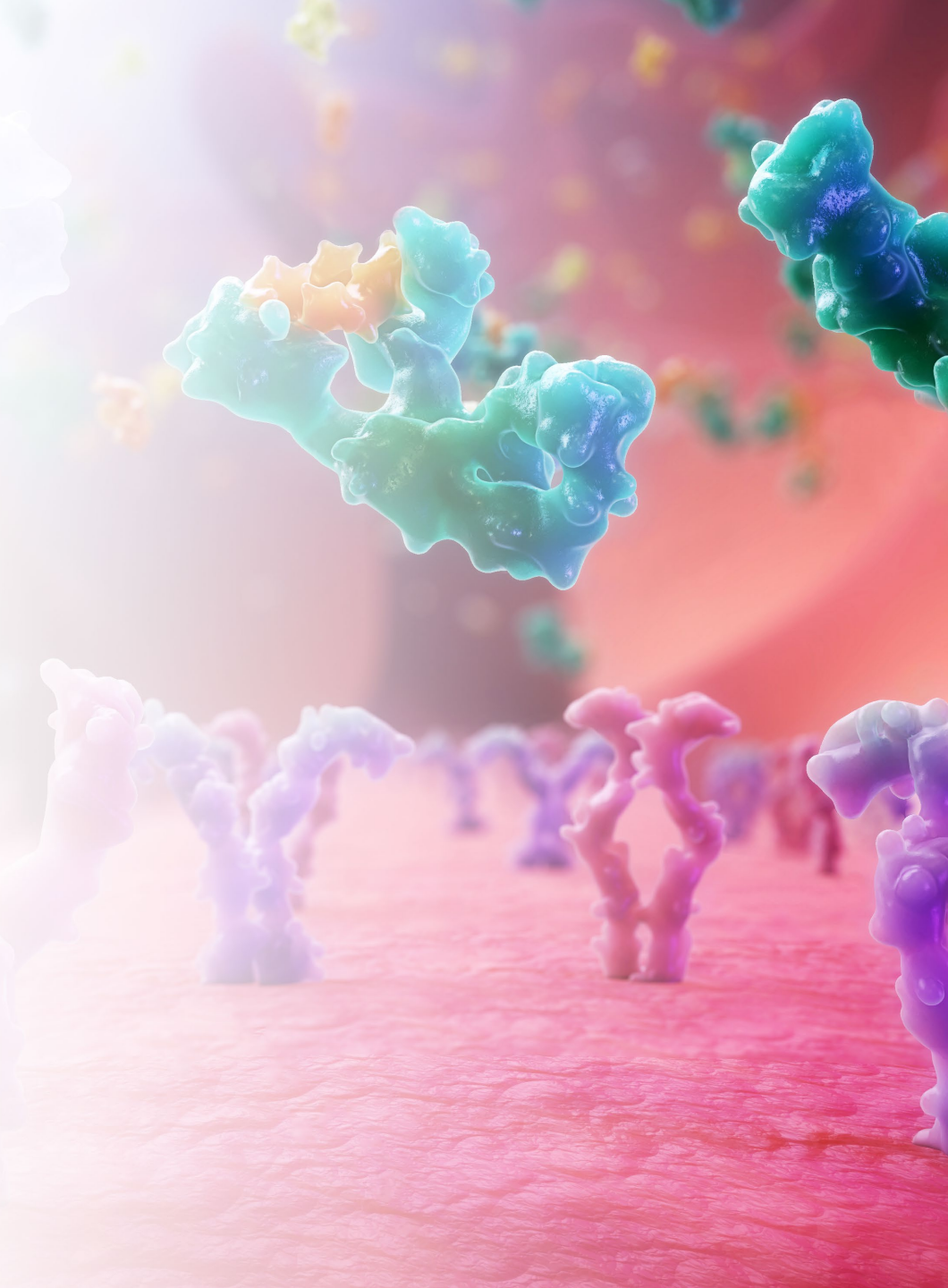
# Leading Therapeutic Innovation in Retinal Diseases



March 2023

Megan Baldwin, Chief Executive Officer
Timothy Morris, Chief Financial Officer

OPTHEA.COM | @OptheaLimited | NASDAQ (OPT); ASX (OPT.AX)

OPTHEA

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# Opthea Limited

## Developing OPT-302, VEGF-C/D “trap” inhibitor for wet AMD

### Company

- 1984: Founded; 1985: ASX listed
- 2007: acquired VEGF-C/D, VEGFR-3 IP portfolio (Uni.Helsinki, LICR Melb)
- 2014: Ophthalmology focus to advance OPT-302
- 2020: IPO NASDAQ 2020
- IP protection for OPT-302 currently to 2034**

### Clinical Program

- Phase 2b 366 patients in wet AMD, completed 2019
- OPT-302 + Ranibizumab showed significant improvement in visual acuity
- Two 990 patient Phase 3 registrational studies currently recruiting globally
- FDA Fast Track Designation

### Financial Highlights

- Project funding agreement with Carlyle/Abingworth for up to $170M completed September 2022
- Annual sales of anti-VEGF-A therapies for wet AMD: $8B
- December 31, 2022
  - Cash on hand $142M*
  - Share price
    - NASDAQ: OPT $5.36
    - ASX: OPT A$0.91
  - Market cap: $US 250M

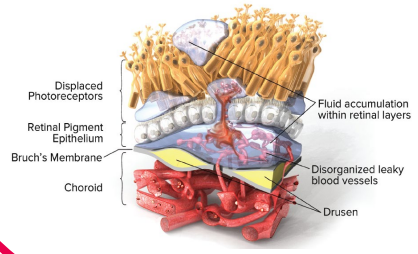
** Unaudited at December 31, 2022 **Does not include potential patent term extension*

