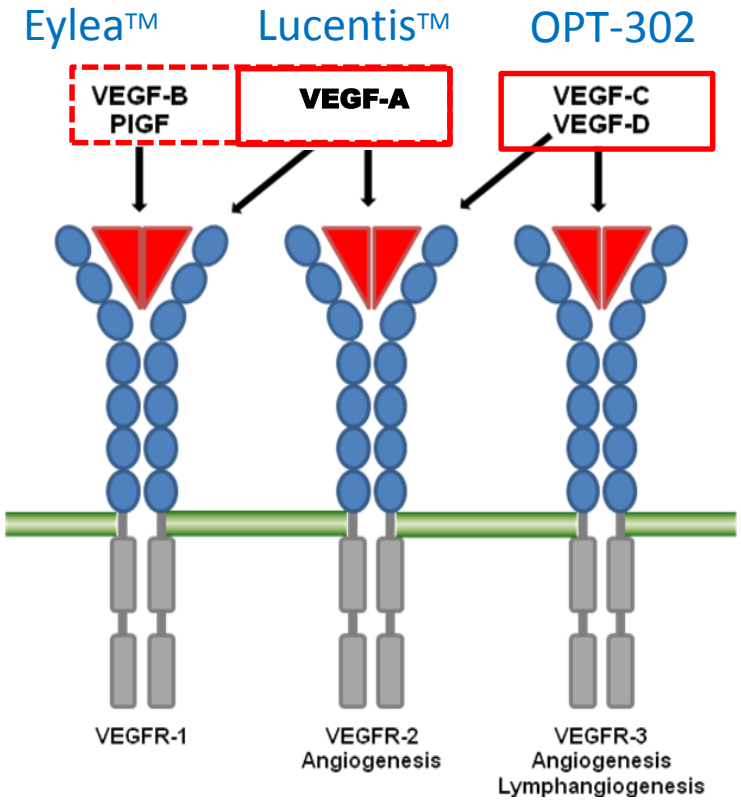
- Opthea Pty Ltd is a 100% owned subsidiary of Circadian Technologies (Melbourne, Aust)
- Extensive IP portfolio around members of the Vascular Endothelial Growth Factor (VEGF) family
  - VEGF-C
  - VEGF-D
  - VEGFR-3
- Lead compound OPT-302 inhibits VEGF-C and VEGF-D
  - Potent inhibitor of angiogenesis & vascular leakage
- OPT-302 in development for treatment of wet AMD
- Potential in a range of eye diseases as a monotherapy or in combination with approved anti-VEGF-A therapies
- Phase 1/2A trial actively recruiting wet AMD patients under IND at US clinical sites

Key Financial Details	ASX: CIR
Ticker Symbol	ASX:CIR OTCQX: CKDXY
Share Price *(Nov 10 2015)*	A$0.29
Market Capitalisation *(Nov 10 2015)*	~A$43M (~USD 30M)



Resistance to anti-VEGF-A monotherapy

- Long-term single-agent therapy with VEGF-A inhibitors is associated with sub-optimal response
  - Sub-optimal improvements in VA (<15-letter gain)
  - Persistent fluid on OCT
- Resistance to VEGF-A monotherapy may be related to other VEGF family members
- VEGF-C and VEGF-D bind and activate VEGFR-2 and VEGFR-3
- Complete blockade of VEGFR-2 requires VEGF-A, VEGF-C and VEGF-D inhibition
- VEGFR-3 also stimulates angiogenesis via a VEGF-A independent pathway

