Beyond VEGF-A: Targeting VEGF-C/D for Wet AMD and DME

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Wet AMD & DME are the leading causes of vision loss in the elderly & diabetics
Increasing prevalence; large unmet medical need

Additional market opportunities:

**Macular Edema Secondary to Retinal Vein Occlusion (RVO)**
Characterized by retinal vein blockage, which selectively leads to edema formation and loss of visual acuity

**Diabetic Macular Edema (DME)**
A complication of diabetes that manifests as edema and hard exudates in the macula and leads to loss of VA

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

**3.5M wAMD**
**2M DME**
**500K RVO**

Additional market opportunities:

**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

Source: GlobalData; EvaluatePharma; PubMed; Physician Interviews.
Retinal Eye Diseases – Angiogenesis and Vascular Permeability

Lead to lesion formation, edema & vision loss

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The VEGF/VEGFR Pathway & Disease Progression

OPT-302 has potential to improve clinical EFFICACY by targeting VEGF-C/D

Ranibizumab (Lucentis®)
Brolucizumab (Beovu®)
Bevacizumab# (Avastin®)
Afibercept (Eylea®)

VEGF-A
VEGF-B
PIGF

VEGF-C
VEGF-D

OPT-302

There remains a significant unmet medical need for the treatment of wet AMD and DME despite the availability of VEGF-A inhibitors

* Bevacizumab is used 'off-label' for the treatment of nAMD
Large Market Opportunity for New Retinal Disease Therapies

### Standard of Care VEGF-A Therapies

<table>
<thead>
<tr>
<th>Therapy</th>
<th>2019 Sales Revenue¹ (all indications)</th>
<th>61% wAMD</th>
<th>22% DME</th>
<th>17% RVO</th>
</tr>
</thead>
<tbody>
<tr>
<td>LUCEPTIS®</td>
<td>USD 3.9 BN</td>
<td></td>
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<tr>
<td>EYLEA®</td>
<td>USD 7.9 BN</td>
<td>USD 11.9 BN</td>
<td></td>
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</tr>
</tbody>
</table>

~46% IVT injections administered globally are Avastin (bevacizumab), administered off-label²

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¹ Evaluate Pharma
Large Market Opportunity for OPT-302 in Retinal Diseases

The OPPORTUNITY for OPT-302

Objective: To develop OPT-302 for use in combination with any VEGF-A inhibitor

A commercial assessment of OPT-302, conducted by an Independent Research Firm, forecasts worldwide annual peak sales of OPT-302 for wet AMD and DME alone to be

US 5.3 BN

Majority of Agents in Development Seeking to Improve Durability of VEGF-A Inhibition

<table>
<thead>
<tr>
<th>Company</th>
<th>Market Cap US $M</th>
<th>Product</th>
<th>MOA</th>
<th>Stage</th>
<th>Disease Focus</th>
<th>Treatment Effect</th>
</tr>
</thead>
<tbody>
<tr>
<td>康弘药业</td>
<td>$5,970</td>
<td>Conbercept</td>
<td>Anti-VEGF-A</td>
<td>Phase III</td>
<td>wAMD, DME,</td>
<td>Durability</td>
</tr>
<tr>
<td>KODIAK</td>
<td>$2,100</td>
<td>KSI-301</td>
<td>Anti-VEGF-A</td>
<td>Phase I – III</td>
<td>wAMD, DME, RVO</td>
<td>Durability</td>
</tr>
<tr>
<td>ADVERUM BIOTECH</td>
<td>$1,440</td>
<td>ADVM-022</td>
<td>Anti-VEGF-A</td>
<td>Phase I/II</td>
<td>DME, DR, wAMD</td>
<td>Durability</td>
</tr>
<tr>
<td>REBEX BIO</td>
<td>$1,280</td>
<td>RGX-314</td>
<td>Anti-VEGF-A</td>
<td>Phase II</td>
<td>wAMD</td>
<td>Durability</td>
</tr>
<tr>
<td>GLAUKOS</td>
<td>$2,070</td>
<td>Bioerodible, drug delivery</td>
<td>Sustained Release</td>
<td>Early Stage</td>
<td>Glaucoma, wAMD, DME</td>
<td>Durability</td>
</tr>
<tr>
<td>Apellis</td>
<td>$2,100</td>
<td>APL-2</td>
<td>Complement C3</td>
<td>Phase III</td>
<td>Dry AMD</td>
<td>Efficacy</td>
</tr>
<tr>
<td>aerie</td>
<td>$552</td>
<td>ROCKi/PKCi implant</td>
<td>Rho kinase, Inflammation</td>
<td>Phase I/II</td>
<td>Glaucoma, wAMD, Dry Eye, Dry AMD</td>
<td>Durability</td>
</tr>
<tr>
<td>iVERIC bio</td>
<td>$380</td>
<td>Zimura</td>
<td>Complement C5</td>
<td>Phase III</td>
<td>GA Dry AMD</td>
<td>Efficacy</td>
</tr>
<tr>
<td>OXURION</td>
<td>$124</td>
<td>THR-687, THR-149</td>
<td>Kallikrein, Pan-RGD integrin</td>
<td>Phase III</td>
<td>DME</td>
<td>Durability</td>
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</tbody>
</table>
## OPT-302 Clinical Program

### Wet 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>
<th>Upcoming Future Milestones</th>
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<tbody>
<tr>
<td>OPT-302</td>
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<td>Target: VEGF-C/D</td>
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<td>VEGF-A inhibitor</td>
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### 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>
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<th>Status</th>
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<th>Upcoming Future Milestones</th>
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<tbody>
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<td>OPT-302</td>
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<td>Target: VEGF-C/D</td>
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<td>Aflibercept</td>
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<td>Target: VEGF-A, PIGF, VEGF-B</td>
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**Phase 1**

- **Combination Agent**
- **Preclinical**
- **Phase 1**
- **Phase 2a**
- **Phase 2b**
- **Phase 3**
- **Status**
- **1º Data Analysis**
- **Upcoming Future Milestones**

