OPT-302: A novel VEGF-C/D ‘trap’ for retinal eye diseases

Corporate Presentation, March 2019
Megan Baldwin PhD, CEO & Managing Director
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### Opthea Limited

**Opthea Limited**

- Public co listed on ASX (ASX:OPT) developing OPT-302 for the treatment of wet AMD and DME

**OPT-302 has a novel mechanism of action**

- OPT-302 (sVEGFR-3) is a biologic administered by IVT injection that targets VEGF-C and VEGF-D
- Blocks the same, as well as independent pathways, to VEGF-A
- In combination with anti-VEGF-A therapies, more completely shuts-down VEGF/VEGFR pathway
- Targets mechanisms of resistance and sub-optimal clinical response to existing therapies

**Strong & growing commercial potential**

- Current & growing market opportunity of $10B+ worldwide
- Broad development opportunity in wet AMD, DME and RVO
- Very few novel agents in development to address unmet medical need

**Well tolerated safety profile & evidence of clinical activity in wet AMD & DME**

- Completed Phase 1/2a trial in 51 wet AMD patients
- Completed Phase 1b dose-escalation trial in 9 persistent DME patients
  - Dose-responsive improvements in visual acuity, reductions in retinal fluid & swelling
- Well tolerated safety profile of OPT-302 admin. in combination with ranibizumab & aflibercept

**Two ongoing Ph 2 trials, data anticipated CY 2019**

- 366 pt Phase 2b wet AMD trial completed recruitment ahead of schedule
  - On-track to report primary data 4Q CY2019
- Currently recruiting in ~108 pt Phase 2a persistent DME trial
- International multi-centre studies recruiting patients in US, EU, Israel and Australia
### Key Financial Details

<table>
<thead>
<tr>
<th>Detail</th>
<th>ASX: OPT</th>
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</thead>
<tbody>
<tr>
<td>Ticker Symbol</td>
<td>ASX:OPT</td>
</tr>
<tr>
<td>Share Price (March 7 2019)</td>
<td>~A$0.78</td>
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<tr>
<td>Total Ordinary Shares on Issue</td>
<td>249,413,639</td>
</tr>
<tr>
<td>Market Capitalisation (March 7 2018)</td>
<td>~A$194m (~USD136m)</td>
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<tr>
<td>Trading Range (last 12 months)</td>
<td>A$0.42 – 0.80</td>
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<tr>
<td>Cash Balance (Dec 31 2018)</td>
<td>~A$40m</td>
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<tr>
<td>Forecast Net Operating Cash Burn (CY 2019)</td>
<td>~$18m</td>
</tr>
<tr>
<td>Top 20 Shareholders Own</td>
<td>69%</td>
</tr>
<tr>
<td>Institutional Holders</td>
<td>84%</td>
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</tbody>
</table>

### Details

- **Cash Positive until CY end 2020**
- Fully funded through two randomised controlled trials:
  - Ph2b wAMD (366 pts)
  - Ph1/2a DME (~117 pts)
- Accumulated tax & capital losses ~A$15m

### Share Price Performance (last 12 months)

![Share Price Chart]

**Shareholders by Region**

- US Funds: 28%
- Australian Funds: 39%
- EU/Other Funds: 18%
- Retail: 15%

**Analyst Coverage (Aust)**

- Shane Storey
- Tanushree Jain
Existing Therapies Primarily Target VEGF-A

- Long-term therapy with selective VEGF-A inhibitors is associated with sub-optimal responses
  - Sub-optimal improvements in visual acuity
  - Persistent retinal fluid
- Resistance to VEGF-A monotherapy may be related to other VEGF family members
- VEGF-C/D are elevated when VEGF-A is inhibited
- OPT-302 combination therapy achieves a more complete suppression of the VEGF/VEGFR pathway
- OPT-302 targets incomplete response to VEGF-A inhibition

OPT-302 inhibits VEGF-C/D

OPT-302: Rationale

- Used in combination with a VEGF-A inhibitor, completely blocks VEGFR-2 and VEGFR-3 signalling
VEGF-A Inhibition Upregulates VEGF-C/D

Clinical data suggest VEGF-C/D may mediate resistance & sub-optimal response to anti-VEGF-A therapy

**Metastatic Colorectal Cancer**

<table>
<thead>
<tr>
<th>Time</th>
<th>VEGF-C (pg/ml)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>500</td>
</tr>
<tr>
<td>Post-Bev</td>
<td>1,000</td>
</tr>
<tr>
<td>Post-FOLFIRI</td>
<td>1,500</td>
</tr>
<tr>
<td>First restaging</td>
<td>2,000</td>
</tr>
<tr>
<td>Second restaging</td>
<td>4,000</td>
</tr>
<tr>
<td>Best response</td>
<td>6,000</td>
</tr>
<tr>
<td>Progressive disease</td>
<td>8,000</td>
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**Neovascular AMD**

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<th>Time</th>
<th>VEGF-C (pg/ml)</th>
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<tr>
<td>Baseline</td>
<td>5.37</td>
</tr>
<tr>
<td>1m</td>
<td>6.91</td>
</tr>
<tr>
<td>2m</td>
<td>8.91</td>
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OPT-302 ongoing clinical trials in wAMD & DME: multiple additional market opportunities

**Wet Age-Related Macular Degeneration**

Edema caused by abnormal vasculature growth which ultimately results in the loss of visual function.

