Phase 2b Clinical Results of OPT-302 (VEGF-C/D ‘Trap’) Combination Treatment in nAMD

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OPT-302 Inhibits VEGF-C and VEGF-D

OPT-302 ‘trap’ blocks VEGF-C and VEGF-D binding to VEGFR-2 and VEGFR-3 receptors
VEGF-A Inhibition Upregulates VEGF-C/D

Upregulation in Neovascular AMD

## OPT-302 Clinical Program

### 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>1° Data Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OPT-302</strong></td>
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</tr>
<tr>
<td>Target: VEGF-C/D</td>
<td>Ranibizumab</td>
<td></td>
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<td>April 2017</td>
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<tr>
<td>Target: VEGF-A</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Complete</td>
<td>Ph 1/2a (n=51)</td>
<td>Primary Endpt Met</td>
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<tr>
<td><strong>OPT-302</strong></td>
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<td></td>
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<td>August 2019</td>
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<tr>
<td>Target: VEGF-C/D</td>
<td>Ranibizumab</td>
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<td></td>
<td></td>
<td>Positive</td>
<td>Ph 2b (n=366)</td>
<td>Primary Endpt Met</td>
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<tr>
<td>Target: VEGF-A</td>
<td></td>
<td></td>
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<td></td>
<td></td>
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<td>Superior Efficacy</td>
</tr>
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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>1° Data Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>OPT-302</strong></td>
<td></td>
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</tr>
<tr>
<td>Target: VEGF-C/D</td>
<td>Aflibercept</td>
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<td>Recruiting</td>
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<tr>
<td>Target: VEGF-A, PIGF, VEGF-B</td>
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<td>2Q CY 2020</td>
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</table>
Phase 2b

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

Conducted at 113 sites across 10 countries: US, EU, Israel

OPT-302-1002; NCT ClinicalTrials.gov Identifier: NCT03345082
OPT-302 Phase 2b wAMD

Randomised 1:1:1 to treatment arms: intravitreal dosing every 4 weeks (x 6)

- Wet AMD Naïve Pts
  - OPT-302 (2.0 mg) + ranibizumab (0.5 mg)
  - OPT-302 (0.5 mg) + ranibizumab (0.5 mg)
  - Sham + ranibizumab (0.5 mg)

Week 24 Follow-up

ClinicalTrials.gov Identifier: NCT03345082
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

Treatment naïve patients with neovascular AMD

Randomised (n=366)

Allocation

ITT Population

sham + 0.5 mg ranibizumab IVT Q4W x 6 n=121

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%)

Completed Study n=112 (91.8%)

Completed Study n=120 (97.6%)

Analysis

mITT Population

Analysed n=119

Analysed n=122

Analysed n=121

CNV – choroidal neovascularisation; IVT – intravitreal; Q4W – once every 4 weeks
ITT – Intent to Treat Population, all participants who were randomised into the study irrespective of whether study medication was administered or not
Safety Population - all participants in the ITT but excluding those who did not receive at least one dose of study medication
mITT – Modified ITT Population, all participants in the Safety Population but excludes any participant without a Baseline VA score and/or any participant who did not return for at least one post-baseline visit
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 ≥15 or more ETDRS letters
- Patients losing ≥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 Pre-Specified Subgroup Analyses:
- Polypoidal Choroidal Vasculopathy (PCV)
- Lesion type
- Retinal angiomatic proliferation (RAP)

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

<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><strong>Mean Age – years ± SD</strong></td>
<td>76.1 ± 9.48</td>
<td>78.8 ± 8.16</td>
<td>77.8 ± 8.82</td>
</tr>
<tr>
<td><strong>Sex – n (%)</strong></td>
<td></td>
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</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>
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<tr>
<td><strong>Caucasian Race – n (%)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>117 (99.2%)</td>
<td></td>
<td>119 (99.2%)</td>
<td>117 (97.5%)</td>
</tr>
<tr>
<td><strong>Mean Visual Acuity (BCVA) – letters ± SD</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>50.7 ± 10.21</td>
<td></td>
<td>51.1 ± 8.96</td>
<td>49.5 ± 10.26</td>
</tr>
<tr>
<td><strong>Mean Total Lesion Area - mm² ± SD</strong></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>6.08 ± 3.21</td>
<td></td>
<td>6.48 ± 3.30</td>
<td>6.62 ± 3.39</td>
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<tr>
<td><strong>Lesion Type</strong></td>
<td></td>
<td></td>
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<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>PCV detected¹ – n (%)</td>
<td>20 (16.5%)</td>
<td>24 (19.7%)</td>
<td>22 (17.9%)</td>
</tr>
<tr>
<td>RAP detected² – n (%)</td>
<td>15 (12.7%)</td>
<td>22 (18.5%)</td>
<td>14 (11.8%)</td>
</tr>
<tr>
<td><strong>Mean central subfield thickness (CST) - mm ±SD</strong></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

¹PCV - polypoidal choroidal vasculopathy, detected by SD-OCT, FA and fundus photography