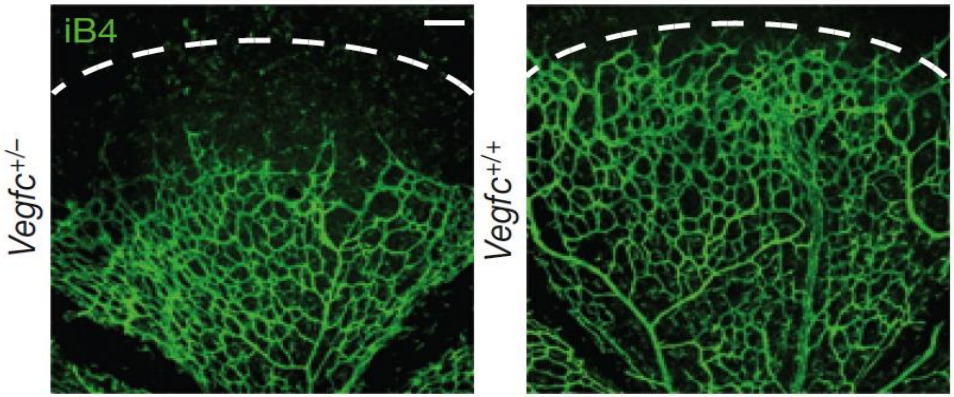


- OPT-302 combination therapy with an anti-VEGF-A inhibitor achieves more complete suppression of the VEGF/VEGFR pathway
- Targets functional redundancy and mechanisms of sub-response to VEGF-A inhibition

VEGF-C stimulates angiogenesis and vascular permeability

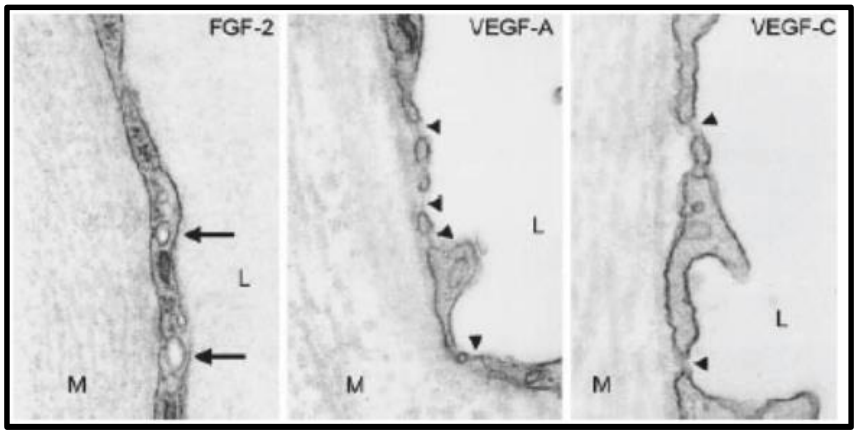
VEGF-C is required for retinal vascular development

Tammela et al., Nature Cell Biology, 2011.