# Wet AMD & DME Are the Leading Causes of Vision Loss in the Elderly and Diabetics

## Increasing prevalence- large & growing market opportunity

### Wet Age-Related Macular Degeneration

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

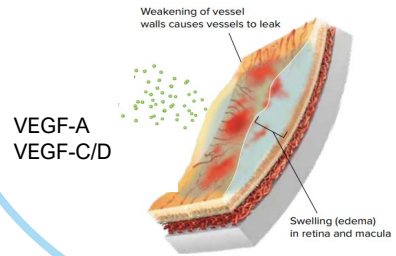



### Epidemiology
*(number of patients)*

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

### Diabetic Macular Edema (DME)

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




*Additional market opportunity:*

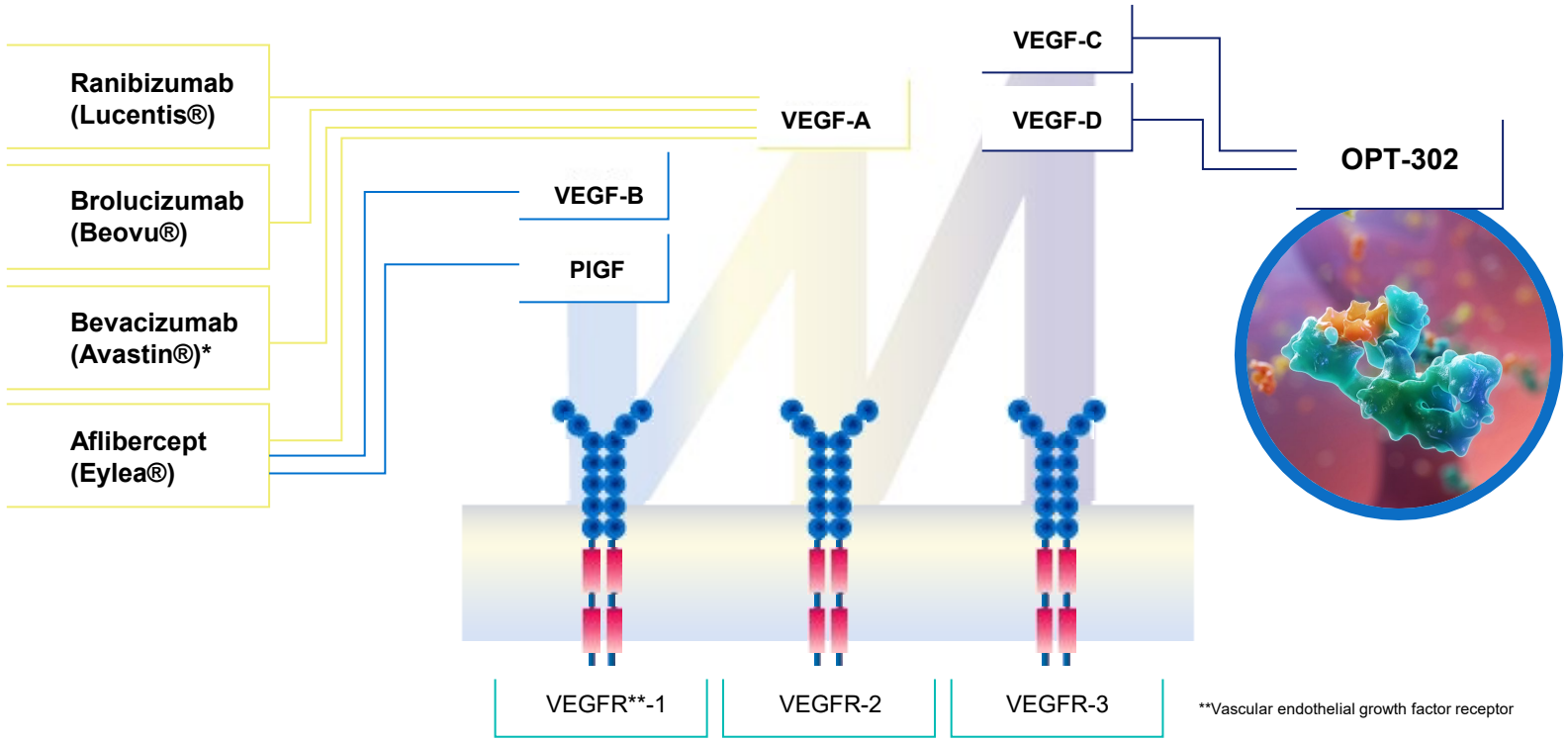
### Macular Edema Secondary to Retinal Vein Occlusion (RVO)

*Characterized by retinal vein blockage that selectively leads to edema formation and loss of visual acuity (VA)*

**United States and Europe; **Worldwide.*

# OPT-302 Combination Therapy Achieves Broad Blockade of the Validated Pathway in Wet AMD

Used in combination with any VEGF-A inhibitor, OPT-302 **completely blocks** VEGFR-2 and VEGFR-3 signaling, inhibiting the most important pathways driving angiogenesis and vascular leakage



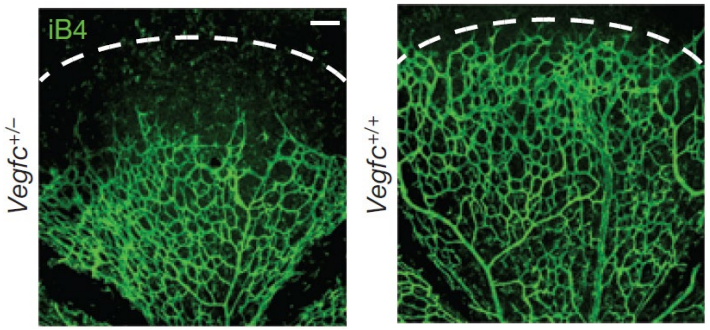

VEGF-A inhibition elevates VEGF-C and VEGF-D which may contribute to sub-optimal clinical efficacy of anti-VEGF-A treatments

*Bevacizumab is used 'off-label' for the treatment of neovascular (wet) AMD.

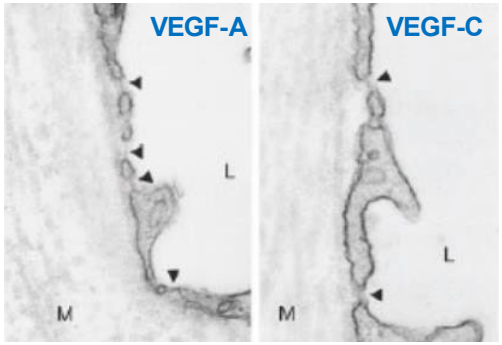
# Role of VEGF-C in Wet AMD

## Published Data Suggest VEGF-C May Contribute to Sub-optimal Responses to Anti-VEGF-A Therapy

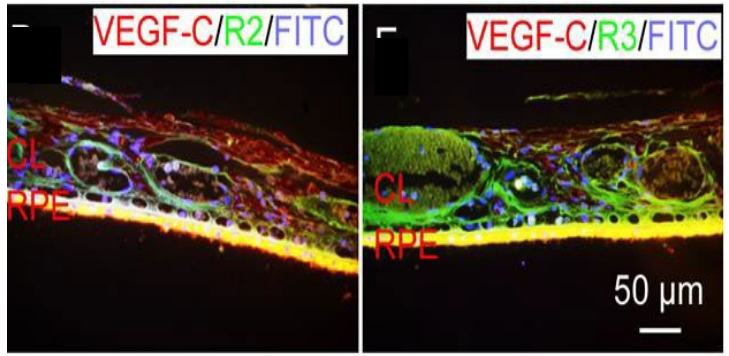
### VEGF-C stimulates retinal angiogenesis^



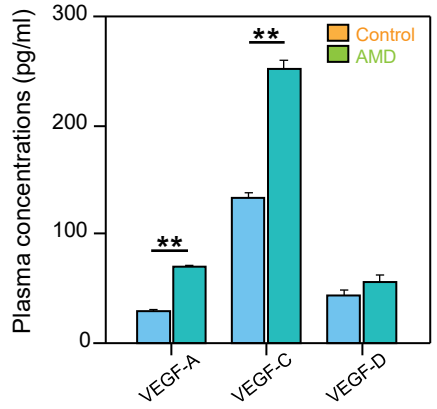

### VEGF-A and VEGF-C induce vascular leakage/permeability#



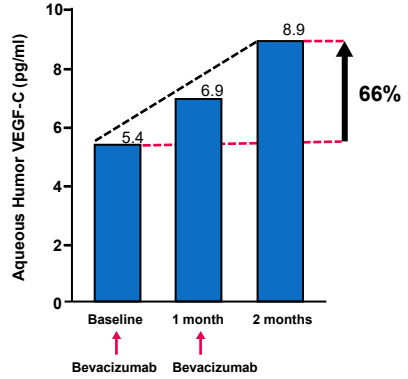

### Elevated VEGF-C and its receptors R2 and R3 in wet AMD clinical specimens†



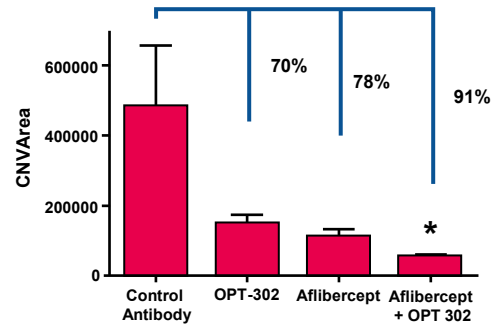

### Circulating VEGF-C levels significantly elevated in AMD patients †




### Elevated VEGF-C in aqueous humor following anti-VEGF-A therapy in Wet AMD Patients*




### Additive benefit of VEGF-A and VEGF-C/D inhibition in mouse Wet AMD model




^Tammela et al., Nature Cell Biology, 2011 , #Zhou et al. BMC Ophthalmology (2020) 20:15; #Cao et al,. Circ Res., 2004; †Lashkari et al , 2013 ARVO Annual Meeting, 4999-A0128; *Cabral et al,. 2018 Ophthalmology Retina (2018).