**Diabetic Macular Edema (DME)**

A complication of diabetes that manifests as edema and hard exudates in the macula and leads to loss of VA.

**Retinal Vein Occlusion (RVO)**

Characterized by retinal vein blockage, which selectively leads to edema formation and loss of visual acuity.

**Diabetic Retinopathy**

Characterized by vascular injury and permeability, which may be followed by active proliferation of new vessels.

**Myopic CNV**

Characterized by ingrowth of new blood vessels beneath the retina in the myopic eye.

**Other non-AMD associated CNV**

May occur secondary to other ophthalmic conditions.

Additional market opportunity: 3 M Wet AMD

850 K RVO

1.3 M DME

U.S. & EU Epidemiology (# patients)

Source: GlobalData; EvaluatePharma; PubMed; Physician Interviews.
Current Treatment Paradigms: Predominantly VEGF-A Inhibitors

### Current Wet AMD Treatment Options

<table>
<thead>
<tr>
<th>Company</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Market Opportunity</th>
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| Genentech | • First therapy FDA-approved for the treatment of wet AMD  
• More flexible dosing in EU | • Perceived to be clinically identical to but more costly than Avastin | • May be used in patients with sub-optimal response to a-VEGF-A Tx |
| REGENERON | • Dosing frequency on U.S. label is lower (every 2 months after loading doses) than Lucentis | • In practice, increased durability is not as pronounced as in trials | • Risk of IOP elevation and cataracts |
| Genentech | • Significantly less costly than other treatment options | | • Total Net Sales in US & EU5 2017 in excess of US$2.4B (~37% mkt) |

### Current DME Treatment Options

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| Genentech | • Significantly less costly than other treatment options | | • Total Net Sales in US & EU5 2017 in excess of US$4.2B (~62% mkt) |

### Advantages, Disadvantages and Market Opportunity

- **Advantages:**
  - Total Net Sales in US & EU5 2017 in excess of US$2.4B (~37% mkt)
  - Total Net Sales in US & EU5 2017 in excess of US$4.2B (~62% mkt)
  - Total Net Sales in US & EU5 2017 in <US$100 M (~1% mkt)
  - Sales driven by Eylea despite ~50% eyes treated with Avastin

- **Disadvantages:**
  - May be used in patients with sub-optimal response to a-VEGF-A Tx

- **Market Opportunity:**
  - Global sales revenue for Eylea & Lucentis exceeded US$9.3B in 2017 and is growing Y2Y due to increasing prevalence of diabetes and ageing population

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*Includes Triamcinolone (generic). Laser not typically used in central-involved DME*
An Unmet Medical Need for Wet AMD and DME

Despite receiving a VEGF-A inhibitor (ranibizumab, aflibercept or bevacizumab)*:

- **wAMD**
  - >50%: Do not achieve significant vision gains
  - 2/3: Will continue to have fluid at the back of the eye
  - 25%: Will have further vision loss at 12 months

- **DME**
  - 2/3: Do not achieve significant vision gains#
  - 25%: Continue to have macula thickening/swelling^

Opportunity: New Products that Improve Efficacy and Durability

* Based on randomised, controlled clinical trial data; # Fail to achieve ≥ 2 lines improvement in BCVA; ^ SD-OCT CST ≥ 300 µM or Time-Domain OCT CST ≥ 250 µM

Ranibizumab: Lucentis® (Genentech/Roche, Novartis); Aflibercept: Eylea® (Regeneron, Bayer); Aflibercept: Avastin® (Genentech/Roche)
**OPT-302**

- Potent inhibitor of VEGF-C (~5pM) and VEGF-D (~0.5 nM)
- A ‘trap’ that blocks VEGF-C and VEGF-D binding to the receptors VEGFR-2 and VEGFR-3

**Ocular Biodistribution OPT-302 vs Aflibercept in Rabbits**

- Non-compartmental OPT-302 PK analysis indicated:
  - Low systemic exposure
  - Half-life of 8 ± 2 days
  - Mean Cmax of ~21 ng/mL at ~31 hours post IVT injection at a dose of 2 mg
  - No accumulation
  - No influence from ranibizumab on the PK profile.

