OPT-302 Phase 2b in wet AMD

A multicenter, randomized, double-masked, sham controlled study of intravitreal OPT-302 in combination with ranibizumab, in participants with wet AMD

Data presented by Professor Timothy Jackson PhD., FRCOphth., King’s College London
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Contact: Megan Baldwin PhD, CEO and Managing Director, Opthea Limited
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OPT-302 Inhibits VEGF-C and VEGF-D

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

* Bevacizumab is used ‘off-label’ for the treatment of nAMD
VEGF-A Inhibition Upregulates VEGF-C/D

Upregulation in Neovascular AMD

<table>
<thead>
<tr>
<th>Time</th>
<th>Aqueous Humor VEGF-C (pg/ml)</th>
</tr>
</thead>
<tbody>
<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>
</tr>
</tbody>
</table>

**66%**

Bevacizumab injection in patients with neovascular Age-Related Macular Degeneration increases angiogenic biomarkers, Ophthalmol Retina, 2(1): 31-37, 2018
Randomised 1:1:1 to treatment arms: intravitreal dosing every 4 weeks (x 6)

- Wet AMD Naïve Pts
  - OPT-302 (0.5 mg) + ranibizumab (0.5 mg)
  - Sham + ranibizumab (0.5 mg)
  - OPT-302 (2.0 mg) + ranibizumab (0.5 mg)
- Week 24 Follow-up
Study Overview

**Screening**
- **Key Inclusion Criteria**
  - Active CNV ≥50% lesion, classic / minimally classic / occult
  - BCVA ≥ 25 and ≤ 60 letters
- **Key Exclusion Criteria**
  - Subfoveal fibrosis or >25% of total lesion
  - Haemorrhage >50% total lesion
  - Other clinically significant ocular disease

**Allocation**
- **sham + 0.5 mg ranibizumab IVT Q4W x 6 n=122**
- **OPT-302 0.5 mg + 0.5 mg ranibizumab IVT Q4W x 6 n=122**
- **OPT-302 2.0 mg + 0.5 mg ranibizumab IVT Q4W x 6 n=123**

**Follow-up**
- **Completed Study**
  - n=116 (95.9%)
  - Discontinued Study
    - n=5 (4.1%)
    - Withdrawal of consent / LTFU: n=2
    - Adverse Event: n=1
    - Death: n=2
- **Completed Study**
  - n=112 (91.8%)
  - Discontinued Study
    - n=10 (8.2%)
    - Withdrawal of consent / LTFU: n=10

**Analysis**
- **Analysed**
  - n=119
- **Analysed**
  - n=122
- **Analysed**
  - n=121

**Completed Study**
- n=112 (91.8%)
- Discontinued Study
  - n=10 (8.2%)
  - Withdrawal of consent / LTFU: n=10
- **Adverse Event**: n=1
- **Death**: n=2

**Completed Study**
- n=120 (97.6%)
- Discontinued Study
  - n=3 (2.4%)
  - Withdrawal of consent / LTFU: n=3

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CNV – choroidal neovascularisation; LTFU – lost to follow up
Study Outcome Measures

Primary Outcome:
- Mean change from Baseline in ETDRS best corrected visual acuity at Week 24

Key Secondary Outcomes at Week 24:
- Patients gaining $\geq 15$ or more ETDRS letters
- Patients losing $\geq 15$ or more ETDRS letters
- Change in central subfield thickness (SD-OCT)
- Change in subretinal fluid and intraretinal fluid (SD-OCT)

Key Exploratory Outcomes at Week 24:
- Change in total lesion area and choroidal neovascularisation (CNV) area

Key Safety Outcome:
- Safety and tolerability
## Study Demographics and Baseline Characteristics