**Wet AMD**

- **OPT-302**
  - Target: VEGF-C/D
  - Ranibizumab
    - Target: VEGF-A
    - Status: Complete
      - Ph 1/2a (n=51)
    - Positive
      - Ph 2b (n=366)
  - Planned
    - Two concurrent Ph 3 trials
      - Finalisation of trial designs post completion of regulatory engagement with FDA and EMA

**Diabetic Macular Edema**

- **OPT-302**
  - Target: VEGF-C/D
  - Aflibercept
    - Target: VEGF-A, PIGF, VEGF-B
    - Status: Week 12 Reported
      - Ph 1b/2a (n=144 randomised)
  - Week 12 Reported
    - Ph 1b/2a (n=144 randomised)

**Future Milestones**

- **April 2017**
  - Primary Endpoint Met
    - Safety
- **August 2019**
  - Primary Endpoint Met
    - Superior Efficacy

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**OPTHEA**
Diabetic Macular Edema

Review & Opthea’s Phase 1b/2a DME Trial

Arshad M. Khanani, MD, MA
Managing Partner, Director of Clinical Research, Sierra Eye Associates, Reno, NV
Practice Setting: Sierra Eye Associates, Reno, Nevada, USA

- Private office-based practice
- Multispecialty with 3 retinal physicians
- 75 employees total
- 8 technicians, 6 research coordinators
- 40+ active clinical trials
- 80 patients a day on average
- Approximately 600 anti-VEGF-A Intravitreal injections a month
Diabetes Associated With Serious Comorbidities: Retinopathy & DME

Diabetic retinopathy\(^1\)
28.5% in patients aged ≥40
≈13.6% have diabetic macular edema (DME)\(^2\)

Diabetic nephropathy\(^3\)
29.9% in diabetic patients

Diabetic neuropathy\(^1\)
60%-70% in diabetic patients

Stroke\(^4\)
11.5 per 1000 persons with diabetes

Ischemic Heart Disease\(^4\)
18.3 per 1000 persons with diabetes

Current First-line DME treatments primarily target VEGF-A
Second-line treatment includes corticosteroids

Current approved and off-label first-line standard of care therapy primarily targeting VEGF-A inhibition:

<table>
<thead>
<tr>
<th>Aflibercept (Eylea)</th>
<th>Ranibizumab (Lucentis)</th>
<th>Bevacizumab (Avastin)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGFR-1/2-Fc fusion protein</td>
<td>Monoclonal humanized antibody fragment</td>
<td>Full antibody (IgG1)</td>
</tr>
<tr>
<td>115 kDa</td>
<td>48 kDa</td>
<td>149 kDa</td>
</tr>
<tr>
<td>2.0 mg</td>
<td>0.3 mg; 0.5 mg</td>
<td>1.25 mg (unlicensed use)</td>
</tr>
</tbody>
</table>

Steroid treatments mostly used as second-line therapy:

- Fluocinolone acetonide
- Dexamethasone
- Triamcinolone
Investigational Treatments in DME Pipeline also Mostly Targeting VEGF-A and/or are Aimed at Durability

Anti-VEGF-A/Ang-2 Bispecific Antibody Faricimab in DME. Results of Phase 2 BOULEVARD trial

Mean BCVA Change From Baseline

RG7716 met its prespecified primary endpoint of efficacy

Mean BCVA Gains From Baseline

BCVA outcome directionally supports primary outcome

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Patients With Persistent DME Are a Significant Unmet Need

There is a need for novel therapeutic approaches to improve clinical outcomes

Many patients have limited BCVA gains despite regular anti-VEGF-A monotherapy

In Protocol I:

- 40% patients gained < 5 letters by week 12
- 23% patients gained 5-9 letters by week 12
  - Only ~25-30% patients show a further ≥ 5 letter gain from 12 weeks to 1 year
  - Mean BCVA from 12 weeks to 1 year only improved by ~1.3 to 3.1 letters

DRCR Protocol I

Sub-optimal responders identified as early as 12 weeks

- Therapeutic options are limited for patients with persistent DME
  - Switching of anti-VEGF-A therapy
  - IVT corticosteroids associated with cataracts & IOP increase

Combination therapy targeting alternative mediators of the disease such VEGF-C/-D may lead to improved outcomes

BCVA Change from Baseline

<table>
<thead>
<tr>
<th>BCVA Change from Baseline</th>
<th>5 letters at 12w (N=135)</th>
<th>5-9 letters at 12w (N=79)</th>
<th>≥10 letters at 12w (N=126)</th>
</tr>
</thead>
<tbody>
<tr>
<td>BCVA</td>
<td>19.2</td>
<td>16.5</td>
<td>12.8</td>
</tr>
<tr>
<td>Baseline</td>
<td>8.3</td>
<td>8.2</td>
<td>8.2</td>
</tr>
<tr>
<td>p=0.001</td>
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</tbody>
</table>

*Based on randomized, controlled clinical trial data; *SD-Oct CST ≥ 300 µM or Time-Domain OCT CST ≥ 250 µM
Role of VEGF-C and -D in the Pathophysiology of DR and DME
Rationale for inhibition of VEGF-C/D in DME

- VEGFR-2 expression is greater in diabetic retina than non-diabetics $^{1,2,3}$
- Elevations of VEGF-C in diabetic retinopathy and VEGF-D in vitreous of diabetics$^{3,4}$
- VEGF-C expression is elevated by glucose & pro-inflammatory cytokines $^{5,6}$
- Advanced glycation end products accumulate faster in diabetics and stimulate VEGF-C expression and secretion from the RPE $^7$
- Single nucleotide polymorphisms (SNPs) in diabetic patients indicate that genetic variation in the VEGF-C gene is associated with DR and DME $^8$

VEGF-C/D Signaling Pathway plays a functional role in the Pathogenesis of DME


DME, diabetic macular edema; DR, diabetic retinopathy; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor
OPT-302: Inhibitor of VEGF-C and -D

Intravitreal OPT-302 combination therapy may improve outcomes in DME

- OPT-302 is a soluble VEGFR-3 ‘trap’ fusion protein
  - Potent inhibitor of VEGF-C/-D interaction with VEGFR-2 & VEGFR-3
  - Existing therapies target VEGF-A but not VEGF-C or VEGF-D

- VEGF-C is elevated in diabetic retinopathy and vitreous levels of VEGF-D are elevated in diabetes
- VEGF-C/-D are upregulated in response to VEGF-A suppression
- OPT-302 combination therapy targets this escape mechanism with broad inhibition of the VEGF/VEGFR pathway
- OPT-302 combination therapy demonstrated superiority in BCVA gains from baseline to week 24 over anti-VEGF-A monotherapy in treatment naïve patients with nAMD*

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*Based on Phase 2b randomized, controlled clinical trial data in 366 patients; Jackson, T, Euretina 2019.