**Mean OPT-302 serum concentrations following IVT injection (Ph 1/2a)**

**OPT-302 Has Comparable Ocular Biodistribution and PK Profile to Eylea, with low systemic exposure**
## OPT-302 Clinical Program

- Two ongoing randomised controlled clinical trials in nAMD & DME

### Neovascular AMD

<table>
<thead>
<tr>
<th>Combination Agent</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2a</th>
<th>Phase 2b</th>
<th>Phase 3</th>
<th>Status</th>
<th>1º Data Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPT-302 Target: VEGF-C/D</td>
<td>Ranibizumab</td>
<td>Ranibizumab Target: VEGF-A</td>
<td>Complete Ph 1/2a (n=51)</td>
<td>April 2017</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>OPT-302 Target: VEGF-C/D</td>
<td>Ranibizumab Target: VEGF-A</td>
<td>Ongoing Ph 2b (n=366)</td>
<td>4Q CY 2019</td>
<td></td>
<td></td>
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</table>

### Diabetic Macular Edema

<table>
<thead>
<tr>
<th>Combination Agent</th>
<th>Preclinical</th>
<th>Phase 1</th>
<th>Phase 2a</th>
<th>Phase 2b</th>
<th>Phase 3</th>
<th>Status</th>
<th>1º Data Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPT-302 Target: VEGF-C/D</td>
<td>Aflibercept</td>
<td>Target: VEGF-A, PIGF, VEGF-B</td>
<td>Ongoing Ph 1b/2a (n=117)</td>
<td>2H CY 2019</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
OPT-302: Phase 1/2a Wet AMD Trial Results

A Phase 1/2A dose escalation study evaluating the safety, pharmacokinetics and pharmacodynamics of OPT-302 in combination with ranibizumab (Lucentis®) in subjects with wet AMD
OPT-302 Phase 1/2a First-in-Human Study in Neovascular AMD (n=51)

Part 1: Dose-escalation (Open-label)

- **Cohort 1**: OPT-302 (0.3 mg) + Ranibizumab (0.5 mg) *IVT Q4W* x 3
  - Comprises of 4 treatment cohorts of 5 subjects each
  - Access to rescue anti-VEGF-A Tx

- **Cohort 2**: OPT-302 (1 mg) + Ranibizumab (0.5 mg) *IVT Q4W* x 3

- **Cohort 3**: OPT-302 (2 mg) + Ranibizumab (0.5 mg) *IVT Q4W* x 3

- **Cohort 4**: OPT-302 (2 mg) Monotherapy* *IVT Q4W* x 3

Part 2: Dose-expansion (Randomised 3:1)

- **OPT-302 (2 mg)** Monotherapy* *IVT Q4W* x 3, n=8 pts

  - 28 Day DLT window

- **OPT-302 (2 mg)** + Ranibizumab (0.5 mg) *IVT Q4W* x 3, n=23 pts

  - Follow-up to week 12

- **OPT-302 (2 mg)** Monotherapy* *IVT Q4W* x 3, n=8 pts

  - Long term follow-up at Week 24

*ClinTrials Identifier NCT 02543229*
OPT-302 Phase 1/2a: Patient Demographics & Safety Summary

- 51 patients, 32 (63%) females, 19 (37%) males, mean age 77 years
- 37/51 (73%) occult, 12/51 (23%) min classic, 2/51 (4%) predominantly classic
- Mean min classic component 5.9%
- 49% treatment-naïve
- 51% difficult to treat patients sub-responsive to anti-VEGF-A therapy
  - Mean number prior anti-VEGF-A injections: 17 (~2 years²)

OPT-302 + Lucentis administered by repeat IVT injection (Baseline, Wk 4, Wk 8)
- No missed doses, safety experience with ~150 intravitreal (ocular) injections of OPT-302

OPT-302 at ocular doses up to 2 mg + Lucentis (0.5 mg):
- No dose limiting toxicities (MTD was not reached)
- No drug-related serious adverse events or systemic adverse events

Majority of ocular emergent adverse events primarily related to IVT injection procedure
- (31 / 51 patients; 59%); majority Grade 1 / Mild or Grade 2 / Moderate and Manageable

Two patients (4%) had ocular adverse events related to OPT-302 study drug
- AEs were Grade 1 / Mild inflammation indicative of anterior uveitis in the low- and mid-dose combination groups
- No OPT-302 related AEs observed in the high dose (2mg) combination or monotherapy treated patients (n=41)

No clinically significant changes in IOP, ECG’s, blood pressure, vitals
No evidence of OPT-302-related immunogenicity

<table>
<thead>
<tr>
<th>Cohort</th>
<th>Treatment</th>
<th># Naïve Patients</th>
<th># Prior-Treated Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>OPT-302 (0.3 mg) + Lucentis (0.5 mg)</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2</td>
<td>OPT-302 (1.0 mg) + Lucentis (0.5 mg)</td>
<td>0</td>
<td>5</td>
</tr>
<tr>
<td>3 &amp; 5</td>
<td>OPT-302 (2.0 mg) + Lucentis (0.5 mg)</td>
<td>16</td>
<td>12a</td>
</tr>
<tr>
<td><strong>Total Combination Tx</strong></td>
<td><strong>18</strong></td>
<td><strong>20</strong></td>
<td></td>
</tr>
<tr>
<td>4 &amp; 6</td>
<td>OPT-302 (2.0 mg)</td>
<td>7b</td>
<td>6</td>
</tr>
<tr>
<td><strong>51 Total Patients</strong></td>
<td><strong>25</strong></td>
<td><strong>26</strong></td>
<td></td>
</tr>
</tbody>
</table>

a. One patient with metastatic ovarian cancer/pulmonary embolism died prior to the week 12 (day 69) visit due to intercurrent illness unrelated to study drugs
b. One patient with a myocardial infarction died prior to the week 12 (day 77) visit (unrelated to study drugs)
². Assuming treatments every 6 weeks, 1.3 years assuming treatment every 4 weeks.
In MARINA trial (Phase 3 registrational):
~6 letters gain in vision compared to baseline at Week 12 in patients with minimally classic/occult wet AMD lesions treated with Lucentis® (ranibizumab)