# OPT-302 is the Next Transformational Step in Treatment for Retinal Diseases

There have been no new targeted therapies with novel mechanisms approved for wet AMD since the approval of the first VEGF-A inhibitor >15 years ago

MACUGEN® PEGAPTANIB SODIUM INJECTION

Isoform-specific VEGF-$A_{165}$ inhibition

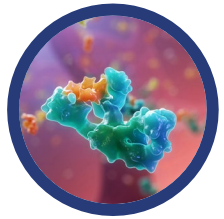
LUCENTIS® RANIBIZUMAB INJECTION

Off-label use AVASTIN® bevacizumab

Target all isoforms of VEGF-A

EYLEA® (aflibercept) Injection For Intravitreal Injection

Targets VEGF-A, VEGF-B, and PlGF



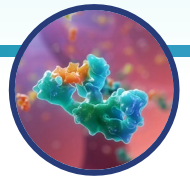
**New Mechanism of Action:**

OPT-302 targets VEGF-C/D

Most advanced product in clinical development with demonstrated potential to **IMPROVE** patient visual outcomes

# Large and Growing Market Opportunity in Wet AMD

## OPT-302 Is Anti-VEGF-A and Durability Agnostic



**>$16B**

**Potential Addressable Market Wet AMD**

**~50% treated patients receive Avastin®**

AVASTIN bevacizumab — Off-label use

LUCENTIS RANIBIZUMAB INJECTION

EYLEA (aflibercept) Injection For Intravitreal Injection

Implied Total Addressable Market for OPT-302 in wet AMD

(Captures Lucentis, Eylea, and Avastin or biosimilar-treated patients worldwide)

**>US$8B**

**Wet AMD**

**~50% treated patients receive Lucentis® or Eylea®**

LUCENTIS RANIBIZUMAB INJECTION

EYLEA (aflibercept) Injection For Intravitreal Injection

Total global revenue for Lucentis and Eylea

**OPT-302 is uniquely positioned to tap into the entire VEGF-A inhibitor market**

# A Need for New Therapies for Wet AMD

## Impact of Vision Loss

Socio-economic impact includes:

- Reduced quality-of-life, independence, mobility, and socialization
- Increased injury and falls
- Worsened mental health

Wills Eye Institute Survey:

A person with 20/40 vision would be willing to trade two of every 10 years of their remaining life to retain perfect vision

## Phase 3 Registrational Trials

Despite regular anti-VEGF-A therapy:

- Majority of patients do not achieve 20/40 vision
- Majority cannot resume routine daily activities

| | % Pts that achieved 20/40 vision at 12 mos |
|---|---|
| Lucentis Ph3 (MARINA[1]) | 40% |
| Lucentis Ph3 (ANCHOR[2]) | 38% |

| | % Pts that gained ≥15 letters |
|---|---|
| Eylea Ph3 (VIEW1[3]) | 33% |
| Eylea Ph3 (VIEW2[3]) | 31% |

## Real-World Data

Patient cohort receiving anti-VEGF-A therapy (after loading doses prn or T&E)[4]

At 10 years follow-up:

- 33% achieved 20/40 vision at 10 years
- 67% did not achieve 20/40 vision
- 14% considered legally blind (≤ 20/200)

1. Rosenfeld et al., NEJM, 2006. 2. Brown et al., NEJM, 2006. 3. Heier et al., Ophthalmology, 2012. 4. Chandra et al., Eye, 2020.

# OPT-302 Combination Therapy Clinical Program

**Now Recruiting**

**Completed**
Phase 1/2a
wet AMD
(n=51)

**Comparator**

**Ranibizumab**
once every month

**OPT-302**
once every month

3 x monthly dosing

Treatment naïve / Prior-treated

**Completed**
Phase 1b/2a
DME
(n=153)

**Comparator**

**Aflibercept**
once every month

**OPT-302**
once every month

3 x monthly dosing

Prior-treated

**Completed**
Phase 2b
wet AMD
(n=366)

**Comparator**

**Ranibizumab**
once every month

**OPT-302**
once every month

6 x monthly dosing

Treatment naïve

**ShORe**
Phase 3
wet AMD
(n=990)

**Comparator**

**Ranibizumab**
once every month

| Standard Dosing | Extended Dosing |
|---|---|
| OPT-302 once every month | OPT-302 once every two months after three monthly doses |
| Monthly dosing | Every two months dosing |

Treatment naïve patients

**COAST**
Phase 3
wet AMD
(n=990)

**Comparator**

**Aflibercept**
once every two months
after three monthly doses

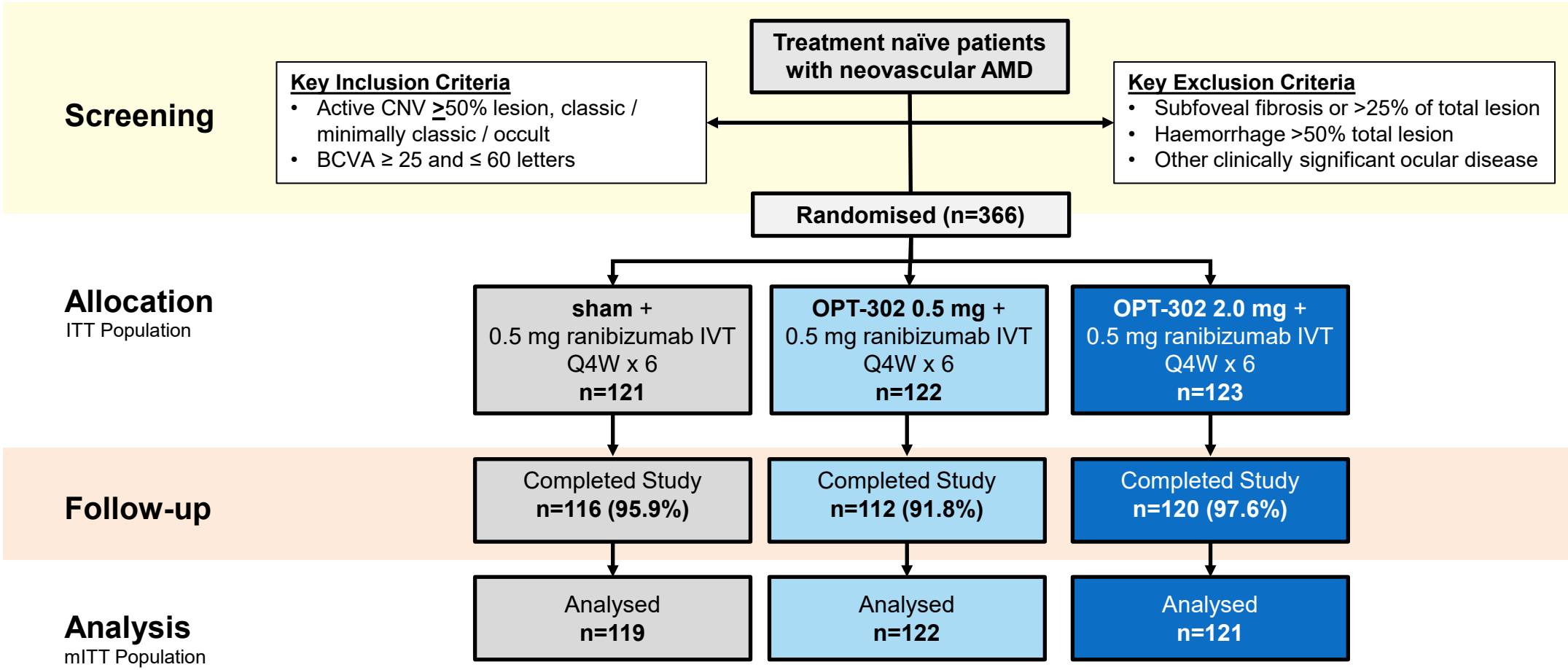
| Standard Dosing | Extended Dosing |
|---|---|
| OPT-302 once every month | OPT-302 once every two months after three monthly doses |
| Monthly dosing | Every two months dosing |

Treatment naïve patients

OPT-302 pivotal registrational Phase 3 wet AMD program designed to maximize outcomes with most flexible SoC dosing regimens

ShORe and COAST Phase 3 pivotal trials incorporate key learnings from our Phase 2b clinical trial in wet AMD patients which demonstrated superior vision outcomes following OPT-302 combination therapy, supporting a high level of confidence in the OPT-302 development program.