BCVA, best-corrected visual acuity; DME, diabetic macular edema; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.
OPT-302 DME Trial Design
Previously anti-VEGF-A-treated patients with persistent DME, a difficult-to-treat population

**Phase 1b Dose Escalation (N=9)**
- OPT-302 (0.3 mg) + Aflibercept (2.0 mg) IVT Q4W x 3, (N=3)
- OPT-302 (1.0 mg) + Aflibercept (2.0 mg) IVT Q4W x 3, (N=3)
- OPT-302 (2.0 mg) + Aflibercept (2.0 mg) IVT Q4W x 3, (N=3)

**14 Day DLT window**

**Phase 2a Dose Expansion: Randomized 2:1 (N~108)**
- OPT-302 (2.0 mg) + Aflibercept (2.0 mg) IVT Q4W x 3, (N~72)
- Sham + Aflibercept (2.0 mg) IVT Q4W x 3, (N~36)

**Follow-up to week 12**

**PRN anti-VEGF-A Week 12 to 24**

**Key Inclusion Criteria**
- Age ≥ 18 years; centre-involving DME
- CST ≥ 320 µm*
- BCVA 73 – 24 ETDRS letters (20/40 – 20/320 Snellen)
- Prior exposure to anti-VEGF-A therapy
  - ≥ 3 intravitreal injections in last 5 months prior to study day 1
  - Last injection ≤ 42 days prior to study day 1
  - Prior off-label bevacizumab only allowed if switched to ≥ 1 injection of aflibercept or ranibizumab prior to study
- 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 dexamethasone or fluocinolone implant in study eye

**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 dexamethasone or fluocinolone implant in study eye

OPT-302-1003 Phase 1b/2a clinical trial (NCT03397264)
*CST as measured by Spectralis (Heidelberg) at screening, ≥ 305 µm for Cirrus.
DLT, Dose Limiting Toxicity; Q4W, once every 4 weeks; VEGF, vascular endothelial growth factor;
Phase 2a Clinical Analyses of OPT-302 Combination Therapy

All patients enrolled had persistent center-involved DME despite prior anti-VEGF-A treatment

Clinical Analyses:

• **All patients in the Per Protocol Population**
  • Heterogeneous all comers’ population for prior anti-VEGF-A history
    • (aflibercept / ranibizumab / bevacizumab)
  • Variable prior-treatment history
    • number and frequency of previous intravitreal anti-VEGF-A injections

• **Patients who had received prior aflibercept therapy (exploratory subgroup)**
  • More homogenous population for prior anti-VEGF-A history
  • Less variable prior treatment history & greater VEGF-A suppression at baseline
  • Most stringent and least variable patient population to test the ability of OPT-302 to provide additional benefit over VEGF-A inhibition
OPT-302 Phase 1b/2a
Phase 1b dose escalation and Phase 2a randomised, controlled, double masked, proof-of-concept study

- Heterogeneous all comers’ population for prior anti-VEGF-A history (aflibercept / ranibizumab / bevacizumab) in patients with persistent DME
- Variable treatment history including number and frequency of prior intravitreal injections of anti-VEGF-A monotherapy

### Previous anti-VEGF-A treatment History

- Aflibercept (2 mg) ^a
  - Ranibizumab (0.3 or 0.5 mg) ^b
  - Bevacizumab (1.25 mg; off-label) ^c
- Mix of Bevacizumab / Aflibercept / Ranibizumab ^d

#### Phase 1b
- Dose escalation (N=9)

#### Phase 2a
- Dose expansion (N=108)

**Study Treatment**

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
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<tbody>
<tr>
<td>OPT-302 (0.3 mg) + Aflibercept (2 mg)</td>
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<tr>
<td>OPT-302 (1.0 mg) + Aflibercept (2 mg)</td>
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<tr>
<td>OPT-302 (2.0 mg) + Aflibercept (2 mg)</td>
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<tr>
<td>Sham + Aflibercept (2 mg)</td>
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</tbody>
</table>

**Primary endpoint at week 12**

### Phase 1b Dose escalation (N=9)

- Time, Weeks
  - 0 4 8 12

### Phase 2a Dose expansion (N=108)

- Time, Weeks
  - 0 4 8 12

**Previous anti-VEGF-A treatment History**

- Max No. of IVT anti-VEGF-A ≤ 24 inj. in 24 months prior to Day 1
  - Mean: 8.2 in 11.3 months
  - Range: (3 to 21 injections)

- Minimum No. of IVT anti-VEGF-A
  - ≥ 3 inj. in 5 months prior to Day 1
  - Mean: 38.7 days
  - Range: 28-42 days

- Last IVT anti-VEGF-A ≤ 42 days prior to Day 1

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### Notes:

- ^a Includes patients receiving only all Aflibercept or last 3 injections of Aflibercept prior to study entry
- ^b Includes patients receiving only all Ranibizumab or last 3 injections of Ranibizumab prior to study entry
- ^c Includes patients receiving only all off-label Bevacizumab. For last injection prior to study entry patients must be switched to 1 injection of either Aflibercept or Ranibizumab
- ^d Includes patients receiving multiple switching of anti-VEGF-A therapy. For last injection prior to study entry patients must be switched to 1 injection of either Aflibercept or Ranibizumab
Phase 1b Dose Escalation of OPT-302 Combination Therapy

Summary of results

Previously anti-VEGF-A treated patients with center-involved DME (N=9)

- OPT-302 (0.3 mg) + aflibercept (2 mg) IVT Q4W x 3
- OPT-302 (1 mg) + aflibercept (2 mg) IVT Q4W x 3
- OPT-302 (2 mg) + aflibercept (2 mg) IVT Q4W x 3