Optea’s Phase 1/2a trial recruited patients with wet AMD lesion types similar to those patients recruited into the MARINA study

<table>
<thead>
<tr>
<th>Study</th>
<th>VA gain at 12 Weeks [ETDRS letters]</th>
<th>Prior-Treatment*</th>
<th>% Lesion Type Classic (C); Predominantly Classic (PC); Minimally Classic (MC); Occult (Oc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPT-302-1001</td>
<td>+10.8</td>
<td>Naive</td>
<td>PC (8%); MC (36%); Oc/other (56%)</td>
</tr>
<tr>
<td>OPT-302-1001</td>
<td>+4.9</td>
<td>Prior-Treated</td>
<td>PC (0%); MC (11%); Oc/other (89%)</td>
</tr>
<tr>
<td>Ranibizumab (Lucentis)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MARINA 1</td>
<td>+5.9</td>
<td>Naive</td>
<td>PC (0%); MC (38%); Oc/other (62%)</td>
</tr>
<tr>
<td>ANCHOR 2</td>
<td>+8.4</td>
<td>Naive</td>
<td>PC (96%); MC (4%); Oc/other (0%)</td>
</tr>
<tr>
<td>VIEW 1 3</td>
<td>+7.3</td>
<td>Naive</td>
<td>PC (27%); MC (33%); Oc/other (40%)</td>
</tr>
<tr>
<td>VIEW 2 3</td>
<td>+7.6</td>
<td>Naive</td>
<td>PC (24%); MC (36%); Oc/other (40%)</td>
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<tr>
<td>CATT 4</td>
<td>+6.1</td>
<td>Naive</td>
<td>PC or MC (39%); Oc/other (61%)</td>
</tr>
</tbody>
</table>

**Phase 1/2a: Monotherapy Patients** OPT-302 (2mg) (Naïve & Prior-Treated)

**Evidence of clinical activity in patients administered OPT-302 monotherapy alone**

**Visual Acuity in Patients who were not rescued by Week 12**
- 7/13 (54%) patients did not require ‘rescue’ therapy
- Patients that did not require rescue therapy had:
  - a mean visual acuity gain of 5.6 letters from baseline (range 0 to 18 letters)
  - a mean decrease in CST of -15 uM (baseline CST non-rescue pts: 390 uM) and
  - a 91 uM reduction in SRF
- 6/13 (46%) patients were rescued with a-VEGF-A therapy
- Despite rescue with Lucentis®, 3/5 evaluable patients at week 12 had a decrease in vision compared to baseline (-2, -3, -5 letters)

Naïve patients:
- Mean gain in visual acuity at week 12 from baseline was +10.8 letters
  - *In the MARINA* trial, ~+6 letters gain in vision compared to baseline at Week 12 in patients treated with monthly Lucentis®
- CST was reduced by 119 μM to 283 μM, approaching normal retinal thickness
- SRF reduced by 83% by Week 12
- At week 12, 72% (13/18) patients had complete (100%) resolution of SRF

* Rosenfeld et al., NEJM, 355;14, pp 1419-1431, 2006

Number of Patients: 18; Mean Baseline VA = 56.5 Letters; MARINA: Mean Baseline VA = 53.7 letters
**Phase 1/2a OPT-302 + Ranibizumab Treatment-Naïve Patients**

**OPT-302 (0.3, 2 mg) + Ranibizumab (0.5 mg)**

- **Reduction in CNV Size on FA**
  - Baseline: 7.71
  - Week 4: 3.74
  - Week 12: 2.03

- **% Pts with Absent CNV on FA**
  - Baseline: 5.6%
  - Week 4: 27.8%
  - Week 12: 50%

- **Absence of SHRM**
  - Baseline: 39%
  - Week 12: 21.5%

- **Reduction in SHRM Width**
  - Baseline: 1711
  - Week 4: 1029
  - Week 8: 804
  - Week 12: 754

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**SHRM: Subretinal Hyper-Reflective Material; Treatment Naïve Patients: n = 18; OPT-302 (0.3, 2.0 mg) + ranibizumab (0.5 mg)**

Prior-Treated Patients: Visual Acuity

- Majority of vision gain in Lucentis® treated patients occurs within 3 months
- Plateau “ceiling effect” of response with no other treatment options
- Difficult to treat patient population, very large market opportunity

- 51% of patients enrolled in the Phase 1/2a study were sub-responsive to prior anti-VEGF-A therapy
- Mean number prior anti-VEGF-A injections: 17 (~2 years#)