# Phase 2b Study Overview




CNV – choroidal neovascularisation; IVT – intravitreal; Q4W – once very 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

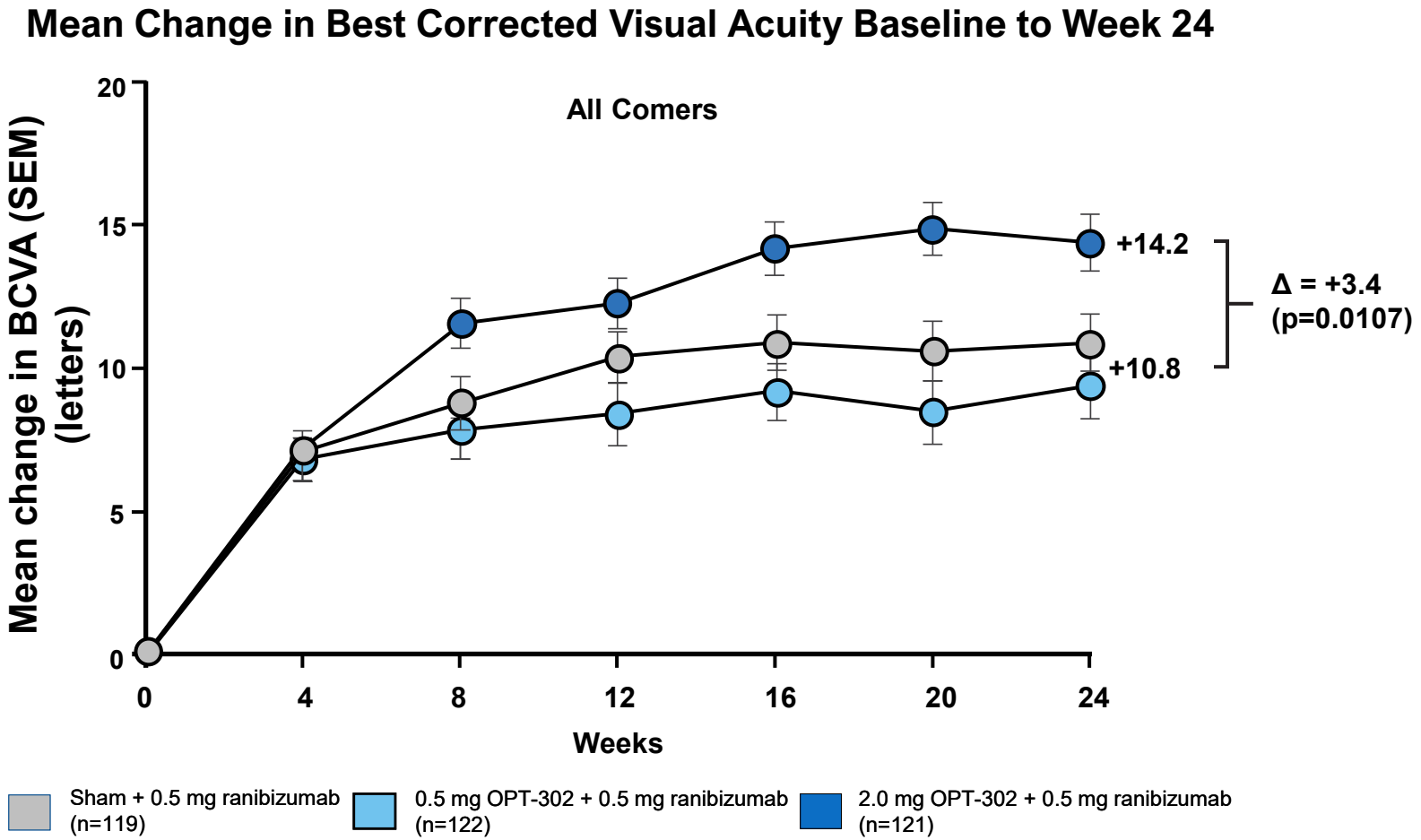
# Phase 2b Study Demographics and Baseline Characteristics

| Demographic/Baseline Disease Characteristic | | Sham + ranibizumab n=121 | 0.5 mg OPT-302 + ranibizumab n=122 | 2.0 mg OPT-302 + ranibizumab n=123 |
|---|---|---|---|---|
| **Mean Age – years ± SD** | | 76.1 ± 9.48 | 78.8 ± 8.16 | 77.8 ± 8.82 |
| **Sex – n (%)** | Male | 48 (39.7%) | 49 (40.2%) | 45 (36.6%) |
| | Female | 73 (60.3%) | 73 (59.8%) | 78 (63.4%) |
| **Caucasian Race – n (%)** | | 117 (99.2%) | 119 (99.2%) | 117 (97.5%) |
| **Mean Visual Acuity (BCVA) – letters ± SD** | | 50.7 ± 10.21 | 51.1 ± 8.96 | 49.5 ± 10.26 |
| **Mean Total Lesion Area - mm$^2$ ± SD** | | 6.08 ± 3.21 | 6.48 ± 3.30 | 6.62 ± 3.39 |
| **Lesion Type** | Predominantly classic – n (%) | 15 (12.4%) | 15 (12.3%) | 16 (13.0%) |
| | Minimally classic – n (%) | 53 (43.8%) | 51 (41.8%) | 53 (43.1%) |
| | Occult - n (%) | 53 (43.8%) | 56 (45.9%) | 54 (43.9%) |
| | PCV detected[1] – n (%) | 20 (16.5%) | 24 (19.7%) | 22 (17.9%) |
| | RAP detected[2] – n (%) | 15 (12.7%) | 22 (18.5%) | 14 (11.8%) |
| Mean central subfield thickness (CST) - mm ±SD | | 412.10 ± 110.62 | 425.18 ± 120.45 | 414.12 ± 123.25 |
| Sub-retinal fluid (SRF) present – % participants | | 89.3% | 84.4% | 87.8% |
| Intra-retinal cysts present – % participants | | 57.9% | 63.9% | 56.1% |

Intent-to-Treat (ITT) population; SD: standard deviation; BCVA: Best Corrected Visual Acuity.
[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.

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

- Primary endpoint achieved

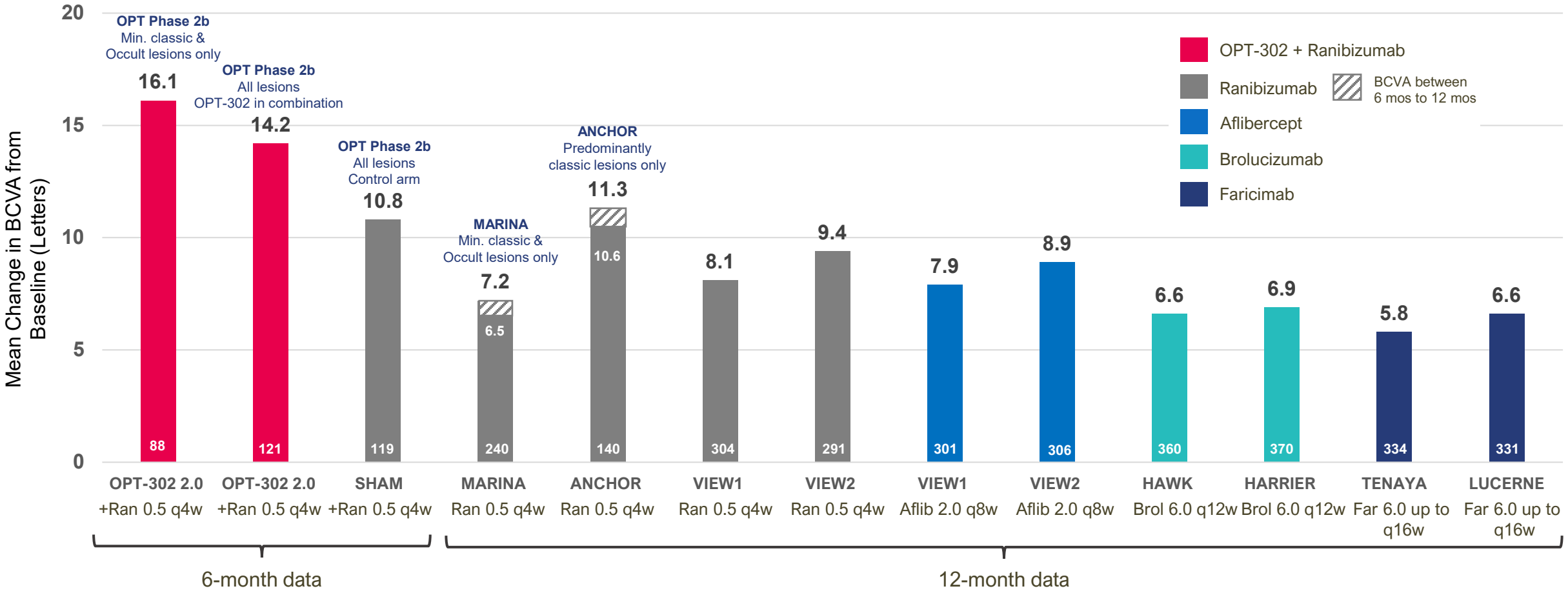



mITT; BCVA – Best Corrected Visual Acuity.
Left: Difference in Least Square Means, using Model for Repeated Measures (MRM) analysis. Right: Graph represents "as observed" data and SEM.