VEGF-C is a potent inducer of vascular leakage

Cao et al,. Circ Res., 2004



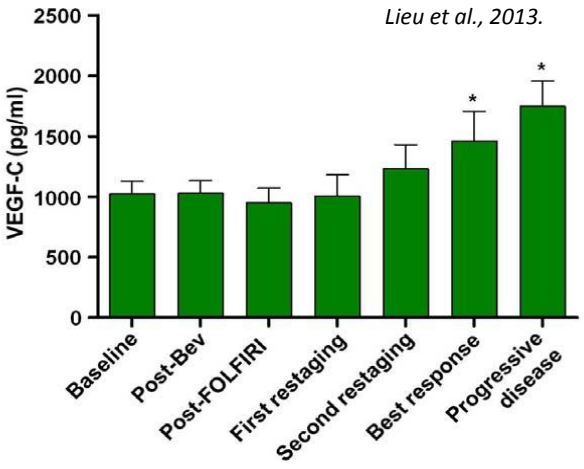
OPTHEA

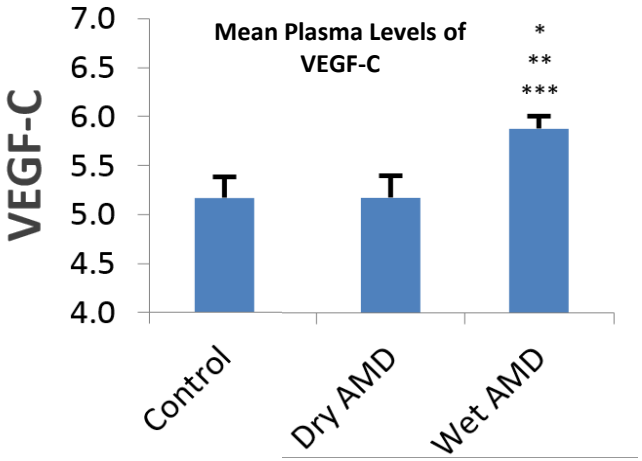
‘Sub-responsiveness’ to anti-VEGF-A therapy is associated with upregulation of VEGF-C and VEGF-D

- Sub-responsiveness to anti-VEGF-A therapy is associated with upregulation of VEGF-C and VEGF-D expression
  - *Lieu et al., 2013; Li et al., 2013; Zhao et al, 2006; Rose et al., 2010; Fan et al,2011, Grau et al.,2011*

- VEGF-C is elevated in the plasma of wet AMD patients compared to healthy volunteers and patients with dry AMD
  - *World Congress on Angiogenesis, Boston, 2015, #1509*

- VEGF-C is expressed in the RPE of healthy eyes.
- In wet AMD, VEGF-C is expressed in RPE and endothelial cells associated with CNV.
- VEGF-C levels in the retina increase with disease severity.
  - *World Congress on Angiogenesis, Boston, 2015, #1509*

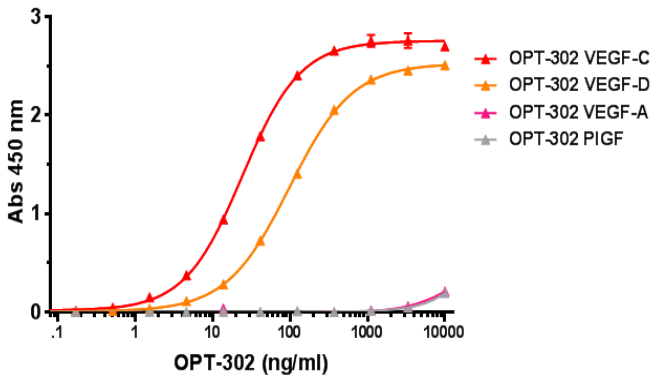




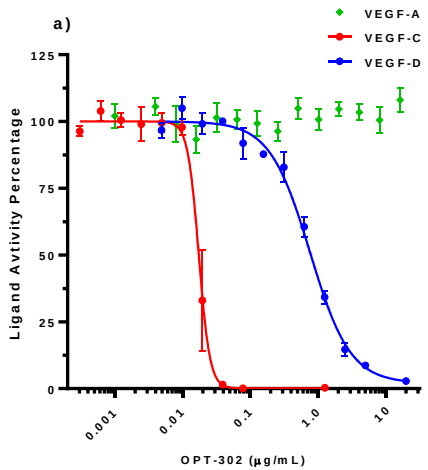
OPT-302

- OPT-302: a soluble form of VEGFR-3
- Comprises the extracellular domains 1-3 of VEGFR-3 and the Fc Fragment of human IgG1
- Potent inhibitor of VEGF-C (~5pM) and VEGF-D (~0.5 nM)
- A ‘trap’ that binds and neutralises the activity of VEGF-C and VEGF-D, blocking binding to the receptors VEGFR-2 and VEGFR-3
- OPT-302 PK in rabbit and cyno vitreous humor following IVT similar to aflibercept, prolonged exposure in posterior and anterior segments
- Completed IND enabling safety toxicology studies in cyno & rodents to support Ph 1/2A (IV and IVT administration, single and repeat-dose, monoTx & Lucentis combination)