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* MARINA Phase 3 in wet AMD. Rosenfeld et al., NEJM, 355;14, pp 1419-1431, 2006
# Assuming treatments every 6 weeks, 1.3 years assuming treatment every 4 weeks.
Phase 1/2a: Prior-Treated Patients

OPT-302 (0.3, 1 & 2mg) + Lucentis® (0.5mg)

Number of Patients: 20 pts (BL, Wk 4, Wk 8), 19 pts (Wk 12)

Prior-Treated Patients at week 12:

- Mean number prior anti-VEGF-A injections per patient: 17
- Mean gain in visual acuity at week 12 from baseline was +4.9 letters
- Mean reductions in CST and SRF at week 12 of 54 uM and 62 uM (51%) respectively from baseline
- 3/19 (16%) patients had complete (100%) resolution of SRF
- 9/19 (47%) had > 50% reduction of SRF at week 12 compared to baseline
OPT-302 Phase 1/2a Key Take-Aways

- OPT-302 met the primary safety objective of its Phase 1/2a study (well tolerated)
- Evidence of clinical activity of OPT-302 (VEGF-C/D ‘trap’), including in treatment naïve (49%) and heavily pre-treated patients (51%), and in a study with a high proportion of patients with occult (73%) wet AMD lesions:
  - **Naïve Patients:**
    - Results suggest OPT-302 + Lucentis may lead to improved outcomes over anti-VEGF-A therapies alone, suggesting additional benefit with more complete suppression of VEGF-A + VEGF-C/D
    - Mean gain in visual acuity at week 12 from baseline was +10.8 letters vs. +5.9 letters for Lucentis alone in the MARINA trial and +6.1 letters for each of Avastin and Lucentis alone in the CATT* study
  - **Prior Treated Patients:**
    - Evidence of improved clinical outcomes, including gain in visual acuity and reduction in retinal fluid (CST and SRF), despite long-term prior treatment with anti-VEGF-A (patients had received an average of 17 prior injections, equating to prior treatment over an average ~1.3 years#)
    - Mean gain in visual acuity at week 12 from baseline was +4.9 letters
    - Mean reductions in CST and SRF at week 12 of 54 mM and 62 mM (51%), respectively, from baseline
  - **Monotherapy Patients:**
    - Evidence of clinical activity and visual acuity gains without background standard of care
    - Mean gain in visual acuity at week 12 from baseline of +5.6 letters for patients who did not require “rescue” therapy (7/13, or 54% of patients)
    - Despite rescue with Lucentis, 3 / 5 evaluable “rescue” patients at week 12 had a decrease in vision compared to baseline (-2, -3, -5 letters)
- A consistency of responses in patients:
  - With different treatment histories
  - Across various secondary outcome measures (VA, OCT)

# Assuming treatments every 4 weeks
Ongoing Clinical Trials

Phase 2b wAMD
A dose-ranging study of intravitreal OPT-302 in combination with ranibizumab, compared with ranibizumab alone, in participants with wet-AMD

Phase 1b/2a DME
Phase 1b/2a study of OPT-302 in combination with aflibercept for persistent central-involved diabetic macular edema
OPT-302 Phase 2b Trial in wet AMD (n=366)

Combination OPT-302 + Lucentis vs Sham + Lucentis

Wet AMD Naïve Pts

- OPT-302 (2 mg) + Lucentis (0.5 mg)
- OPT-302 (0.5 mg) + Lucentis (0.5 mg)
- Sham + Lucentis (0.5 mg)

Randomized 1:1:1 to treatment arms: IVT dosing at every 4 weeks (x 6)

• Primary Objective:
  - Mean change from baseline in BCVA (visual acuity) (ETDRS) at week 24

• Secondary Objectives:
  - The proportion of patients gaining ≥15 or more ETDRS letters from baseline at week 24
  - Area under the BCVA over time curve
  - The proportion of patients losing ≥15 or more ETDRS letters from baseline at week 24
  - Change in central subfield thickness (CST) from baseline at week 24 (SD-OCT)
  - Change in intra-retinal fluid and sub-retinal fluid from baseline to week 24 (SD-OCT)
  - Safety and tolerability

Primary data analysis: est. 4Q CY 2019

Opthea enrolled patients at sites in the US, Europe (United Kingdom, France, Poland, Hungary, Spain, Latvia, Italy and Czech Republic) and Israel
VEGF-C and its interaction with VEGFR-2 and VEGFR-3 plays a functional role in pathogenesis of DME:

- OPT-302 has shown evidence of activity to resolve retinal fluid
- VEGFR-2 expression is greater in diabetic retina than non-diabetics
- VEGF-C is elevated in diabetic retinopathy
- Vitreous levels of VEGF-D are elevated in diabetes
- VEGF-C expression is elevated by glucose & pro-inflammatory cytokines
- Inhibition of VEGF-C and VEGF-D in adipose tissue of mice improves metabolic parameters and insulin sensitivity
- Advanced glycation end products accumulate faster in diabetics and stimulate VEGF-C expression and secretion from the RPE
- Single nucleotide polymorphisms (SNPs) in diabetic patients indicate that genetic variation in the VEGF-C gene is associated with diabetic retinopathy and diabetic macular edema