# OPT-302 Combination Therapy

## Mean Visual Acuity Higher Relative to Previous VEGF-A Inhibitor Trials

**Efficacy at 6 months is typically maintained or greater at 12 months in Phase 3 trials with VEGF-A inhibitors**

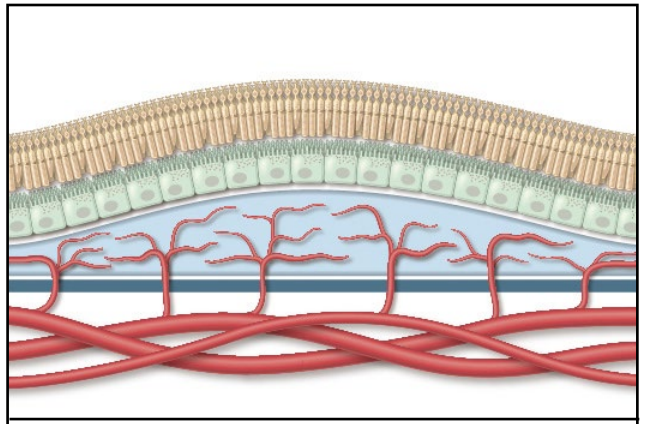



All trials shown, excluding Opthea's Phase 2b data, are Phase 3 registrational studies. Number of patients randomised to treatment group (n, bottom of bars). Mean change in Best Corrected Visual Acuity (BCVA) from baseline shown in ETDRS letters (top of bars). Aflib 2.0, aflibercept 2.0mg; Brol 6.0, brolucizumab 6.0mg; Far 6.0, faricimab 6.0mg; OPT-302 2.0, 2.0mg OPT-302; P2B, Phase 2b study OPT-302-1002; Ran 0.5, ranibizumab, 0.5 mg; administered every four weeks; q8w, administered every 8 weeks (following 3 x 4-weekly loading doses); q12w, administered every 12 weeks; up to q16w, administered up to every 16 weeks based on protocol defined disease activity assessments.

# Neovascular (Wet) AMD Lesion Types

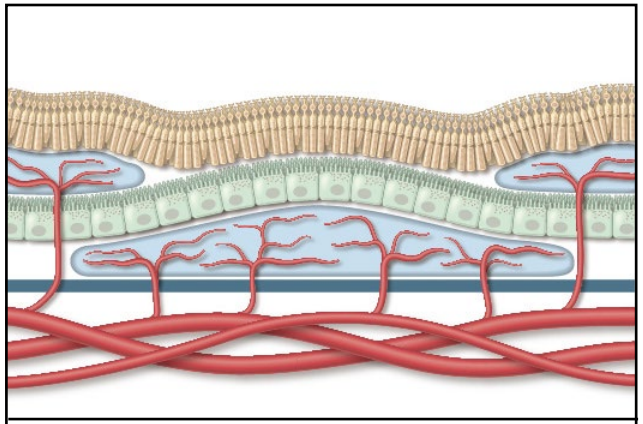
## Differ in Vessel Location, Leakiness, and Responsiveness to VEGF-A Inhibitors

**OCCULT**



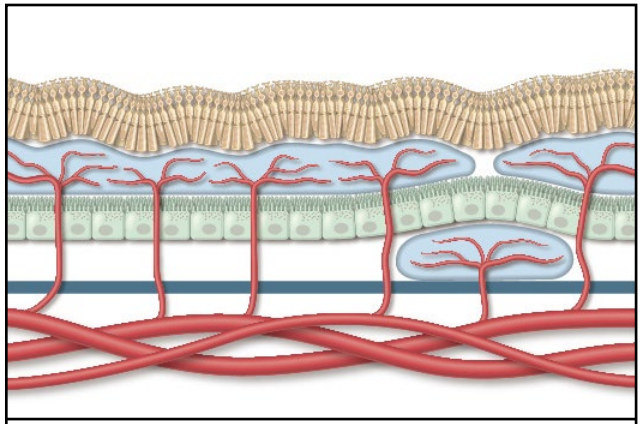
**LEAST RESPONSIVE**
to VEGF-A inhibition

**MINIMALLY CLASSIC**



**MODERATELY RESPONSIVE**
to VEGF-A inhibition

**PREDOMINANTLY CLASSIC**

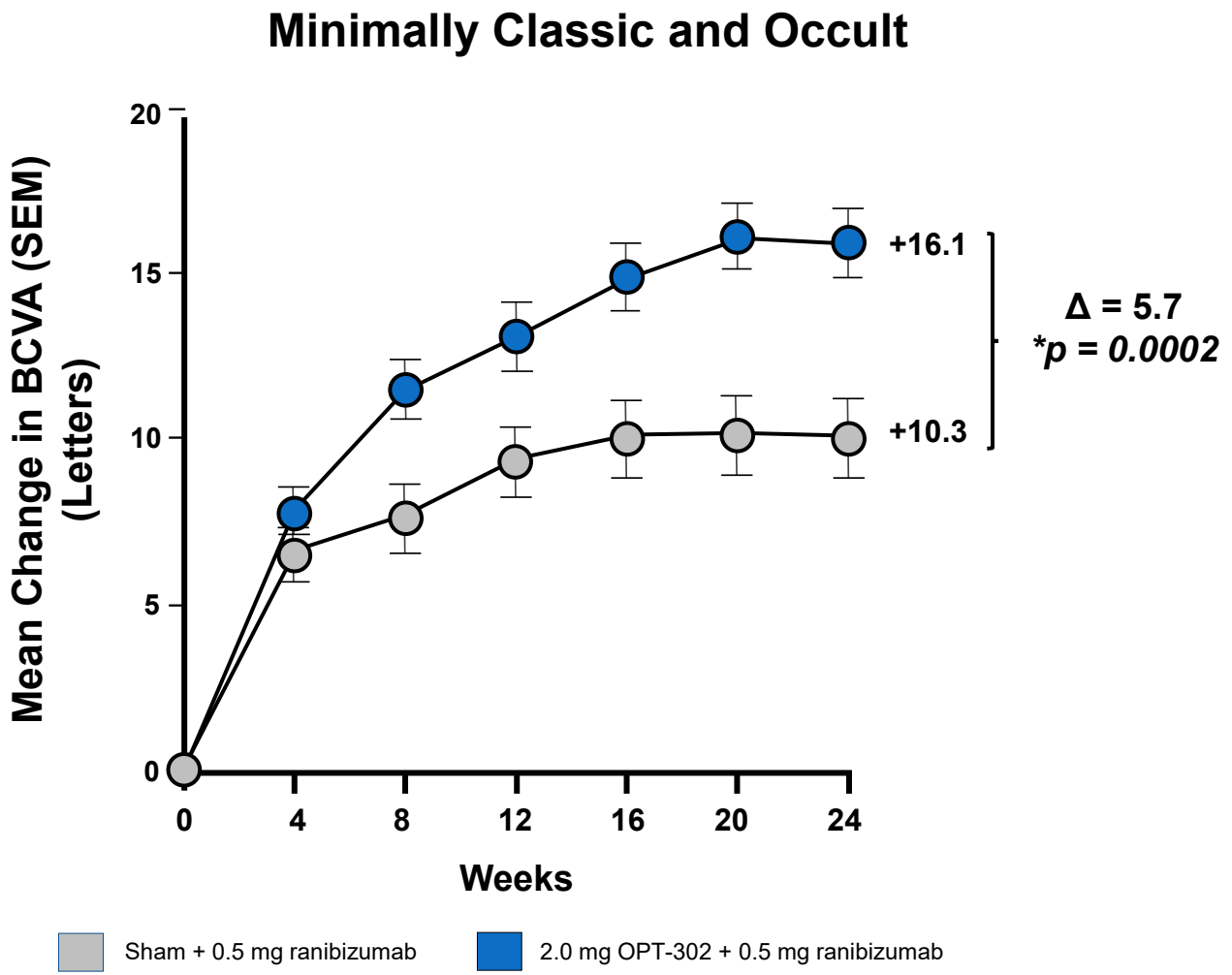


**HIGHLY RESPONSIVE**
to VEGF-A inhibition

A majority of wet AMD patients, 65-80% of the real-world population, have occult and minimally classic lesions