Safety / Tolerability:
- IVT OPT-302 up to 2 mg in combination with aflibercept (2 mg) was well tolerated
- No dose limiting toxicities
- Maximum Tolerated Dose not reached
- No study drug related adverse events

- OPT-302 + Aflibercept showed a dose-response for BCVA gains to Week 12 with a corresponding decrease in CST
## Baseline Demographics

Well balanced across treatment groups in Phase 2a

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Aflibercept (2mg) + Sham (N = 48)</th>
<th>Aflibercept (2mg) + OPT-302 (2 mg) (N = 96)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>61.2 (9.40)</td>
<td>61.8 (10.07)</td>
</tr>
<tr>
<td>Male, n (%)</td>
<td>30 (62.5%)</td>
<td>60 (62.5%)</td>
</tr>
<tr>
<td>Race, n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>American Indian or Alaska native</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Asian</td>
<td>1 (2.1%)</td>
<td>1 (1.0%)</td>
</tr>
<tr>
<td>Black or AfricanAmerican</td>
<td>8 (16.7%)</td>
<td>8 (8.3%)</td>
</tr>
<tr>
<td>White</td>
<td>37 (77.1%)</td>
<td>87 (90.6%)</td>
</tr>
<tr>
<td>Other</td>
<td>2 (4.2%)</td>
<td>0 (0%)</td>
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<tr>
<td>Mean duration of diabetes, years (SD)</td>
<td>15 (9.23)</td>
<td>14.5 (8.97)</td>
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<tr>
<td>Diabetes Type n (%)</td>
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</tr>
<tr>
<td>Type I</td>
<td>3 (6.3%)</td>
<td>5 (5.2%)</td>
</tr>
<tr>
<td>Type II</td>
<td>45 (93.8%)</td>
<td>87 (90.6%)</td>
</tr>
<tr>
<td>Type not reported</td>
<td>0 (0%)</td>
<td>4 (4.2%)</td>
</tr>
<tr>
<td>Mean HbA1c, % (SD)</td>
<td>8.1 (1.27)</td>
<td>7.5 (1.37)</td>
</tr>
</tbody>
</table>
## Baseline Demographics
Well balanced across treatment groups in Phase 2a

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>2.0 mg aflibercept + Sham (N=48)</th>
<th>2.0 mg aflibercept + 2.0 mg OPT-302 (N=96)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vision</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean best corrected visual acuity (BCVA) – letters (±SD)</td>
<td>63.9 (9.44)</td>
<td>63.3 (8.31)</td>
</tr>
<tr>
<td>&gt;55 letters vision - n (%)</td>
<td>41 (85.4%)</td>
<td>81 (84.4%)</td>
</tr>
<tr>
<td>≤55 letters vision - n (%)</td>
<td>7 (14.6%)</td>
<td>15 (15.6%)</td>
</tr>
<tr>
<td><strong>Anatomic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean central subfield thickness (CST) - µm (±SD)</td>
<td>427.3 (99.7)</td>
<td>433.8 (104.5)</td>
</tr>
<tr>
<td>CST &gt;450 µm - n (%)</td>
<td>17 (35.4%)</td>
<td>30 (31.3%)</td>
</tr>
<tr>
<td>CST ≤450 µm - n (%)</td>
<td>31 (64.6%)</td>
<td>66 (68.8%)</td>
</tr>
<tr>
<td><strong>Diabetic Retinopathy Severity Score</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Absent or mild NPDR (level 10-20)</td>
<td>4 (8.4%)</td>
<td>4 (4.4%)</td>
</tr>
<tr>
<td>Mild-moderate NPDR (level 35)</td>
<td>4 (8.3%)</td>
<td>13 (14.2%)</td>
</tr>
<tr>
<td>Moderate NPDR (level 43)</td>
<td>11 (22.9%)</td>
<td>15 (16.5%)</td>
</tr>
<tr>
<td>Moderately Severe NPDR (level 47)</td>
<td>20 (41.7%)</td>
<td>46 (50.5%)</td>
</tr>
<tr>
<td>Severe NPDR (level 53)</td>
<td>7 (14.6%)</td>
<td>13 (14.3%)</td>
</tr>
<tr>
<td>Mild PDR (level 61)</td>
<td>2 (4.2%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

Intent to Treat population (n=144)
## Prior Treatment History Study Eye

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>2.0 mg aflibercept + Sham (N=40)</th>
<th>2.0 mg aflibercept + 2.0 mg OPT-302 (N=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean Duration of Diabetic Macular Edema – years (±SD)</td>
<td>1.6 (1.70)</td>
<td>1.3 (1.30)</td>
</tr>
<tr>
<td>Mean Number of Prior IVT Anti-VEGF-A Injections for CI-DME (±SD)</td>
<td>8.4 (4.56)</td>
<td>8.0 (4.35)</td>
</tr>
<tr>
<td>Mean Duration of Prior IVT Anti-VEGF-A injections – months (±SD)</td>
<td>12.4 (6.43)</td>
<td>10.7 (5.95)</td>
</tr>
<tr>
<td>Mean time from Prior Treatment to Day 1 – days (±SD)</td>
<td>38.4 (3.59)</td>
<td>38.8 (3.87)</td>
</tr>
</tbody>
</table>

### Prior Anti-VEGF-A Therapies n (%)

<table>
<thead>
<tr>
<th></th>
<th>2.0 mg aflibercept + Sham (N=40)</th>
<th>2.0 mg aflibercept + 2.0 mg OPT-302 (N=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3 injections</td>
<td>4 (10.0%)</td>
<td>6 (8.0%)</td>
</tr>
<tr>
<td>4-6 injections</td>
<td>13 (32.5%)</td>
<td>33 (44.0%)</td>
</tr>
<tr>
<td>7-12 injections</td>
<td>15 (37.5%)</td>
<td>24 (32.0%)</td>
</tr>
<tr>
<td>13-24 injections</td>
<td>8 (20.0%)</td>
<td>12 (16.0%)</td>
</tr>
</tbody>
</table>

