Clinical results of OPT-302 (VEGF-C/D ‘Trap’) Combination Treatment in nAMD and DME
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OPT-302 Inhibits VEGF-C and VEGF-D

VEGF-B (PIGF) → VEGFR-1
VEGF-A → VEGFR-2
VEGF-C → VEGFR-3

OPT-302 blocks VEGF-C and VEGF-D

Angiogenesis
Vascular Permeability

Ligand
Ig-like domain
Kinase domain
Pathway blocked by OPT-302

Neovascular AMD

Aqueous Humor VEGF-C (pg/ml)

Baseline
Bevacizumab

1m
Bevacizumab

2m
Bevacizumab

5.37
6.91
8.91

66%

ARVO (Association for Research in Vision & Ophthalmology) Annual Meeting 2016, Cabral et al., Program 3341, Poster D0144
An Unmet Medical Need for nAMD & DME

Despite receiving a VEGF-A inhibitor (Ranibizumab, Afibercept or Bevacizumab)*:

**nAMD**
- **>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
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

Extra-Cellular Domains 1-3
hVEGFR-3

hIgG1 Fc

Mean (±SD) OPT-302 Serum Concentrations (ng/mL)

Time (hours)

• Non-compartmental OPT-302 PK analysis indicated:
  • Low systemic exposure
  • Half-life of 8 ± 2 days
  • Mean $C_{\text{max}}$ 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.
Part 1: Dose-escalation (Open-label)

- Cohort 1: OPT-302 (0.3 mg) + Ranibizumab (0.5 mg) IVT Q4W x 3
- 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

28 Day DLT window

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

- OPT-302 (2 mg) Monotherapy* IVT Q4W x 3, n=8 pts
- OPT-302 (2 mg) + Ranibizumab (0.5 mg) IVT Q4W x 3, n=23 pts

Follow-up to week 12

Long term follow-up at Week 24

ClinTrials Identifier NCT 02543229

- Comprises of 4 treatment cohorts of 5 subjects each

*Access to rescue anti-VEGF-A Tx
OPT-302 +/- Ranibizumab - Phase 1/2a Safety Summary

OPT-302 + Lucentis administered by repeat IVT injection (Baseline, Week 4, Week 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

*OPT-302 has consistently demonstrated a favourable safety profile +/- ranibizumab*
Evidence of biological activity in patients treated with intravitreal OPT-302 (2 mg) monotherapy

- Of the 13 patients who received OPT-302 monotherapy treatment:
  - 7/13 (54%) did not receive anti-VEGF-A rescue therapy through week 12
  - An additional 5/13 (38%) received only 1 rescue injection through week 12
  - One subject (8%) received 2 rescue injections.
  - The mean time to rescue therapy was 58 days.
  - Use of rescue therapy in 4/6 cases was based on Investigator discretion.

Mean Baseline VA = 55.7 Letters
Ranibizumab rescue therapy available week 2 through week 12 at investigator discretion or if patients met pre-defined criteria:
<10% decrease in CST and ≥5 letter loss of BCVA
Gains in Visual Acuity and Reduced Retinal Thickness in Patients with OPT-302 + Ranibizumab Therapy

**Change in mean BCVA**

- **Naïve pts (n=18)**
  - Mean Baseline VA = 56.5 Letters
  - Change from baseline in Visual Acuity (ETDRS Letters): +10.8 letters

- **Prior treated pts (n=20)**
  - Mean number prior anti-VEGF-A injections = 17
  - Change from baseline in Visual Acuity (ETDRS Letters): +4.9 letters

**Change in mean Central Subfield Thickness**

- **Naïve pts (n=18)**
  - Mean Baseline VA = 64.5 Letters
  - Change from baseline in CST (µM): -54 µM

- **Prior treated pts (n=20)**
  - Mean Baseline VA = 64.5 Letters
  - Change from baseline in CST (µM): -119 µM