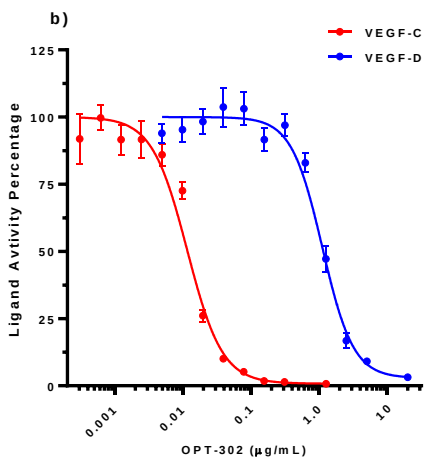
ELISA



VEGFR-2 bioassay

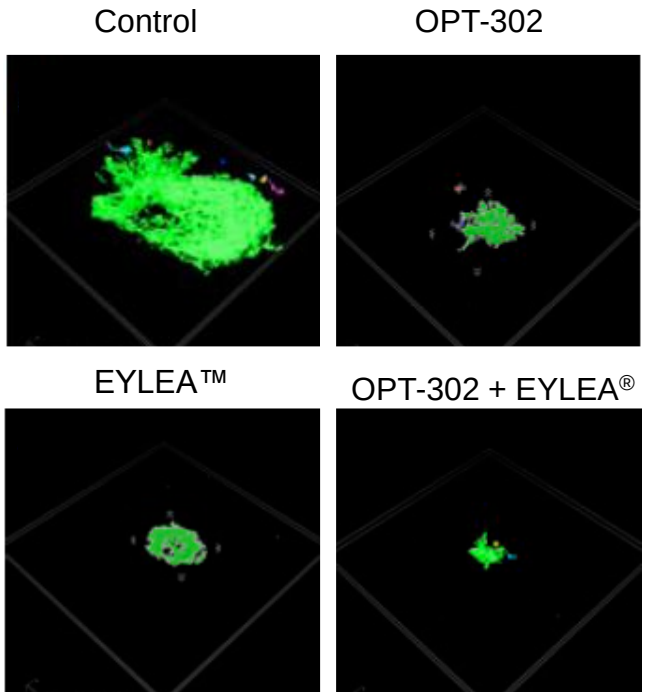


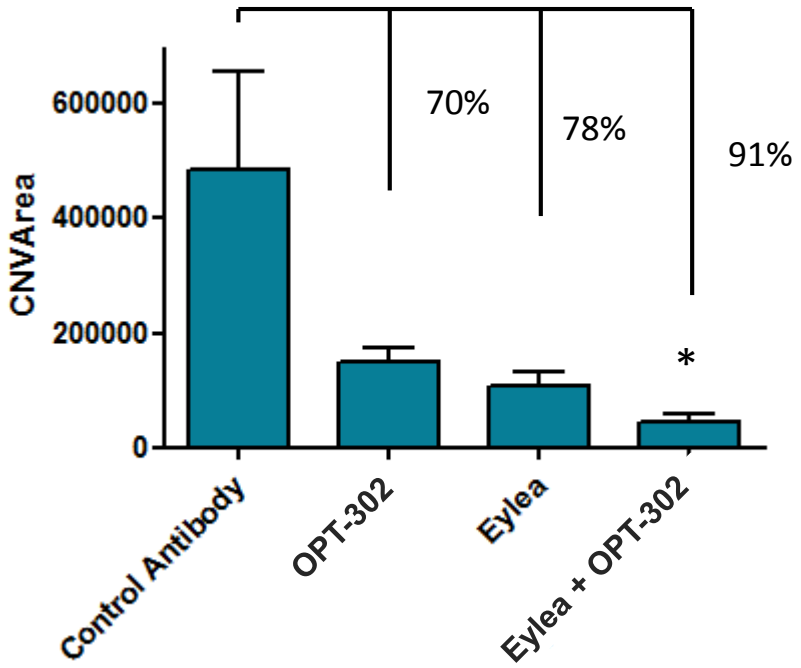
VEGFR-3 bioassay



OPT-302 has comparable single-agent and additive activity with 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)