### Prior Anti-VEGF-A Treatment n (%)

<table>
<thead>
<tr>
<th></th>
<th>2.0 mg aflibercept + Sham (N=40)</th>
<th>2.0 mg aflibercept + 2.0 mg OPT-302 (N=75)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflibercept a</td>
<td>13 (32.5%)</td>
<td>22 (29.3%)</td>
</tr>
<tr>
<td>Ranibizumab b</td>
<td>4 (10.0%)</td>
<td>9 (12.0%)</td>
</tr>
<tr>
<td>Bevacizumab c</td>
<td>19 (47.5%)</td>
<td>35 (46.7%)</td>
</tr>
<tr>
<td>Multiple switching of anti-VEGF-A therapy (aflibercept, ranibizumab, bevacizumab) d</td>
<td>4 (10.0%)</td>
<td>9 (12%)</td>
</tr>
</tbody>
</table>

Per Protocol population (n=115), must have received all 3 intravitreal study treatments and evaluable at Baseline through Week 12 and sufficiently compliant with the protocol.

- a Includes patients receiving only all Aflibercept or last 3 injections of Aflibercept prior to study entry
- b Includes patients receiving only all Ranibizumab or last 3 injections of Ranibizumab prior to study entry
- c Includes patients receiving only all Bevacizumab. For last injection prior to study entry patients must be switched to 1 injection of either Aflibercept or Ranibizumab
- d Includes patients receiving multiple switching of anti-VEGF-A therapy. For last injection prior to study entry patients must be switched to 1 injection of either Aflibercept or Ranibizumab
## Safety

Well tolerated & consistent with previous OPT-302 Phase 1 and Phase 2b clinical trials in wet AMD

<table>
<thead>
<tr>
<th>Selected Adverse Events</th>
<th>Aflibercept (2mg) + Sham (N = 49)</th>
<th>Aflibercept (2mg) + OPT-302 (2 mg) (N =95)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intraocular inflammation</td>
<td>1 (2.0%)</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>Endophthalmitis</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Retinal detachment</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Cataract</td>
<td>1 (2.0%)</td>
<td>3 (3.2%)</td>
</tr>
<tr>
<td>Intraocular Pressure Increased^</td>
<td>3 (6.1%)</td>
<td>14 (14.7%)</td>
</tr>
<tr>
<td>Non-fatal myocardial infarction</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Non-fatal stroke*</td>
<td>0 (0%)</td>
<td>1 (1.1%)</td>
</tr>
<tr>
<td>Vascular death</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
<tr>
<td>Any other death</td>
<td>0 (0%)</td>
<td>0 (0%)</td>
</tr>
</tbody>
</table>

- A total of 299 intravitreal injections of OPT-302 (any dose) were co-administered with aflibercept (2 mg) in the Phase 1b/2a DME trial

Safety population (n=144); TEAEs reported through Week 12.

^Changes in IOP were transient and there were no sustained changes to post-treatment mean IOP values compared to baseline.

*Grade 3 cerebrovascular accident, 21 days following the second dosing of study products, participant was hospitalized. No evidence of occlusion of the great vessels.

It was concluded that a CVA could not be ruled out however its location is unclear. The event was assessed as possibly related as it was confounded by the underlying diabetes mellitus, which is a risk factor for the event, as well as underlying Bladder cancer as having potential to induce thrombotic events. Participant withdrew consent and was discontinued due to the event.
Primary Efficacy Endpoint: Response Rate of ≥ 5 letter gain to Week 12
Previously anti-VEGF-A treated DME patients after switching to OPT-302 + aflibercept combination therapy

* A one stage design was used (Sargent, Control Clin Trials 2001;22:117–125) based on the pre-specified response rate primary outcome of a total of 72 evaluable patients receiving aflibercept + OPT-302, in Per Protocol population, must have received all 3 intravitreal study treatments and evaluable at Baseline through Week 12, and sufficiently compliant with the protocol.

- Clinical activity if ≥ 27 of 72 patients have a ≥ 5 letter gain in BCVA from baseline to week 12, Type I and II error rates set to 5% and with probability of at least 90%
- Bars represent 95% Confidence Intervals
Mean Change in BCVA and % Vision Gains & Loss - Baseline to Week 12

Persistent DME patients: Prior anti-VEGF-A therapy of aflibercept /ranibizumab / bevacizumab

Per Protocol population (n=115), must have received all 3 intravitreal study treatments and evaluable at Baseline through Week 12 and sufficiently compliant with the protocol.
Mean Change in Central Subfield Thickness - Baseline to Week 12
Persistent DME patients: Prior anti-VEGF-A therapy of aflibercept /ranibizumab / bevacizumab

Per Protocol population (n=115), must have received all 3 intravitreal study treatments and evaluable at Baseline through Week 12 and sufficiently compliant with the protocol.

Error bars (± SEM)
OPT-302 Phase 2a DME Study
Exploratory subgroup analysis in patient population receiving previous aflibercept

- More homogeneous population of anti-VEGF-A prior treatment history of previous aflibercept in patients with persistent DME
  - Less variable prior treatment history & greater VEGF-A suppression at baseline
  - Most stringent and least variable patient population to test the ability of OPT-302 to provide additional benefit over VEGF-A inhibition

Previous anti-VEGF-A treatment History

- Aflibercept (2 mg) a

<table>
<thead>
<tr>
<th>Time, Months</th>
<th>-24</th>
<th>-21</th>
<th>-18</th>
<th>-15</th>
<th>-12</th>
<th>-9</th>
<th>-6</th>
<th>-3</th>
<th>0</th>
</tr>
</thead>
</table>

Max No. of IVT anti-VEGF-A ≤ 24 inj. in 24 months prior to Day 1

For Sham control group:
Mean: 9.8 inj. once every 5.5 weeks
Range: (3 to 19 injections)

For OPT-302 combination group:
Mean: 9.4 inj. once every 4.8 weeks
Range: (3 to 21 injections)