# Patients with Minimally Classic and Occult Lesions (RAP Absent) Responded Best in Phase 2b

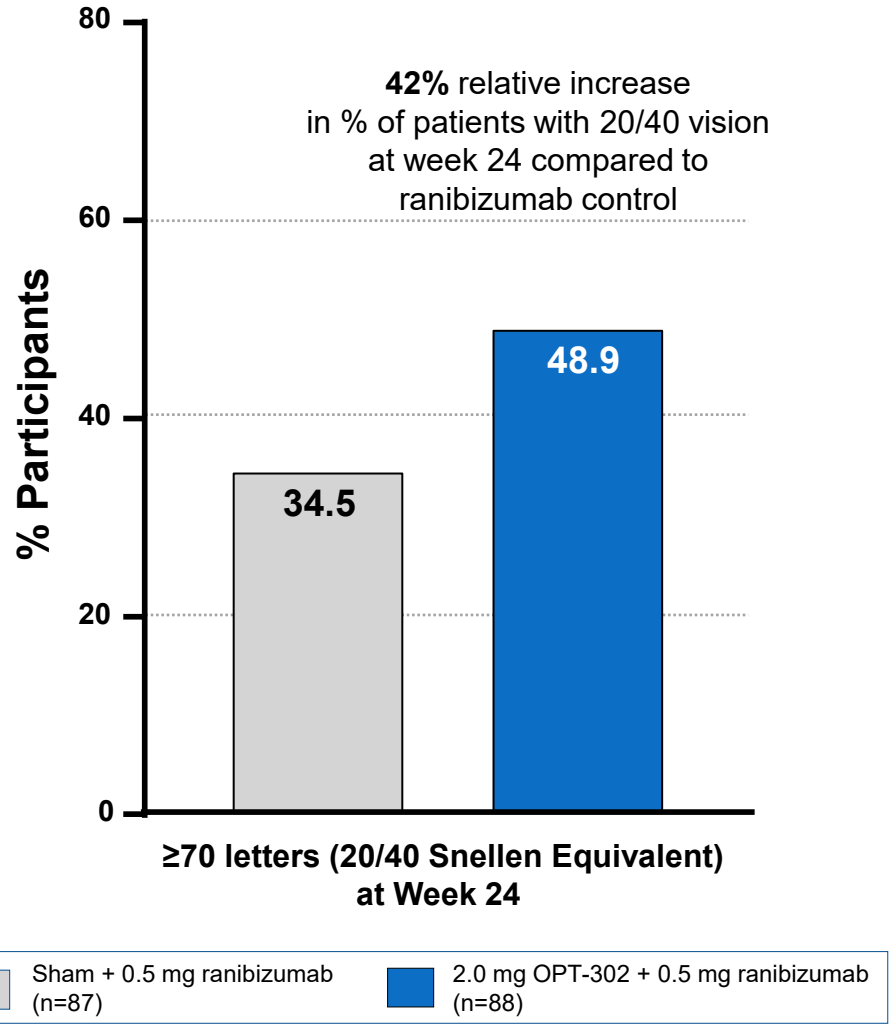
- Achieved greatest vision benefit
- Represents primary analysis population in OPT-302 Phase 3 program




*Unadjusted p-value.

# BCVA (Snellen Equivalent) at Week 24 (Min.Classic & Occult, RAP Absent)

## Higher Proportion of Patients with 20/40 Vision or Better in OPT-302 Combination Group

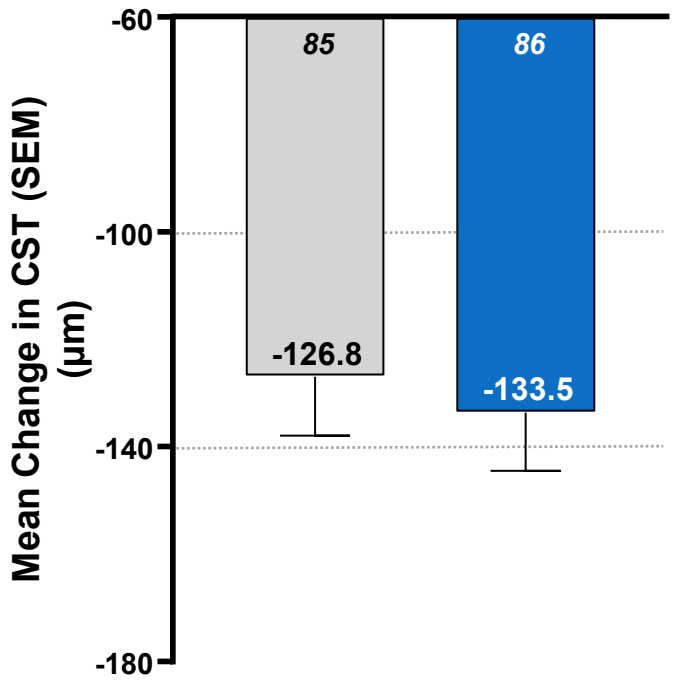



Modified Intent-to-Treat (mITT) population; as observed.

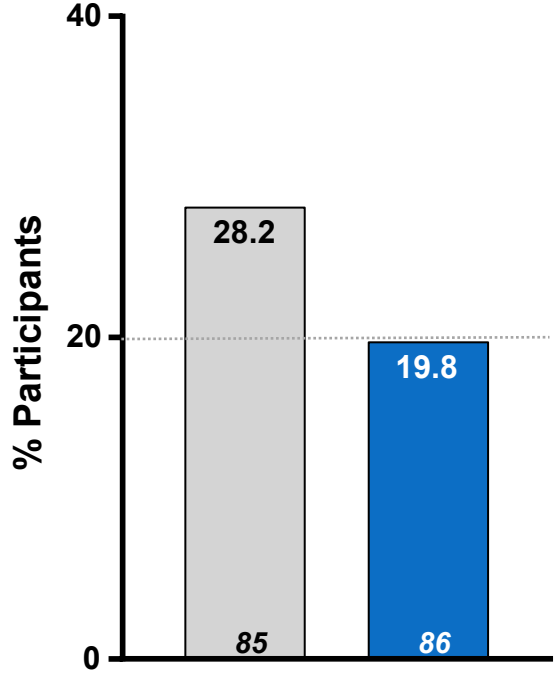
# Reduced Retinal Thickness and Better ‘Retinal Drying’

## With OPT-302 Combination Therapy in Min.Classic & Occult, RAP Absent Patients

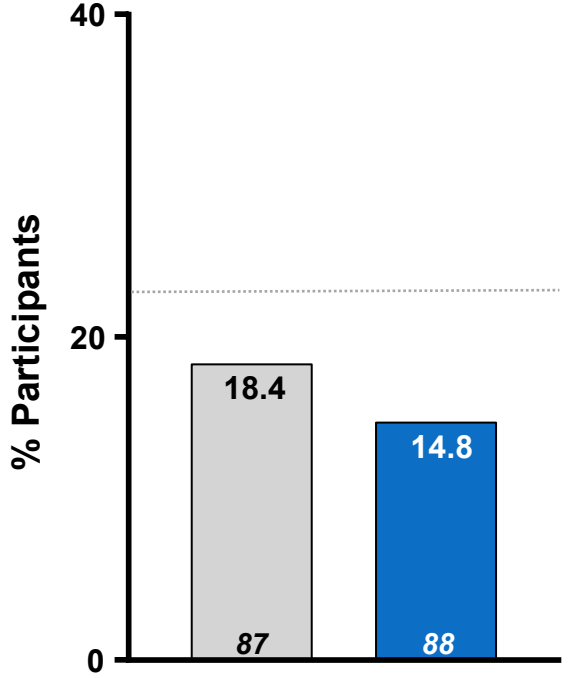
### Mean Change in CST Baseline to Week 24