Protocol OPT-302-1001: Phase 1/2A study in wet AMD

A Phase 1/2A Dose Escalation Study Evaluating the Safety, Pharmacokinetics and Pharmacodynamics of OPT-302 in combination with Ranibizumab in subjects with wet AMD

Two stage Design

Part 1 Dose escalation – Open Label

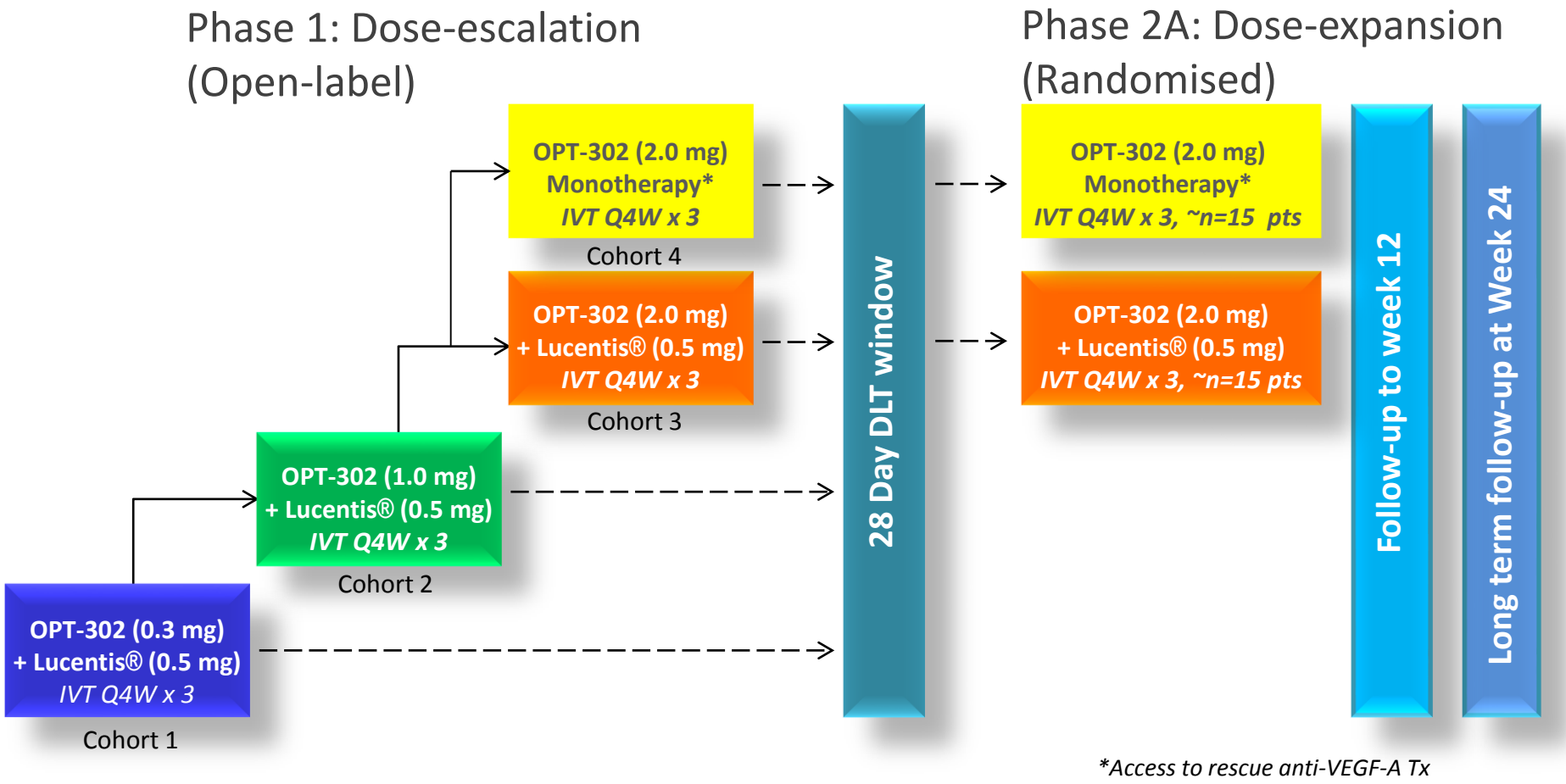
Part 2 Dose expansion - Randomized

Subjects with active CNV associated with wet AMD including those that are either treatment naive or have received prior therapy will be eligible for the study.

IND #: 122162
Sterling IRB study #: 5123 (*Approved*)
ClinTrials.gov ID#: NCT02543229

OPT-302 Phase 1/2A: Protocol: OPT-302-1001

Dose-escalation & dose-expansion of repeated IVT injections



*Access to rescue anti-VEGF-A Tx

- *Comprises of 4 treatment cohorts of 5 subjects each.*
- *Should a dose limiting toxicity (DLT) occur, 3 additional subjects will be enrolled in that cohort.*
- *OPT-302 and ranibizumab given as separate IVT injections (each 0.05 mL) once every 4 weeks at day 1, 29 and 57.*
- *When used in combination, the ranibizumab IVT injection will be given 30 mins prior to sequential IVT OPT-302.*

OPT-302 Phase 1/2A study objectives

Primary Objectives:

- To evaluate the safety and establish the dose of OPT-302 administered by intravitreal (IVT) injection in combination with IVT ranibizumab in subjects with wet AMD

Secondary Objectives:

- mean change in central retinal thickness from baseline (SD-OCT)
- mean change in CNV lesion area from baseline (FA)
- mean change in BCVA (ETDRS) from baseline
- mean time to, and number of, retreatment injections of anti-VEGF-A therapy during long term follow-up (week 12 to 24)