Minimum No. of IVT anti-VEGF-A ≥ 3 inj. in 5 months prior to Day 1

For Sham control group:
Mean: 37.5 days

For OPT-302 combination group:
Combo Mean: 39.3 days

Last IVT anti-VEGF-A ≤ 42 days prior to Day 1

For Sham control group:
Mean: 37.5 days

For OPT-302 combination group:
Combo Mean: 39.3 days

Study Treatment

- OPT-302 (2.0 mg) + Aflibercept (2 mg) (N=22)
- Sham + Aflibercept (2 mg) (N=13)
- Primary endpoint at week 12

a Includes patients receiving only all Aflibercept or last 3 injections of Aflibercept prior to study entry
Sham = Sham + Aflibercept (2 mg); Combo = OPT-302 (2 mg) + Aflibercept (2 mg); inj. = injections;
Visual Acuity Gain following OPT-302 combination therapy
Exploratory Subgroup Analysis in patient population with a prior treatment history of previous aflibercept

Per Protocol population prior aflibercept subgroup (n=35), must have received all 3 intravitreal study treatments and evaluable at Baseline through Week 12 and sufficiently compliant with the protocol. Error bars (± SEM)
Gains in Visual Function, Reduced Vision Loss with OPT-302
Exploratory Subgroup Analysis in patient population with a prior treatment history of previous aflibercept

≥10 Letter Gain At Week 12

≥15 Letter Gain At Week 12

≥1 Letter Loss At Week 12

For Protocol population prior aflibercept subgroup (n=35), must have received all 3 intravitreal study treatments and evaluable at Baseline through Week 12 and sufficiently compliant with the protocol.
Reduced Retinal Thickness with OPT-302 Combination Therapy
Exploratory Subgroup Analysis in patient population with a prior treatment history of previous aflibercept

Per Protocol population prior aflibercept subgroup (n=35), must have received all 3 intravitreal study treatments and evaluable at Baseline through Week 12 and sufficiently compliant with the protocol.

Error bars (± SEM)
Conclusions
OPT-302 Combination therapy in Previously Treated Patients with Persistent DME

Primary safety endpoint met:
• The safety profile of OPT-302 combination therapy is favorable and consistent across two eye indications where a total of >1850 intravitreal injections have been administered to patients with nAMD and DME

Efficacy outcomes were assessed in a heterogenous previously treated all-comer’s population with variable treatment history including number and frequency of prior intravitreal injections of anti-VEGF-A monotherapy

The primary efficacy endpoint was achieved:
• Totality of secondary functional and anatomical responses indicate biological effects for OPT-302 combination therapy

Exploratory subgroup analysis in a difficult to treat patient population with a more homogenous prior treatment history of previous aflibercept indicates VEGF-C/D blockade with OPT-302 showed positive improvements and additive benefit to aflibercept anti-VEGF-A monotherapy

These results in previously-treated patients warrant further evaluation of OPT-302 combination therapy in larger patient populations with DME
Wet AMD

Review & Opthea’s Phase 2b wet AMD Trial

Jason Slakter, MD, Vitreous Retina Macula Consultants, New York City, NY
Practice Setting: Vitreous Retina Macula Consultants, New York

- Practice encompasses 3 Locations in Brooklyn, Manhattan & Westchester
- Multispecialty with 11 retinal physicians
- Strong research focus on the development of new diagnostic and therapeutic strategies
- Approximately 1500 anti-VEGF-A Intravitreal injections a month

Medical Director – Digital Angiography Reading Center
Most commonly used wet AMD therapies primarily target VEGF-A

<table>
<thead>
<tr>
<th></th>
<th>Bevacizumab(^a) (Avastin)</th>
<th>Ranibizumab (Lucentis)</th>
<th>Aflibercept (Eylea)</th>
<th>Brolucizumab(^b) (Beovu)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Format</td>
<td>Full antibody (IgG1)</td>
<td>Monoclonal humanized antibody fragment</td>
<td>VEGFR-1/2-Fc fusion protein</td>
<td>Single-chain antibody fragment (scFv)</td>
</tr>
<tr>
<td>Molecular structure</td>
<td><img src="image1" alt="Full antibody" /></td>
<td><img src="image2" alt="Monoclonal antibody fragment" /></td>
<td><img src="image3" alt="VEGFR-1/2-Fc fusion protein" /></td>
<td><img src="image4" alt="Single-chain antibody fragment" /></td>
</tr>
<tr>
<td>Molecular weight</td>
<td>149 kDa</td>
<td>48 kDa</td>
<td>115 kDa</td>
<td>26 kDa</td>
</tr>
<tr>
<td>Clinical dose for nAMD</td>
<td>1.25 mg (unlicensed use)</td>
<td>0.5 mg</td>
<td>2.0 mg</td>
<td>6.0 mg</td>
</tr>
</tbody>
</table>
Current Management of wet AMD and Major Unmet Medical Need

Current management: Anti-VEGF-A therapy individualized for patients:
- Most commonly used are ranibizumab, aflibercept and bevacizumab
  - Each have similar efficacy and safety
  - Mean gain in visual acuity is ~9 letters for wet AMD
  - Only a ~third of patients achieve 3 or more lines of vision improvement
  - Best outcomes with frequent dosing regimens
  - Treat and extend is often utilized in attempt to reduce treatment burden
  - “Real World” experience: Undertreatment = suboptimal outcomes > 2 years

Major unmet need:
- Need for **better efficacy** resulting in improved visual outcomes
  - Immediate and long-term VA gains to help with patient interest and compliance
  - Decreased burden
- New treatment modalities including **combination therapy** are needed to improve vision outcomes and/or durability of responses
Further Vision Gains Possible with VEGF-A Blockade in wet AMD

Wet AMD – Shortcomings of VEGF-A Blockade

>70% VA REMAINS TO BE GAINED

#1 EFFICACY

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Investigational treatments in pipeline also mostly targeting VEGF-A and aimed at improving durability
HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BEOVU safely and effectively. See full prescribing information for BEOVU.

BEOVU® (brolucizumab-dbll) injection, for intravitreal use
Initial U.S. Approval: 2019

------------------- WARNINGS AND PRECAUTIONS -------------------
• Endophthalmitis and retinal detachment may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay (5.1).

• Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported following BEOVU injections. Patients should be instructed to report any change in vision without delay (5.2).