Evenly balanced across groups

<table>
<thead>
<tr>
<th>Demographic / Baseline Disease Characteristic</th>
<th>Sham + ranibizumab N=121</th>
<th>0.5 mg OPT-302 + ranibizumab N=122</th>
<th>2.0 mg OPT-302 + ranibizumab N=123</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Age – years ± SD</td>
<td>76.1 ± 9.48</td>
<td>78.8 ± 8.16</td>
<td>77.8 ± 8.82</td>
</tr>
<tr>
<td>Sex – n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>48 (39.7%)</td>
<td>49 (40.2%)</td>
<td>45 (36.6%)</td>
</tr>
<tr>
<td>Female</td>
<td>73 (60.3%)</td>
<td>73 (59.8%)</td>
<td>78 (63.4%)</td>
</tr>
<tr>
<td>Caucasian Race – n (%)</td>
<td>117 (99.2%)</td>
<td>119 (99.2%)</td>
<td>117 (97.5%)</td>
</tr>
<tr>
<td>Mean Visual Acuity (BCVA) – letters ± SD</td>
<td>50.7 ± 10.21</td>
<td>51.1 ± 8.96</td>
<td>49.5 ± 10.26</td>
</tr>
<tr>
<td>Mean Total Lesion Area - mm² ± SD</td>
<td>6.08 ± 3.21</td>
<td>6.48 ± 3.30</td>
<td>6.62 ± 3.39</td>
</tr>
<tr>
<td>Lesion type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Predominantly classic – n (%)</td>
<td>15 (12.4%)</td>
<td>15 (12.3%)</td>
<td>16 (13.0%)</td>
</tr>
<tr>
<td>Minimally classic – n (%)</td>
<td>53 (43.8%)</td>
<td>51 (41.8%)</td>
<td>53 (43.1%)</td>
</tr>
<tr>
<td>Occult - n (%)</td>
<td>53 (43.8%)</td>
<td>56 (45.9%)</td>
<td>54 (43.9%)</td>
</tr>
<tr>
<td>Mean central subfield thickness (CST) - mm ±SD</td>
<td>412.10 ± 110.62</td>
<td>425.18 ± 120.45</td>
<td>414.12 ± 123.25</td>
</tr>
<tr>
<td>Sub-retinal fluid (SRF) present – % participants</td>
<td>89.3%</td>
<td>84.4%</td>
<td>87.8%</td>
</tr>
<tr>
<td>Intra-retinal cysts present – % participants</td>
<td>57.9%</td>
<td>63.9%</td>
<td>56.1%</td>
</tr>
</tbody>
</table>

*Intent-to-Treat (ITT) population; SD: standard deviation; BCVA: Best Corrected Visual Acuity*
Primary Analysis – Mean Change in BCVA Baseline to Week 24
Primary endpoint achieved

OPT-302 Combination Therapy Demonstrated Superiority in Visual Acuity over Ranibizumab

Modified Intent-to-Treat (mITT) population; BCVA – Best Corrected Visual Acuity;
Graph represents difference in Least Square Means, using Model for Repeated Measures (MRM) analysis, and standard error of the mean (SEM);
Control of Type I error via the Hochberg Procedure
Mean Change in BCVA Over Time
Additive benefit of OPT-302 evident from 8-weeks
Mean Change in Central Subfield Thickness - Baseline to Week 24
Reductions in CST in OPT-302 combination groups compared to sham + ranibizumab

Mean change in CST (SEM) (μm)

Sham + 0.5 mg ranibizumab
0.5 mg OPT-302 + 0.5 mg ranibizumab
2.0 mg OPT-302 + 0.5 mg ranibizumab

mITT; as observed; CST – central subfield thickness
Sub-retinal Fluid and Intra-retinal Cysts at Week 24
Fewer participants with retinal fluid present in OPT-302 combination groups compared to sham + ranibizumab

% Participants with SRF present

% Participants with IR Cysts present

<table>
<thead>
<tr>
<th>Group</th>
<th>% Participants</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham + 0.5 mg ranibizumab</td>
<td>29.3</td>
</tr>
<tr>
<td>0.5 mg OPT-302 + 0.5 mg ranibizumab</td>
<td>23.2</td>
</tr>
<tr>
<td>18.5</td>
<td></td>
</tr>
<tr>
<td>2.0 mg OPT-302 + 0.5 mg ranibizumab</td>
<td>21.6</td>
</tr>
<tr>
<td>19.6</td>
<td></td>
</tr>
<tr>
<td>16.8</td>
<td></td>
</tr>
</tbody>
</table>
Mean Change in Total Lesion Area and CNV Area – Baseline to Week 24
Greater reduction in Total Lesion and CNV Area in OPT-302 combination groups compared to sham + ranibizumab

Mean Change in Total Lesion Area

Mean Change in CNV Area

Sham + 0.5 mg ranibizumab
0.5 mg OPT-302 + 0.5 mg ranibizumab
2.0 mg OPT-302 + 0.5 mg ranibizumab

Mean change in Total Lesion Area (SEM) (mm²)

Mean change in CNV Area (SEM) (mm²)