- need for 'rescue therapy' with ranibizumab in subjects receiving OPT-302 monotherapy
- pharmacokinetics (PK) of OPT-302
- incidence of anti-OPT-302 antibody formation

Exploratory Objective(s):

- To evaluate changes in systemic levels of angiogenesis-related biomarkers

Clinical Advisory Board & Investigators
Near-term Clinical Milestones

- Clinical Advisory Board of internationally recognised and experienced key opinion leaders from Australia and US
- Extensive experience in development of novel and FDA approved therapeutics for wet AMD, including Macugen™, Fovista ™, Eylea ™ and Lucentis™
  - Pravin Dugel MD (Retinal Consultants Arizona, Keck School of Medicine USC)
  - Mark Gillies MD (Save Sight Institute, Sydney Uni.)
  - Peter Campochiaro MD (Johns Hopkins, Wilmer Eye Institute)
  - Kameran Lashkari MD (Schepens Eye Research Inst., Mass.Eye & Ear)
- Actively recruiting
- ClinTrials.gov ID#: NCT02543229

OPT-302 Wet AMD Program: Milestones

IND Approval & Ph1/2A Initiated June 2015 ✓

Ph 1 Primary Data Analysis: 1Q16

Ph 2A Primary Data Analysis: 2H16

In combination with a VEGF-A inhibitor, OPT-302 achieves more effective VEGF suppression

- OPT-302 is a novel ‘trap’ that blocks the alternative VEGF-C/VEGF-D pathway
- Used in combination, OPT-302 can achieve more effective VEGF suppression and target a key mechanism of sub-responsiveness to existing therapies
- Combination OPT-302 + a-VEGF-A therapy may improve visual acuity outcomes, reduce retreatment rates and lead to larger treatment free intervals for patients
  - Potential for:
    - Improved patient responses
    - Reduced treatment burden

Thank-you

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