The Majority of DME Patients Sub-Optimally Respond to a-VEGF-A

- DRCR Protocol I evaluated response to anti-VEGF-A from baseline to 156 weeks
- IVT ranibizumab and sham injections every 4 weeks to week 12, then as needed
- At week 12:
  - 40% patients gained < 5 letters (mean -0.3) by week 12
  - > 60% patients gained < 10 letters of improvement in mean BCVA after 3 IVT injections

<table>
<thead>
<tr>
<th>Response Category (Mean Change BCVA BL to Wk 12)</th>
<th>Mean Change BCVA at Wk 12 in Response Category</th>
<th># and % Eyes in Response Category at Wk 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt; 5 Letters</td>
<td>- 0.3 Letters</td>
<td>39.7% (135/340 eyes)</td>
</tr>
<tr>
<td>5 – 9 Letters</td>
<td>6.9 Letters</td>
<td>23.2% (79/340 eyes)</td>
</tr>
<tr>
<td>≥ 10 Letters</td>
<td>15.2 Letters</td>
<td>37% (126/340)</td>
</tr>
</tbody>
</table>

Mean BCVA response at 52 weeks did not vary by more than 5 letters from the mean BCVA response at 12 weeks.
Phase 1b Dose Escalation study of OPT-302 + Aflibercept in DME

Key Inclusion Criteria

- Age ≥ 18 years; centre-involving DME
- CST ≥ 335 µm*
- BCVA 73 – 24 ETDRS letters (20/40 – 20/320 Snellen)
- Prior exposure to anti-VEGF-A therapy with sub-optimal therapeutic response
  - ≥ 3 intravitreal injections
  - Last injection ≤ 6 wks prior to study day 1
  - Prior bevacizumab only allowed if switched to IVT aflibercept or ranibizumab prior to study

* CST as measured by Spectralis (Heidelberg) at screening, ≥ 320 µm for Cirrus.

Key Exclusion Criteria

- HbA1c ≥ 12%
- Uncontrolled hypertension ≥ 180 mmHg systolic or ≥ 110 mmHg diastolic
- Eyes needing PRP within 3 months of screening
- Concurrent / prior use of intravitreal injections of steroids within 4 months of study start
- Concurrent / prior use of dexamethasone or fluocinolone implant in study eye
### Phase 1b: Baseline Ocular Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>OPT-302 (0.3 mg) + Aflibercept (2.0 mg) (N=3)</th>
<th>OPT-302 (1.0 mg) + Aflibercept (2.0 mg) (N=3)</th>
<th>OPT-302 (2.0 mg) + Aflibercept (2.0 mg) (N=3)</th>
<th>Total Number of Subjects (N=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vision</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean BCVA, ETDRS letters (SD)</td>
<td>64.3 (9)</td>
<td>64.6 (5)</td>
<td>66.7 (3.1)</td>
<td>65 (5.5)</td>
</tr>
<tr>
<td>Better than 55 letters vision, n (%)</td>
<td>3 (100%)</td>
<td>3 (100%)</td>
<td>3 (100%)</td>
<td>9 (100%)</td>
</tr>
<tr>
<td>Worse than 55 letters vision, n (%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td><strong>Anatomic</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean CST, µm (SD)</td>
<td>460 (103)</td>
<td>410 (26)</td>
<td>432 (24)</td>
<td>434 (58)</td>
</tr>
<tr>
<td>CST ≤ 450 µm, n (%)</td>
<td>1 (33%)</td>
<td>3 (100%)</td>
<td>2 (67%)</td>
<td>6 (67%)</td>
</tr>
<tr>
<td>CST ≥ 450 µm, n (%)</td>
<td>2 (67%)</td>
<td>0 (0%)</td>
<td>1 (33%)</td>
<td>3 (33%)</td>
</tr>
<tr>
<td>Mean duration of diabetes at screening, years (SD)</td>
<td>14 (7.9)</td>
<td>17.3 (13)</td>
<td>10.9 (12.6)</td>
<td>14.1 (10.3)</td>
</tr>
<tr>
<td>Mean prior intravitreal injections of anti-VEGF-A therapy, number (SD)</td>
<td>5 (2.6)</td>
<td>7.3 (2.5)</td>
<td>6.7 (2.3)</td>
<td>6.3 (2.4)</td>
</tr>
<tr>
<td>Mean time from prior Tx to day 1, days</td>
<td>42 (0)</td>
<td>33.7 (7.2)</td>
<td>31 (4.4)</td>
<td>35.6 (6.5)</td>
</tr>
<tr>
<td>Mean HbA1c*, % (SD)</td>
<td>7.5 (2.4)</td>
<td>7.1 (0.3)</td>
<td>7.4 (1.4)</td>
<td>7.3 (1.4)</td>
</tr>
</tbody>
</table>