• Increases in intraocular pressure (IOP) have been seen within 30 minutes of an intravitreal injection (5.3).

• There is a potential risk of arterial thromboembolic events (ATE) following intravitreal use of VEGF inhibitors (5.4).

------------------- ADVERSE REACTIONS -------------------
The most common adverse reactions (≥5%) reported in patients receiving BEOVU are vision blurred (10%), cataract (7%), conjunctival hemorrhage (6%), eye pain (5%), and vitreous floaters (5%) (6.1).

Intraocular Safety of Newer Longer-Acting anti-VEGF-A agents

Allergan, an AbbVie Company, and Molecular Partners Receive Complete Response Letter from FDA on Biologics License Application for Abicipar pegol

June 03, 2020

NORTH CHICAGO, Ill., June 03, 2020 /PRNewswire/ -- Allergan, an AbbVie Company (NYSE: ABBV), and Molecular Partners (EUV: MOLN), a clinical-stage biotechnology company developing a new class of custom-built protein therapeutics known as DARPin® therapeutics, today announced that the U.S. Food and Drug Administration (FDA) has issued a Complete Response Letter to the Biologics License Application (BLA) for Abicipar pegol, a novel, investigational DARPin® therapy for patients with neovascular (wet) age-related macular degeneration (AMD).

This letter from the FDA indicates that the rate of intraocular inflammation observed following administration of Abicipar pegol 2mg/0.05 mL results in an unfavorable benefit-risk ratio in the treatment of neovascular (wet) age-related macular degeneration (AMD). AbbVie plans to meet with the FDA to discuss their comments and determine next steps.

SEQUOIA STUDY

<table>
<thead>
<tr>
<th>Intraocular Inflammation Events</th>
<th>100%</th>
<th>90%</th>
<th>80%</th>
<th>70%</th>
<th>60%</th>
<th>50%</th>
<th>40%</th>
<th>30%</th>
<th>20%</th>
<th>10%</th>
<th>0%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abicipar Q8</td>
<td>15.7%</td>
<td></td>
<td></td>
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<td></td>
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<tr>
<td>Abicipar Q12</td>
<td>15.3%</td>
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<tr>
<td>Ranibizumab Q4</td>
<td>0.6%</td>
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</tbody>
</table>

CEDAR STUDY

<table>
<thead>
<tr>
<th>Intraocular Inflammation Events</th>
<th>100%</th>
<th>90%</th>
<th>80%</th>
<th>70%</th>
<th>60%</th>
<th>50%</th>
<th>40%</th>
<th>30%</th>
<th>20%</th>
<th>10%</th>
<th>0%</th>
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</thead>
<tbody>
<tr>
<td>Abicipar Q8</td>
<td>15.1%</td>
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</tr>
<tr>
<td>Abicipar Q12</td>
<td>15.4%</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Ranibizumab Q4</td>
<td>0.0%</td>
<td></td>
<td></td>
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</tbody>
</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
### Study Overview

#### 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

<table>
<thead>
<tr>
<th>iTT Population</th>
<th>sham + 0.5 mg ranibizumab IVT Q4W x 6 n=121</th>
<th>OPT-302 0.5 mg + 0.5 mg ranibizumab IVT Q4W x 6 n=122</th>
<th>OPT-302 2.0 mg + 0.5 mg ranibizumab IVT Q4W x 6 n=123</th>
</tr>
</thead>
<tbody>
<tr>
<td>Completing Study</td>
<td>Completed Study n=116 (95.9%)</td>
<td>Completed Study n=112 (91.8%)</td>
<td>Completed Study n=120 (97.6%)</td>
</tr>
</tbody>
</table>

#### Follow-up

#### Analysis

<table>
<thead>
<tr>
<th>mITT Population</th>
<th>Analysed n=119</th>
<th>Analysed n=122</th>
<th>Analysed n=121</th>
</tr>
</thead>
<tbody>
<tr>
<td>n=112 (91.8%)</td>
<td>n=120 (97.6%)</td>
<td>n=116 (95.9%)</td>
<td>n=121</td>
</tr>
</tbody>
</table>

**Abbreviations:**
- CNV: choroidal neovascularisation
- IVT: intravitreal
- Q4W: once every 4 weeks
- mITT: Modified Intent to Treat Population

**Note:** For personal use only.
## 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>
<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><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>
</tr>
<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>
</tr>
<tr>
<td>6.08 ± 3.21</td>
<td></td>
<td>6.48 ± 3.30</td>
<td>6.62 ± 3.39</td>
</tr>
<tr>
<td><strong>Lesion Type</strong></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>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>

1. PCV - polypoidal choroidal vasculopathy, detected by SD-OCT, FA and fundus photography
2. RAP - retinal angiomatous proliferation, detected by SD-OCT, FA and fundus photography
Superior Vision Gain at Week 24 with OPT-302 (2mg) Combination Therapy

Primary Endpoint Achieved:
Mean Change in Best Corrected Visual Acuity Baseline to Week 24

Δ = +3.4 (p=0.0107)

Sham + 0.5 mg ranibizumab (n=119)
0.5 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
Left: Difference in Least Square Means, using Model for Repeated Measures (MRM) analysis. Right: Graph represents "as observed" data and SEM
Greater Reduction in Retinal Thickness with OPT-302 Combination Therapy

Mean Change in CST – Baseline to Week 24

Mean change in CST (SEM) (μm)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change (μm)</th>
<th>Sample Size</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sham + 0.5 mg ranibizumab (n=116)</td>
<td>-133.80</td>
<td></td>
</tr>
<tr>
<td>2.0 mg OPT-302 + 0.5 mg ranibizumab (n=119)</td>
<td>-146.70</td>
<td></td>
</tr>
</tbody>
</table>

Modified Intent-to-Treat (mITT) population; as observed; CST – central subfield thickness
Better ‘Retinal Drying’ with OPT-302 Combination Therapy

% Participants with SRF present

% Participants with IR Cysts present

Modified Intent-to-Treat (mITT) population; as observed; SRF – sub-retinal fluid; IR – intra-retinal
Greater Reduction in Total Lesion and CNV Area