**Error Bars:** SEM
Reductions in CNV in Treatment-Naïve Patients with OPT-302 + Ranibizumab Therapy

**Reduction in CNV Size on FA**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>CNV Size (mm²)</td>
<td>7.71</td>
<td>3.74</td>
<td>2.03</td>
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</tbody>
</table>

**% Patients with Absent CNV on FA**

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>Week 4</th>
<th>Week 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>% Patients with Absent CNV on FA</td>
<td>5.6 %*</td>
<td>27.8 %</td>
<td>50 %</td>
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</tbody>
</table>

CNV: Choroidal Neovascularisation
Treatment Naïve Patients:
*n = 18; OPT-302 (0.3, 2.0 mg) + ranibizumab (0.5 mg); * Absent on FA, present on OCT
OPT-302 +/- Ranibizumab Phase 2b Trial in Treatment-Naïve nAMD (n=351)

- Currently enrolling
- Primary data analysis early 2020

**Treatment-Naïve Neovascular AMD**

- OPT-302 (2 mg) + Ranibizumab (0.5 mg) n=117
- OPT-302 (0.5 mg) + Ranibizumab (0.5 mg) n=117
- Sham + Ranibizumab (0.5 mg) n=117

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

ClinTrials Identifier NCT 03345082
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

Phase 1b Dose Escalation study of OPT-302 + Aflibercept in DME

**Phase 1b Dose-Escalation**  
N=9 patients

- **Cohort 1**
  - OPT-302 (0.3 mg) + Aflibercept (2.0 mg)  
  - IVT Q4W x 3, n=3

- **Cohort 2**
  - OPT-302 (1.0 mg) + Aflibercept (2.0 mg)  
  - IVT Q4W x 3, n=3
  - 14 Day DLT window

- **Cohort 3**
  - OPT-302 (2.0 mg) + Aflibercept (2.0 mg)  
  - IVT Q4W x 3, n=3

**Phase 2a Dose-Expansion**  
(Randomised 2:1 ratio)

- **OPT-302 (2.0 mg) + Aflibercept (2.0 mg)**  
  - IVT Q4W x 3, n=72 pts
  - Follow-up to week 12
  - PRN anti-VEGF-A
  - Week 12 to 24

ClinTrials Identifier NCT 03397264

**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

**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

*CST as measured by Spectralis (Heidelberg) at screening, ≥ 320 µm for Cirrus.
Baseline Ocular Characteristics – Prior Treated

<table>
<thead>
<tr>
<th>Characteristic</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>Vision</td>
<td></td>
<td></td>
<td></td>
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</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>Anatomic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean CST, µm (SD)</td>
<td>460 (103)</td>
<td>396 (42)</td>
<td>432 (24)</td>
<td>430 (63)</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 Safety Results

- 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)
OPT-302 + Aflibercept – Safety Summary of selected AEs

<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 (33%)*</td>
<td>0</td>
<td>0</td>
<td>1 (11%)*</td>
</tr>
<tr>
<td>APTC events*</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Nonfatal myocardial infarction</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Nonfatal stroke</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vascular or cardiac death or death of unknown cause</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Combined APTC events</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Any other death</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>IOP, mmHg: Baseline, week 12; (change from baseline)</td>
<td>13.0; 15.7 (2.7)</td>
<td>17.3; 15.3 (-2.0)</td>
<td>16.7; 17.0 (0.3)</td>
<td>15.7; 16.0 (0.3)</td>
</tr>
</tbody>
</table>

- No safety signals or unexpected findings

*APTC = Antiplatelet Trialists’ Collaboration
*Determined by treating investigator as unrelated to study drug(s)
Dose Response in BCVA changes from Baseline to Week 12

Mean Change in BCVA Baseline to Week 12

Mean Change in BCVA (Letters)

Aflibercept (2 mg) + OPT-302
- 2 mg
- 1 mg
- 0.3 mg

Error Bars: SEM
OPT-302 + Aflibercept: Gains in BCVA at Week 12
Dose Response Relationship