### % of Participants with SRF at Week 24




### % of Participants with IR Cysts at Week 24



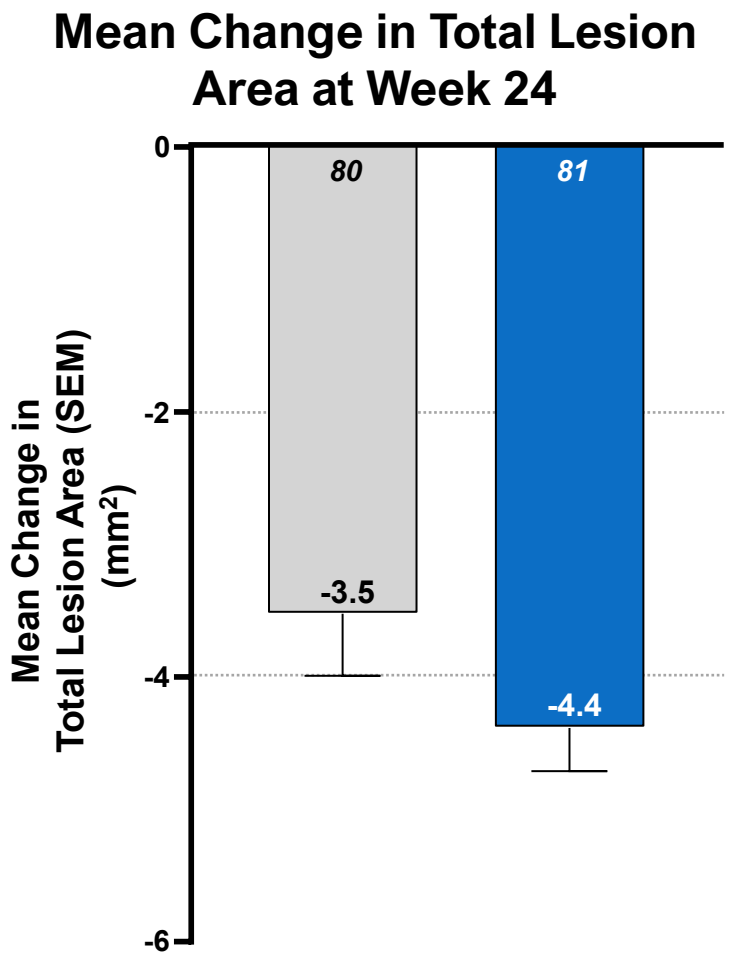

Sham + 0.5 mg ranibizumab (n=87)

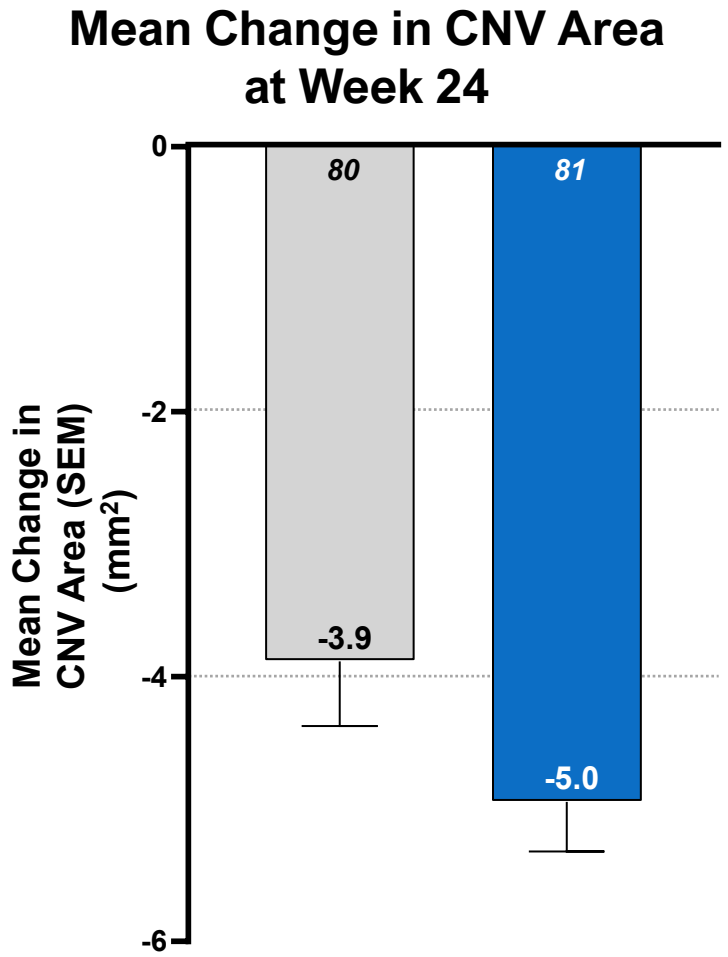
2.0 mg OPT-302 + 0.5 mg ranibizumab (n=88)

mITT; as observed; top of bar – statistic, bottom of bar - n.

# Total Lesion Area at Week 24 (Min.Classic Occult, RAP Absent)

## Greater Reduction in Total Lesion Area in OPT-302 2.0 mg Combination Group



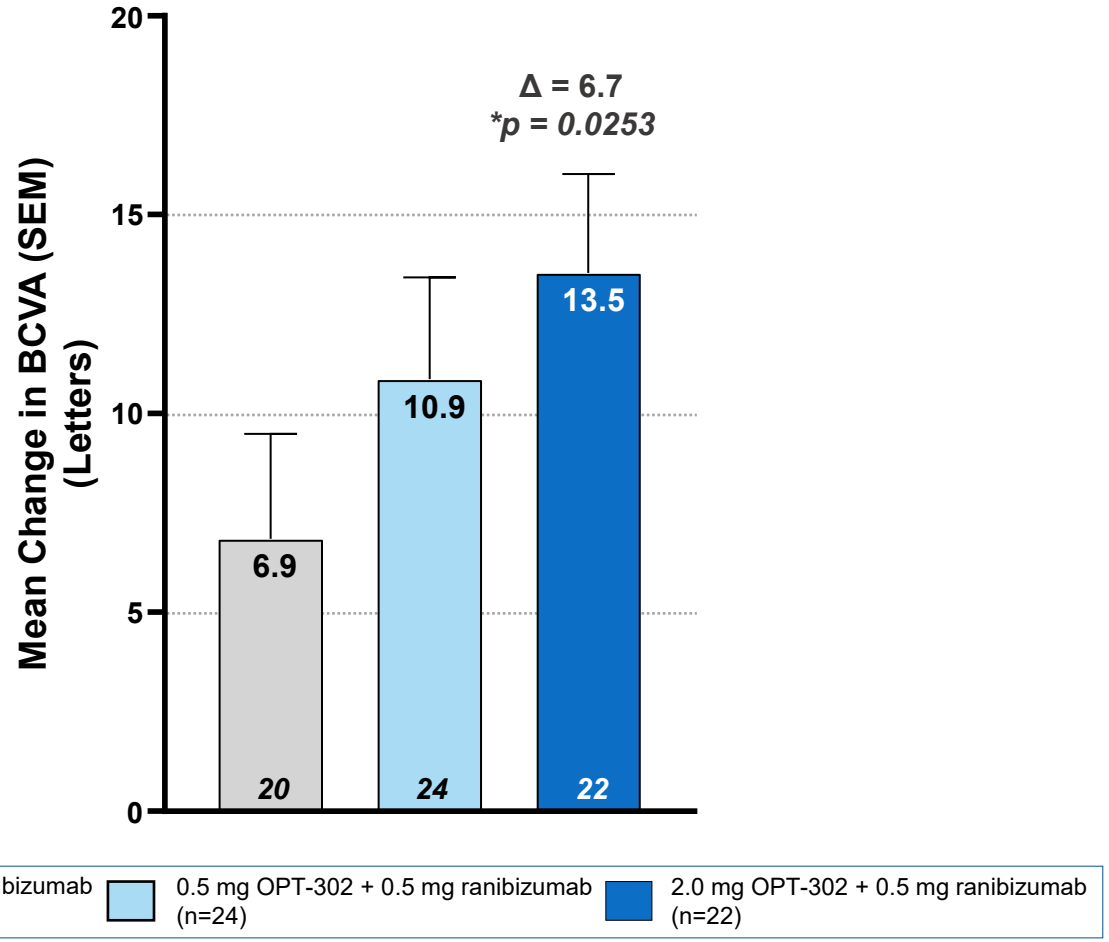

mITT; as observed; top of bar – statistic, bottom of bar – n.