²RAP - retinal angiomatous proliferation, detected by SD-OCT, FA and fundus photography
Primary Analysis – Mean Change in BCVA Baseline to Week 24

Primary endpoint achieved

OPT-302 (2.0 mg) Combination Therapy Demonstrated Superiority in Visual Acuity over Ranibizumab

Δ = +3.4 (p=0.0107)

Mean change in BCVA (letters)

Sham + 0.5 mg ranibizumab (n=119)
2.0 mg OPT-302 + 0.5 mg ranibizumab (n=122)
2.0 mg OPT-302 + 0.5 mg ranibizumab (n=121)

mITT; BCVA – best corrected visual acuity
Difference in Least Square Means, using Model for Repeated Measures (MRM) analysis
Mean Change in BCVA Over Time
Additive visual acuity benefit of OPT-302 evident from 8-weeks
Vision Gain - Baseline to Week 24
Higher proportion of patients gaining ≥15, ≥10 and ≥5 letters of vision in OPT-302 combination group

Modified Intent-to-Treat (mITT) population; as observed
Vision Loss - Baseline to Week 24
Fewer patients lose ≥15, ≥10 and ≥5 letters of vision in OPT-302 combination group

Modified Intent-to-Treat (mITT) population; as observed
Mean Change in BCVA Baseline to Week 24
Vision gain in OPT-302 combination group compared to sham + ranibizumab is independent of baseline VA

mITT; least square means (LSM) determined using Model for Repeated Measures (MRM) analysis (adjusted for baseline vision and lesion type as used in the randomisation as covariates).
Central Subfield Thickness
Reduction in CST in OPT-302 combination group compared to sham + ranibizumab

**Mean Change in CST – Baseline to Week 24**

-133.80 to -146.70 µm

**Mean CST at Week 24**

277.84 to 265.57 µm

*Modified Intent-to-Treat (mITT) population; 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 group compared to sham + ranibizumab

% Participants with SRF present

% Participants with IR Cysts present

Modified Intent-to-Treat (mITT) population; as observed; SRF – sub-retinal fluid; IR – intra-retinal
Total Lesion Area and CNV Area – Baseline to Week 24
Greater reduction in Total Lesion and CNV Area in OPT-302 combination group compared to sham + ranibizumab

Modified Intent-to-Treat (mITT) population; as observed; CNV – choroidal neovascularisation; Difference in Least Square Means
Polypoidal Choroidal Vasculopathy
Mean change in BCVA to Week 24 in participants with and without PCV at baseline

\[ \Delta = 6.70 \quad ({}^* p = 0.0253) \]

\[ \Delta = 2.71 \quad ({}^* p = 0.0491) \]

mITT; PCV – polypoidal choroidal vasculopathy;
Least square means determined using Model for Repeated Measures (MRM) analysis (adjusted for baseline vision and lesion type (randomisation) as covariates).
PCV determination by SD-OCT, FA and fundus photography.
Mean Change in BCVA Over Time by Lesion Type

Small number of predominantly classic patients

Predominantly Classic

Minimally Classic

Occult

Sham + 0.5 mg ranibizumab (n = 15)
2.0 mg OPT-302 + 0.5 mg ranibizumab (n = 15)

Sham + 0.5 mg ranibizumab (n = 53)
2.0 mg OPT-302 + 0.5 mg ranibizumab (n = 53)

Sham + 0.5 mg ranibizumab (n = 51)
2.0 mg OPT-302 + 0.5 mg ranibizumab (n = 53)
Mean Change in BCVA at week 24 by Lesion Type

Greater vision gains at Week 24 in OPT-302 2.0 mg group in minimally classic and occult lesions

Greater vision gains at Week 24 in OPT-302 2.0 mg group in minimally classic and occult lesions

mITT; Least square means determined using Model for Repeated Measures (MRM) analysis (adjusted for baseline vision and lesion type (randomisation) as covariates).
3-Line Vision Gain at Week 24 by Lesion Type

>20% increase in 3-line gainers in participants with occult lesions treated with OPT-302 combination therapy

mITT, as observed
2-Line Vision Gain at Week 24 by Lesion Type

Greater proportion of 2-line gainers in participants with minimally classic and occult lesions following OPT-302 combination therapy

\[\text{Minimally Classic}\]

\[\text{Occult}\]

\[\text{Sham + 0.5 mg ranibizumab (n = 52)}\]
\[\text{2.0 mg OPT-302 + 0.5 mg ranibizumab (n = 53)}\]

\[\text{Sham + 0.5 mg ranibizumab (n = 50)}\]
\[\text{2.0 mg OPT-302 + 0.5 mg ranibizumab (n = 52)}\]
3-Line Vision Loss Baseline to Week 24
Fewer patients with minimally classic and occult lesions lose ≥15 letters following OPT-302 combination therapy

mITT, as observed
2-Line Vision Loss Baseline to Week 24
Fewer patients with minimally classic and occult lesions lose ≥10 letters following OPT-302 combination therapy.
Central Subfield Thickness by Lesion Type
Reduction in CST in participants with occult lesions treated with OPT-302 combination compared to sham + ranibizumab