**Mean Change in Total Lesion Area**

- Sham + 0.5 mg ranibizumab (n=109): p=0.0137
- 2.0 mg OPT-302 + 0.5 mg ranibizumab (n=112): p=0.0055

**Mean Change in CNV Area**

- Sham + 0.5 mg ranibizumab (n=109): p=0.0137
- 2.0 mg OPT-302 + 0.5 mg ranibizumab (n=112): p=0.0055

*Modified Intent-to-Treat (mITT) population; as observed; CNV – choroidal neovascularisation; Difference in Least Square Means*
Phase 2b

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

Pre-Specified Subgroup Analyses

OPT-302-1002; NCT ClinicalTrials.gov Identifier: NCT03345082
Neovascular (wet) AMD Lesion Types
Differ in vessel location, leakiness and responsiveness to VEGF-A inhibitors

- **PREDOMINANTLY CLASSIC**
  - ≥50% vessels above RPE
  - Highly responsive to VEGF-A inhibition

- **MINIMALLY CLASSIC**
  - <50% vessels above RPE
  - Moderately responsive to VEGF-A inhibition

- **OCCULT**
  - 100% beneath RPE
  - Least responsive to VEGF-A inhibition
Mean Change in BCVA Over Time by Lesion Type

Small number of predominantly classic patients

**Predominantly Classic**

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

**Minimally Classic**

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

**Occult**

- Sham + 0.5 mg ranibizumab (n = 51)
- 2.0 mg OPT-302 + 0.5 mg ranibizumab (n = 53)
Greater Vision Gains in Minimally Classic and Occult lesions

**Minimally Classic**

- Mean change in BCVA (SEM) = 2.7
- Δ = 6.0
- (*p = 0.0008)

**Occult**

- Mean change in BCVA (SEM) = 2.7
- Δ = 6.0
- (*p = 0.0008)

mITT; Least square means determined using Model for Repeated Measures (MRM) analysis (adjusted for baseline vision and lesion type (randomisation) as covariates).
Retinal Angiomatous Proliferation (RAP) Lesions
Have a distinct biology and vessel proliferation occurs within the retina (not the choroid)

- No consensus of which treatment is optimal for RAP lesions*
- Favorable short-term results with anti-VEGF-A treatments but long-term results are conflicting

Improved Visual Acuity in OPT-302 + ranibizumab treated patients
In participants without RAP at baseline (>86% study participants)

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

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 Over Time by Lesion Type (RAP Absent)

In participants without RAP at baseline, +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, Δ based on least square means determined using Model for Repeated Measures (MRM) analysis (adjusted for baseline vision and lesion type (randomisation) as covariates).
Improved Visual Acuity in patients with Min-Classic & Occult lesions (RAP Absent)

71% study participants had occult-containing lesions with RAP absent at baseline

\[ \Delta = 5.74 \]
\[ *p = 0.0002 \]

Mean change in BCVA (SEM) (letters)

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

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).
## Safety

OPT-302 well tolerated with very low incidence of ocular inflammation

<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><strong>Treatment emergent AEs (TEAEs)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ocular AEs - Study Eye – related to study product(s)</td>
<td>84 (69.4%)</td>
<td>87 (72.5%)</td>
<td>93 (75.0%)</td>
</tr>
<tr>
<td>Ocular AEs - Study Eye – Severe</td>
<td>17 (14.0%)</td>
<td>17 (14.2%)</td>
<td>19 (15.3%)</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 (1.7%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td><strong>Intraocular inflammation</strong> – Study Eye</td>
<td>2 (1.7%)</td>
<td>2 (1.7%)</td>
<td>1 (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>1 (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 (0.8%)</td>
<td>0 (0.0%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>2 (1.7%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
</tr>
</tbody>
</table>

Safety population analysed according to medication received

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. Transient anterior chamber cell (trace 1-4 cells)
6. Not reported as a TEAE
7. Squamous cell carcinoma of the lung diagnosed shortly after Baseline visit
8. Non-fatal myocardial infarction
9. Pneumonia (n=1), infective endocarditis (n=1)
Safety – Intraocular Inflammation – Study Eye (All OPT-302 Trials)

Incidence of intraocular inflammation similar to control

<table>
<thead>
<tr>
<th>Study Eye</th>
<th>OPT-302 Any dose N=399 Inj=1,842</th>
<th>2.0 mg OPT-302 N=263 Inj=1,121</th>
<th>Sham + anti-VEGF-A control N=169 Inj=854</th>
</tr>
</thead>
<tbody>
<tr>
<td>N Participants (%)</td>
<td>Intraocular inflammation¹</td>
<td>Intraocular inflammation¹</td>
<td>Intraocular inflammation¹</td>
</tr>
<tr>
<td>OPT-302-1001</td>
<td>7 (1.8%)</td>
<td>3 (1.1%)</td>
<td>3 (1.8%)</td>
</tr>
<tr>
<td>Uveitis with anterior chamber cell 1+ (6-10)</td>
<td>2</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Uveitis with anterior chamber cell 2+ (11-20)</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>OPT-302-1002</td>
<td>3</td>
<td>1</td>
<td>2²</td>
</tr>
<tr>
<td>Endophthalmitis with anterior chamber cell 1+ (5-10) and hypopyon</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Vitritis</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Anterior chamber cell, trace (1-4 cells)</td>
<td>1</td>
<td>1</td>
<td>2²</td>
</tr>
<tr>
<td>OPT-302-1003</td>
<td>2</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Iritis with keratic precipitates and anterior chamber cell 2+ (11-20)</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Iritis with anterior chamber cell 2+ (11-20)</td>
<td>0</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Anterior chamber cell, 4+ (&gt;50 cells) associated with cataract extraction/intraocular lens implant and hyphema</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
</tbody>
</table>

¹ AEs and considered to be indicative of intraocular inflammation, defined prior to database lock: Iritis, anterior uveitis/Iritis, anterior chamber cells, endophthalmitis, vitritis and mutton fat keratic precipitate on endothelium

² Observed during ophthalmic examination, but not reported as TEAEs

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Conclusions – OPT-302 Phase 2b wet AMD 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**