# OPT-302 Combination Therapy: Demonstrated potential to improve vision outcomes in patients with PCV lesions

Polypoidal Choroidal Vasculopathy (PCV) is a difficult-to-treat wet AMD subtype with a large unmet need

In Phase 2b, OPT-302 combination therapy demonstrated potential to improve vision outcomes for patients with PCV

- **PCV is highly prevalent in Asian populations (up to ~60%)**
- **Described as the most prevalent form of wet AMD worldwide**




*Unadjusted p-value

# OPT-302 Was Well-tolerated with Very Low Incidence of Ocular Inflammation, Comparable to Standard-of-Care Therapy

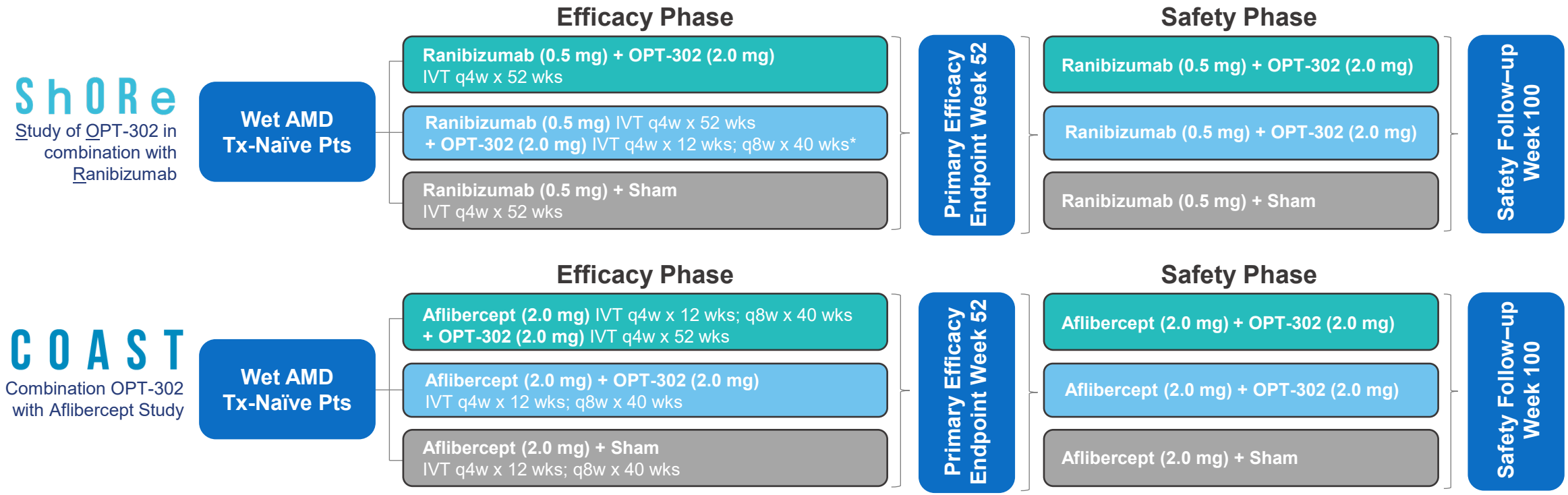
| N Participants (%) | Sham + ranibizumab n=121 | 0.5 mg OPT-302 + ranibizumab n=120 | 2.0 mg OPT-302 + ranibizumab n=124 |
|---|---|---|---|
| **Treatment emergent AEs (TEAEs)** | 84 (69.4%) | 87 (72.5%) | 93 (75.0%) |
| **Ocular AEs - Study Eye – related to study product(s)[1]** | 17 (14.0%) | 17 (14.2%) | 19 (15.3%) |
| **Ocular AEs - Study Eye – Severe[2]** | 1 (0.8%) | 2 (1.7%) | 1 (0.8%) |
| **Serious AEs** | 10 (8.3%) | 16 (13.3%) | 7 (5.6%) |
| **Ocular SAEs in Study Eye** | 0 (0.0%) | 2[3] (1.7%) | 0 (0.0%) |
| **Intraocular inflammation[4] – Study Eye** | 2[5,6] (1.7%) | 2[3] (1.7%) | 1[5] (0.8%) |
| **Participants with AEs leading to study IP discontinuation only** | 2 (1.7%) | 3 (2.5%) | 0 (0.0%) |
| **Participants with AEs leading to study discontinuation** | 1[7] (0.8%) | 0 (0.0%) | 0 (0.0%) |
| **Any APTC event** | 0 (0.0%) | 1[8] (0.8%) | 0 (0.0%) |
| **Deaths** | 2[9] (1.7%) | 0 (0.0%) | 0 (0.0%) |

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).

# OPT-302 Phase 3 Pivotal Program

## Topline Primary Data Analysis

- Opthea intends to submit Biologics License Application (BLA) and Marketing Authorization Application (MAA) with the FDA and EMA, respectively, following completion of the primary efficacy phase of the trials




- **Design:** Multi-centre, double-masked, randomised (1:1:1), sham control
- **Regulatory quality:** 90% power, 5% type I error rate
- **Sample size:** 330 patients per arm, 990 per study
- **Primary Objective:** Mean change from Baseline in BCVA at Wk 52

*Sham administered at visits when OPT-302 is not administered.

# Phase 3 Clinical Program Is Informed by Phase 2b and Optimized for Success

### Enrichment of patient population

- Exclusion of retinal angiomatous proliferation (RAP) lesions
- Increases the additional mean BCVA gain in the total study population from +3.4 letters to +4.4 letters

### Hierarchical primary analysis

- First conducted in the occult and minimally classic population followed by total patient population
- Maximises opportunity to demonstrate most compelling vision benefit by increasing the additional mean BCVA gain from +4.4 letters to +5.7 letters
- Highly statistically powered to detect superior BCVA gains

### Maximizing commercial opportunity

- OPT-302 investigated in combination with two standard-of-care treatments to be positioned as agnostic to combined anti–VEGF-A agent

### Aligned with U.S. (FDA) and European (EMA) regulatory agencies feedback on Phase 3 trial design and analysis plan

- OPT-302 granted Fast-Track designation by FDA

# Summary
## OPT-302 for Wet AMD

### ✓ Differentiated MOA to improve efficacy

- OPT-302 is a biologic VEGF-C/D “trap”
- First and only therapy directly targeting VEGF-C&D inhibiting angiogenic signaling through VEGFR-2 and -3

### ✓ Strong Phase 2b Data

- Superior vision gains of OPT-302 combination therapy over standard of care
- Anatomical improvements
- Safety profile similar to standard of care

### ✓ Pivotal Phase 3 trials

- Informed by Phase 2b data to maximize POS
- Aligned with FDA and EMA review of protocols
- Granted FDA Fast Track designation

### ✓ Multi-billion dollar commercial opportunity

- Existing $8BN p.a. global market for wet AMD alone
- Only VEGF-C/D “trap”, no viable threat in competitive pipelines
- Most advanced product in clinical development to address #1 unmet need for wet AMD patients – improvement in vision outcomes
- Clinical development agreement with Carlyle/Abingworth for up to $170m in place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