*HbA1c = glycated hemoglobin*
## OPT-302 + Aflibercept – Phase 1b Safety Results

<table>
<thead>
<tr>
<th>Selected Adverse Events: Ocular or Systemic</th>
<th>OPT-302 (0.3 mg) + Aflibercept (2.0 mg) (N=3)</th>
<th>OPT-302 (1 mg) + Aflibercept (2.0 mg) (N=3)</th>
<th>OPT-302 (2 mg) + Aflibercept (2.0 mg) (N=3)</th>
<th>Total Number of Subjects (N=9)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraocular inflammation</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vitreous hemorrhage</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Hypertension</td>
<td>1*</td>
<td>0</td>
<td>0</td>
<td>1*</td>
</tr>
</tbody>
</table>

### APTC events

- Nonfatal myocardial infarction: 0
- Nonfatal stroke: 0
- Vascular or cardiac death or death of unknown cause: 0
- Combined APTC events: 0
- Any other death: 0

### IOP, mmHg: Baseline, week 12; (change from baseline)

- OPT-302 (0.3 mg) + Aflibercept (2.0 mg) (N=3): 13.0; 15.7 (2.7)
- OPT-302 (1 mg) + Aflibercept (2.0 mg) (N=3): 17.3; 15.3 (-2.0)
- OPT-302 (2 mg) + Aflibercept (2.0 mg) (N=3): 16.7; 17.0 (0.3)

OPT-302 (0.3, 1 or 2 mg) + aflibercept (2 mg) administered by IVT injection (Baseline, Week 4, Week 8)

OPT-302 intravitreal doses up to 2 mg in combination with aflibercept (2 mg)

- No dose limiting toxicities (Maximum Tolerated Dose not reached)
- No study drug related adverse events

Ocular AEs in the study eye primarily related to IVT injection procedure (Mild/moderate, resolved)

No clinically significant changes in IOP, ECG’s, or vitals.

OPT-302 was generally safe and well tolerated + aflibercept

OPT-302 has a favorable safety profile when administered with aflibercept (DME) expanding upon similar results when given as monotherapy or in combination with ranibizumab (wet AMD)

---

*APTC = Antiplatelet Trialists’ Collaboration

* Determined by treating investigator as unrelated to study drug(s)
OPT-302 + Aflibercept: Gains in BCVA at Week 12
Dose Response Relationship & Reductions in Retinal Swelling in Phase 1b

- Mean Change from baseline in BCVA (Letters)
  - Dose of OPT-302 + Aflibercept (2 mg)
    - 0.3 mg: 1/3 (33%) gain ≥ 5 letters, Mean # prior anti-VEGF-A injections: 5
    - 1.0 mg: 2/3 (67%) gain ≥ 5 letters, Mean # prior anti-VEGF-A injections: 7.3
    - 2 mg: 3/3 (100%) gain ≥ 5 letters, Mean # prior anti-VEGF-A injections: 6.7
    - 0.3 to 2.0 mg: 6/9 (67%) gain ≥ 5 letters, Mean # prior anti-VEGF-A injections: 6.3

Error Bars: SEM; Mean Baseline CST = 434 µm
DME Patients with Bilateral Disease*  
Study Eye vs Fellow Eye (N=5)

**Mean Change in BCVA Baseline to Week 12**

<table>
<thead>
<tr>
<th>Study Eye</th>
<th>Fellow Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Change BCVA (Letters)</strong></td>
<td><strong>Mean Change BCVA (Letters)</strong></td>
</tr>
<tr>
<td><strong>OPT-302 + Aflibercept</strong></td>
<td><strong>0.3 – 2mg OPT-302 + 2 mg Aflibercept</strong></td>
</tr>
<tr>
<td>15</td>
<td>10</td>
</tr>
<tr>
<td>+10.0</td>
<td>+2.6</td>
</tr>
</tbody>
</table>

**Mean Change in CST (µM) Baseline to Week 12**

<table>
<thead>
<tr>
<th>Study Eye</th>
<th>Fellow Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Mean Change CST (µM)</strong></td>
<td><strong>Mean Change CST (µM)</strong></td>
</tr>
<tr>
<td><strong>OPT-302 + Aflibercept</strong></td>
<td><strong>Anti-VEGF-A Monotherapy</strong></td>
</tr>
<tr>
<td>0</td>
<td>-6.0 µM</td>
</tr>
<tr>
<td>-80 µM</td>
<td></td>
</tr>
</tbody>
</table>

**% Pts with ≥ 50% Reduction in Excess Foveal Thickness**

<table>
<thead>
<tr>
<th>Study Eye</th>
<th>Fellow Eye</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Percentage Patients</strong></td>
<td><strong>Percentage Patients</strong></td>
</tr>
<tr>
<td><strong>OPT-302 + Aflibercept</strong></td>
<td><strong>Anti-VEGF-A Monotherapy</strong></td>
</tr>
<tr>
<td>60%</td>
<td>20%</td>
</tr>
</tbody>
</table>

*Patients with bilateral disease and persistent DME in the fellow eye receiving anti-VEGF-A (ranibizumab or aflibercept) monotherapy
Prior anti-VEGF-A therapy in Fellow Eyes BL to Wk 12: 3x Aflibercept, 3x Ranibizumab, 1x Ranibizumab, 4x Ranibizumab, 3x Aflibercept