<table>
<thead>
<tr>
<th>Dose of OPT-302 + Aflibercept (2 mg)</th>
<th>% of pts with BCVA gain ≥ 5 letters</th>
<th>Mean # prior anti-VEGF-A injections</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.3 mg</td>
<td>1/3 (33%)</td>
<td>5</td>
</tr>
<tr>
<td>1 mg</td>
<td>2/3 (67%)</td>
<td>7.3</td>
</tr>
<tr>
<td>2 mg</td>
<td>3/3 (100%)</td>
<td>6.7</td>
</tr>
<tr>
<td>0.3 to 2 mg</td>
<td>6/9 (67%)</td>
<td>6.3</td>
</tr>
</tbody>
</table>

Mean Change from baseline in BCVA (Letters)

- 0.3 mg OPT-302: +3.0 (N=3)
- 1 mg OPT-302: +5.7 (N=3)
- 2 mg OPT-302: +14.3 (N=3)
- 0.3 - 2 mg OPT-302: +7.7 (N=9)
OPT-302 (0.3-2 mg) + Aflibercept (2 mg): Mean changes in CST from Baseline to Week 12

Error Bars: SEM; Mean Baseline CST = 430 µm
DME Patients with Bilateral Disease*  
Study Eye vs Fellow Eye (N=5)

<table>
<thead>
<tr>
<th>Mean Change in BCVA Baseline to Week 12</th>
<th>Mean Change in CST (µM) Baseline to Week 12</th>
<th>% Pts with ≥ 50% Reduction in Excess Foveal Thickness</th>
</tr>
</thead>
<tbody>
<tr>
<td>OPT-302 + Aflibercept</td>
<td>Anti-VEGF-A Monotherapy</td>
<td>OPT-302 + Aflibercept</td>
</tr>
<tr>
<td>+10.0</td>
<td>-6.0 µM</td>
<td>80%</td>
</tr>
<tr>
<td>+2.6</td>
<td>-90 µM</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, 437 µM); Fellow Eye (73 letters, 383 µM)

# Excess foveal thickness was determined by using 300 µm Spectralis scan values and 285 µm Cirrus scan values
Phase 2a Randomised Dose Expansion study of OPT-302 + Aflibercept in Persistent DME

- Phase 2a currently enrolling patients in US and Australia
- Primary data analysis 2019
OPT-302 Clinical Program

- Two ongoing randomised controlled clinical trials in nAMD & DME

<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>
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<tbody>
<tr>
<td>Neovascular AMD</td>
<td></td>
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<tr>
<td>OPT-302</td>
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<tr>
<td>Target: VEGF-C/D</td>
<td>Ranibizumab</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<tr>
<td>Target: VEGF-A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Complete Ph 1/2a (n=51)</td>
<td>April 2017</td>
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<tr>
<td>OPT-302</td>
<td>Ranibizumab</td>
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<td></td>
<td></td>
<td></td>
<td>Ongoing Ph 2b (n=351)</td>
<td>Early 2020</td>
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<tr>
<td>Target: VEGF-C/D</td>
<td>Ranibizumab</td>
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<tr>
<td>Target: VEGF-A</td>
<td></td>
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<tr>
<td>Diabetic Macular Edema</td>
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<tr>
<td>OPT-302</td>
<td>Aflibercept</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Ongoing Ph 1b/2a (n=117)</td>
<td>2019</td>
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<tr>
<td>Target: VEGF-C/D</td>
<td>Aflibercept</td>
<td></td>
<td></td>
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<tr>
<td>Target: VEGF-A, PIGF, VEGF-B</td>
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Current treatments target primarily VEGF-A; OPT-302 inhibits VEGF-C/D

The successful dose escalation of OPT-302 in combination with aflibercept in DME builds upon the similar favourable safety profile in combination with ranibizumab in nAMD

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

Currently recruiting patients in two Phase 2 multi-center international trials:
  • ~108 patient randomised controlled Phase 2a trial in DME
  • 351 patient randomised controlled Phase 2b trial in nAMD
  • Primary data readouts 2019 (DME) and early 2020 (nAMD)