0
-2
-4
-6
-4.33
-4.23
-3.11
-4.97
-4.45
-3.59

p=0.0257
p=0.0137
p=0.0052
## Safety – Adverse Events (AEs)

<table>
<thead>
<tr>
<th>N Participants (%)</th>
<th>Sham + ranibizumab N=121</th>
<th>0.5 mg OPT-302 + ranibizumab N=120</th>
<th>2.0 mg OPT-302 + ranibizumab N=124</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment emergent AEs</td>
<td>84 (69.4%)</td>
<td>87 (72.5%)</td>
<td>93 (75.0%)</td>
</tr>
<tr>
<td>Ocular AEs - Study Eye – related to study product(s)&lt;sup&gt;1&lt;/sup&gt;</td>
<td>17 (14.0%)</td>
<td>17 (14.2%)</td>
<td>19 (15.3%)</td>
</tr>
<tr>
<td>Ocular AEs - Study Eye – Severe&lt;sup&gt;2&lt;/sup&gt;</td>
<td>1 (0.8%)</td>
<td>2 (1.7%)</td>
<td>1 (0.8%)</td>
</tr>
<tr>
<td>Serious AEs</td>
<td>10 (8.3%)</td>
<td>16 (13.3%)</td>
<td>7 (5.6%)</td>
</tr>
<tr>
<td>Ocular SAEs in Study Eye</td>
<td>0 (0.0%)</td>
<td>2&lt;sup&gt;3&lt;/sup&gt; (1.7%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Intraocular inflammation&lt;sup&gt;4&lt;/sup&gt; – Study Eye</td>
<td>0 (0.0%)</td>
<td>2&lt;sup&gt;3&lt;/sup&gt; (1.7%)</td>
<td>1&lt;sup&gt;5&lt;/sup&gt; (0.8%)</td>
</tr>
<tr>
<td>AEs leading to study IP discontinuation only</td>
<td>2 (1.7%)</td>
<td>3 (2.5%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>AEs leading to study discontinuation</td>
<td>1&lt;sup&gt;6&lt;/sup&gt; (0.8%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Any APTC event</td>
<td>0 (0.0%)</td>
<td>1&lt;sup&gt;7&lt;/sup&gt; (0.8%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>2&lt;sup&gt;8&lt;/sup&gt; (1.7%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

Safety population analysed according to medication received

<sup>1</sup> Assessed by investigator to be “possibly related”, “probably related” or “definitely related” to administration of study drug(s)

<sup>2</sup> Assessed by Investigator to be National Institutes of Health (NIH) Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or above, or, if CTCAE grade is unavailable, an AE assessed as “causing an inability to perform normal daily activities”

<sup>3</sup> SAE of endophthalmitis, with AEs of hypopyon and anterior chamber cell (n=1), SAE of vitritis (n=1)

<sup>4</sup> AEs considered to be indicative of intraocular inflammation, defined prior to database lock as: Endophthalmitis, iritis, vitritis, iridocyclitis, uveitis, hypopyon, viral iritis, or anterior chamber inflammation

<sup>5</sup> Anterior chamber cell (trace 1-4 cells)

<sup>6</sup> Squamous cell carcinoma of the lung diagnosed shortly after Baseline visit

<sup>7</sup> Non-fatal myocardial infarction

<sup>8</sup> Pneumonia (n=1), Infective endocarditis (n=1)
Thank you to all study participants and over 100 sites across 10 countries

Czech Republic – 3 sites
France – 6 sites
Hungary – 5 sites
Italy – 5 sites
Israel – 8 sites
Latvia – 4 sites
Poland – 7 sites
Spain – 8 sites
United Kingdom – 7 sites
United States – 56 sites
Conclusions

• **Phase 2b trial met primary endpoint**
  - OPT-302 (2.0 mg) combination therapy demonstrated superiority in visual acuity over ranibizumab + sham
  - Vision gain of 3.4 letters
  - Statistically significant (p=0.0107)
  - High ranibizumab control arm

• **Secondary outcomes were supportive of the primary endpoint:**
  - **Vision**
    - More patients gained ≥ 15 letters of vision
    - Fewer patients lost ≥ 15 letters of vision
  - **Retinal anatomical improvements**
    - Reductions in CST, subretinal and intraretinal fluid
    - Greater decreases in Total Lesion Area and CNV Area

• **Favourable safety profile similar to ranibizumab alone**