Mean baseline BCVA, CST: Study Eyes (63 letters, 445 µM); Fellow Eye (73 letters, 389 µM)
# Excess foveal thickness was determined by using 300 µm Spectralis scan values and 285 µm Cirrus scan values

Mean baseline BCVA, CST: Study Eyes (63 letters, 445 µM); Fellow Eye (73 letters, 389 µM)
# OPT-302 Intellectual Property

## Summary covering sVEGFR-3 for Eye Disease

<table>
<thead>
<tr>
<th>COMPOSITION OF MATTER</th>
<th>TERM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Covering sVEGFR-3 (inc. OPT-302)</td>
<td></td>
</tr>
<tr>
<td>• Granted Patents: Europe, Japan, Canada, Australia</td>
<td>2022</td>
</tr>
<tr>
<td>• Granted Patent: USA</td>
<td>2026</td>
</tr>
<tr>
<td>Covering OPT-302</td>
<td></td>
</tr>
<tr>
<td>• Granted US Patent for new specific composition of matter &amp; use</td>
<td>2034</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>‘USE’ PATENT</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>• 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</td>
<td>2023</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>PATENT TERM EXTENSION/EXCLUSIVITY</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>+5 years under patent term extension</td>
<td></td>
</tr>
<tr>
<td>OPT-302 entitled to data exclusivity (DE) and market exclusivity (ME) in many jurisdictions, eg.</td>
<td></td>
</tr>
<tr>
<td>• US (12 years DE for biologics)</td>
<td></td>
</tr>
<tr>
<td>• Europe (10 years made up of 8 years DE + 2 years ME)</td>
<td></td>
</tr>
<tr>
<td>• Japan (up to 8 years de facto DE)</td>
<td></td>
</tr>
<tr>
<td>• South Korea (5 years DE)</td>
<td></td>
</tr>
<tr>
<td>• Canada (up to 8 years incl. up to 6 years DE + 2 years ME)</td>
<td></td>
</tr>
<tr>
<td>• Australia (5 years DE)</td>
<td></td>
</tr>
</tbody>
</table>
OPT-302: Multiple Upcoming Clinical Milestones

### Wet AMD

**Phase 1/2a** (n=51) **Complete**
- OPT-302, OPT-302 + Ranibizumab

**Phase 2b** (n=366)
- OPT-302 vs OPT-302 + Ranibizumab

### DME

**Phase 1b/2a** (n=~117)
- OPT-302 vs OPT-302 + Aflibercept

*Dates shown refer to calendar year*
OPT-302: An asset with strategic flexibility looking to enter the retinal disease market

Key Insights

1. OPT-302, with strong early stage clinical data, has the potential to address unmet needs by offering a novel mechanism to treat wet AMD, DME and other retinal diseases.

2. The retinal disease market, particularly wet AMD and DME, is forecast to grow given the increasing prevalence of elderly and diabetic populations.

3. OPT-302 is being developed as a distinct product and may also be developed as a co-formulated product with an anti-VEGF-A (branded or biosimilar). Market opportunities exist beyond wet AMD and DME, and may include RVO.

4. As an IVT anti-angiogenesis agent, OPT-302 may allow for potential synergies with ophthalmology pipelines/franchises.
Opthea – Developing OPT-302 for Eye Diseases

- OPT-302 has broad development potential in a range of eye diseases, including wet AMD and DME
- Targets validated pathway involved in wet AMD & DME progression and mechanism of escape from existing therapies that is differentiated to VEGF-A inhibitors and other agents in development
- Wet AMD & DME landscape includes only a limited number of novel combination therapies that may address the sub-optimal clinical responses that many patients experience on anti-VEGF-A therapies
- OPT-302 met primary safety objective and demonstrated evidence of clinical activity in a 51 pt Phase 1/2a wAMD clinical trial that enrolled treatment-naïve and prior treated patients administered OPT-302 monotherapy and OPT-302 in combination with Lucentis®
- OPT-302 has demonstrated a favourable safety profile in combination with both ranibizumab (Lucentis) and aflibercept (Eylea)
- Evidence of a dose response for OPT-302 combination treatment on gains in BCVA in persistent DME, together with biological responses on anatomic measures in nAMD and DME indicates that Pan-VEGF (A, C and D) inhibition may offer benefits that exceed the inhibition of VEGF-A alone
- Opthea is fully funded through its clinical development program:
  - A randomised Phase 2b clinical trial of OPT-302 + Lucentis® compared to Lucentis® alone in 366 wet AMD patients
  - A randomised Phase 1b/2a clinical trial of OPT-302 + Eylea® compared to Eylea® alone in ~117 DME patients
- Opthea fully enrolled 366 pts in the Ph 2b wAMD study ahead of schedule and is actively enrolling patients in the Phase 2a DME trial
- Multiple near-term clinical milestones: Opthea anticipates reporting primary data from the Phase 2b wet AMD trial and Phase 2a DME study by the end of CY 2019