Modified Intent-to-Treat (mITT) population; as observed; CST – central subfield thickness
Sub-Retinal Fluid at Week 24 by Lesion Type

Fewer participants with minimally classic & occult lesions have SRF at week 24 following OPT-302 combination therapy.

mITT; as observed
Intra-Retinal Cysts at Week 24 by Lesion Type

Fewer participants with minimally classic & occult lesions have intra-retinal cysts following OPT-302 combination therapy

mITT: as observed
Total Lesion Area at Week 24 in Minimally Classic and Occult Lesions

Greater reductions in Total Lesion Area following OPT-302 combination therapy

![Graph showing mean change in Total Lesion Area (SEM) for Minimally Classic and Occult lesions](image)

- Minimally Classic
  - Sham + 0.5 mg ranibizumab (n = 49)
  - 2.0 mg OPT-302 + 0.5 mg ranibizumab (n = 49)

- Occult
  - Sham + 0.5 mg ranibizumab (n = 49)
  - 2.0 mg OPT-302 + 0.5 mg ranibizumab (n = 49)

mITT; as observed
CNV Area at Week 24 in Minimally Classic and Occult Lesions

Greater reductions in CNV Area following OPT-302 combination therapy

**Sham + 0.5 mg ranibizumab (n = 49)**

**2.0 mg OPT-302 + 0.5 mg ranibizumab (n = 49)**

**Sham + 0.5 mg ranibizumab (n = 47)**

**2.0 mg OPT-302 + 0.5 mg ranibizumab (n = 49)**

mITT; as observed; p based on difference in least square means determined using Model for Repeated Measures (MRM) analysis (adjusted for baseline vision and lesion type (randomisation) as covariates).
Lesion classification at Baseline and at Week 24

Lesions shift to an occult, quiescent biology or no CNV following treatment.

Lesion Classification at Baseline

- Predominantly Classic
- Minimally Classic
- Occult

Lesion Classification at Week 24

- Predominantly Classic
- Minimally Classic
- Occult
- Quiescent
- No CNV

Sham + 0.5 mg ranibizumab
(n=119)

2.0 mg OPT-302 + 0.5 mg ranibizumab
(n=121)

mITT, as observed
Retinal Angiomatous Proliferation (RAP) Lesions
Mean change in BCVA to Week 24 in participants without RAP at baseline

\[ \Delta = 4.4 \]
\[ *p = 0.0025 \]

mITT; RAP – retinal angiomatous proliferation;
Least square means (LSM) determined using Model for Repeated Measures (MRM) analysis (adjusted for baseline vision and lesion type as used in the randomisation as covariates).

Mean change in BCVA (SEM) (letters)

- Sham + 0.5 mg ranibizumab
- 2.0 mg OPT-302 + 0.5 mg ranibizumab
Mean Change in BCVA Over Time by Lesion Type, RAP Absent

In RAP absent participants, +4.7 letter gain in minimally classic and +6.5 letter gain in occult participants treated with OPT-302 combination therapy compared to sham + ranibizumab

mITT, as observed, $\Delta$ based on least square means determined using Model for Repeated Measures (MRM) analysis (adjusted for baseline vision and lesion type (randomisation) as covariates).
mITT; Least square means (LSM) determined using Model for Repeated Measures (MRM) analysis (adjusted for baseline vision and lesion type as used in the randomisation as covariates).

Mean Change in BCVA at Week 24 by Lesion Type, RAP Absent

Minimally Classic

$\Delta = 4.7$
$p = 0.0415$

Occult

$\Delta = 6.5$
$p = 0.0005$
## 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)¹</td>
<td>17 (14.0%)</td>
<td>17 (14.2%)</td>
<td>19 (15.3%)</td>
</tr>
<tr>
<td>Ocular AEs - Study Eye – Severe²</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>2³ (1.7%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Intraocular inflammation⁴ – Study Eye</td>
<td>0 (0.0%)</td>
<td>2³ (1.7%)</td>
<td>1⁵ (0.8%)</td>
</tr>
<tr>
<td>Participants with 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>Participants with AEs leading to study discontinuation</td>
<td>1⁶ (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>1⁷ (0.8%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>2⁸ (1.7%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

1. Assessed by investigator to be "possibly related", "probably related" or "definitely related" to administration of study drug(s)
2. 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"
3. SAE of endophthalmitis, with AEs of hypopyon and anterior chamber cell (n=1), SAE of vitritis (n=1)
4. 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
5. Anterior chamber cell (trace 1-4 cells)
6. Squamous cell carcinoma of the lung diagnosed shortly after Baseline visit
7. Non-fatal myocardial infarction
8. Pneumonia (n=1), infective endocarditis (n=1)
Conclusions – OPT-302 Phase 2b nAMD Trial

- **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

- **Exploratory & pre-specified subgroup analyses**
  - Suggest greater activity of OPT-302 in lesion-types considered more difficult to treat with anti-VEGF-A therapy & highest unmet need
  - Promising evidence of activity in polypoidal AMD (PCV) and minimally classic/occult lesions that are less responsive to VEGF-A inhibitors

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