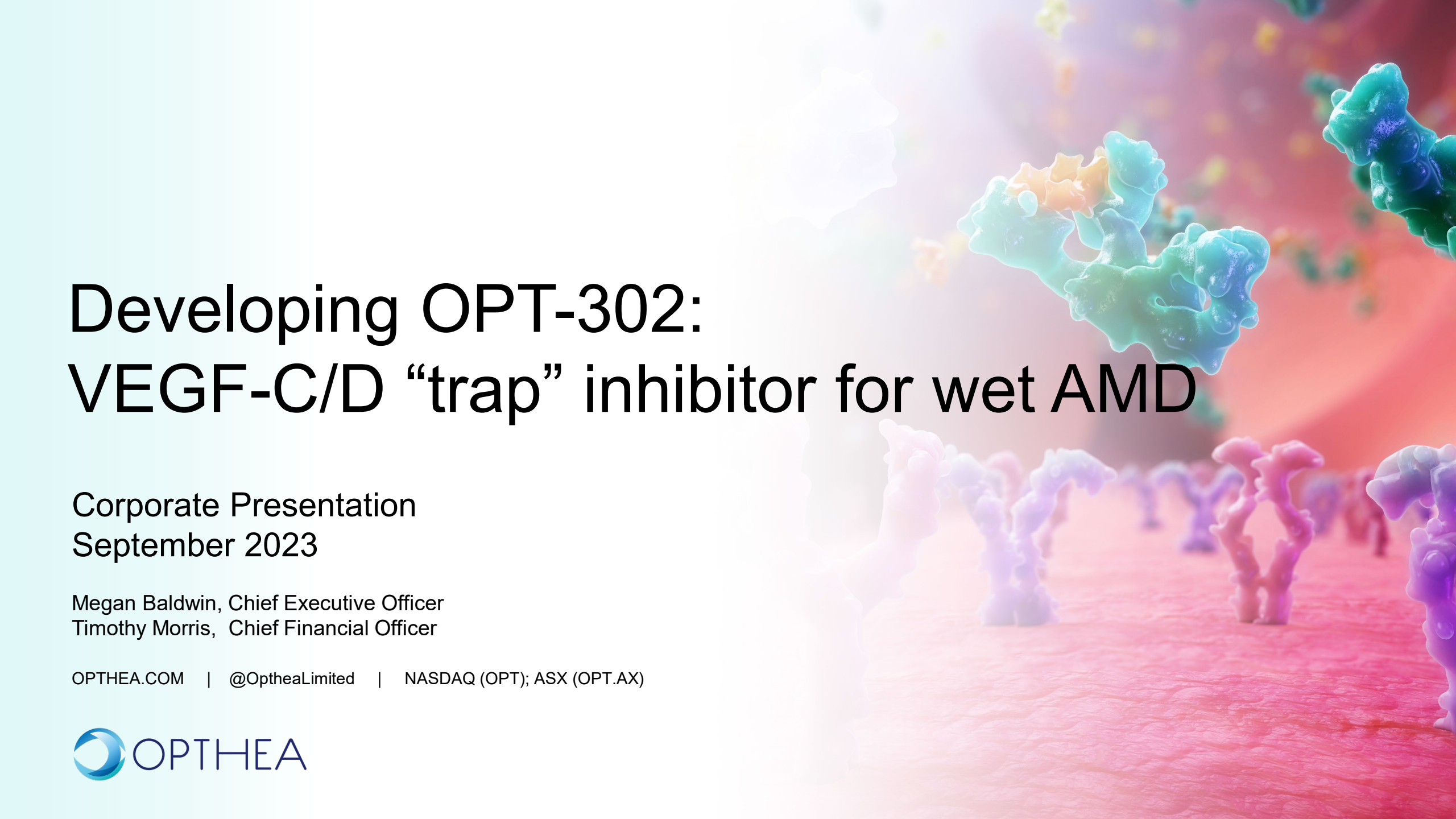
Developing OPT-302: VEGF-C/D “trap” inhibitor for wet AMD



Corporate Presentation
September 2023

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

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

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Investment Highlights

- Wet AMD is the leading cause of vision loss in the elderly, impacting **3.5 million** patients in the US and Europe
- Revenues for current standard-of-care VEGF-A inhibitors for wet AMD are **>US$8 billion/year**
- **OPT-302 is:**
  - a unique and **proprietary*** biologic with a novel mechanism of action targeting VEGF-C/D and validated disease pathways, being developed for use in combination with approved standard-of-care VEGF-A inhibitors
  - a retina asset in development with clinical evidence of **better visual outcomes** over anti-VEGF-A therapy for wet AMD, with well tolerated safety profile
- Treatment options in development focus on reducing burden of care, **OPT-302 is designed to transform patient outcomes by improving vision.** Better efficacy may also lead to prolonged vision responses & greater durability of Tx
- FDA granted **Fast-Track** designation based on unmet medical need and superior Phase 2b results
- Pivotal Phase 3 trials in nearly 2,000 patients worldwide, completion of patient enrollment expected for COAST 1Q CY 2024 and ShORe 2Q CY 2024
- OPT-302 represents an estimated **>US$8 billion dollar** commercial opportunity**

** Composition of Matter and Methods of Use Patents through 2034. **Based on annual worldwide sales of over US$8 billion in 2022 for ranibizumab and aflibercept for wet AMD. In addition, nearly half of wet AMD patients are treated with off-label bevacizumab as a lower cost alternative anti-VEGF-A therapy. Hence, the total addressable market (TAM) for OPT-302 is potentially greater than the current combined sales of ranibizumab and aflibercept for wet AMD.*

Opthea Update

Development Funding Agreement ("DFA") with Carlyle and Abingworth

- Completed in August 2022, total capacity US$170 million, with US$120 million committed at signing with the ability to provide an additional US$50 million
- Provides non-equity funding for the development of OPT-302 for wet AMD
- Amounts received from Carlyle and Abingworth repaid at 4x following receipt of regulatory approval in the United States or EU
- No amounts owed if the clinical trials do not meet the primary endpoint or if regulatory approval is not received
- Repayment split between fixed payments (7 in 6 years) and variable payments at 7% of revenues
- Payment schedule under the DFA:

Upfront payment	US$50 million	Received Sept 2022
2nd Tranche	US$35 million	Received Dec 2022
3rd Tranche	US$35 million	Due by Dec 31, 2023

- A new co-investor of Carlyle and Abingworth intends to participate in a funding under the DFA of US$50 million to increase total DFA funding from $120 million to $170 million which is subject to the co-investor's final due diligence and approvals, appropriate documentation and compliance with closing conditions[a]

Cash runway (proforma)*

- Net proceeds from the Equity Financing of US$50.8 million, the 3rd Tranche of US$35 million under the DFA and the additional US$50 million under the DFA (described above)[a] and, along with existing cash balance of US$89 million at June 30, 2023, are expected to fund the company through 3Q CY 2024, assuming, among other things that, Phase 3 clinical trial enrollment is completed on the timeline described below.
- Preliminary unaudited estimated cash used in operations for FY 2023: US$121 million (reflects extensions in timeline for enrollment and higher CRO and related costs for the Phase 3 clinical trials during the year).

Clinical trial timeline

- Phase 3 clinical trials ~ 75% enrolled at the beginning of August 2023
- Based on observed monthly enrollment rates in the Phase 3 program, completion of patient enrollment is expected:
  - COAST 1Q CY 2024
  - ShORe 2Q CY 2024
- Top-line data expected when all patients complete 52-week treatment period

OPT-302 Safety update

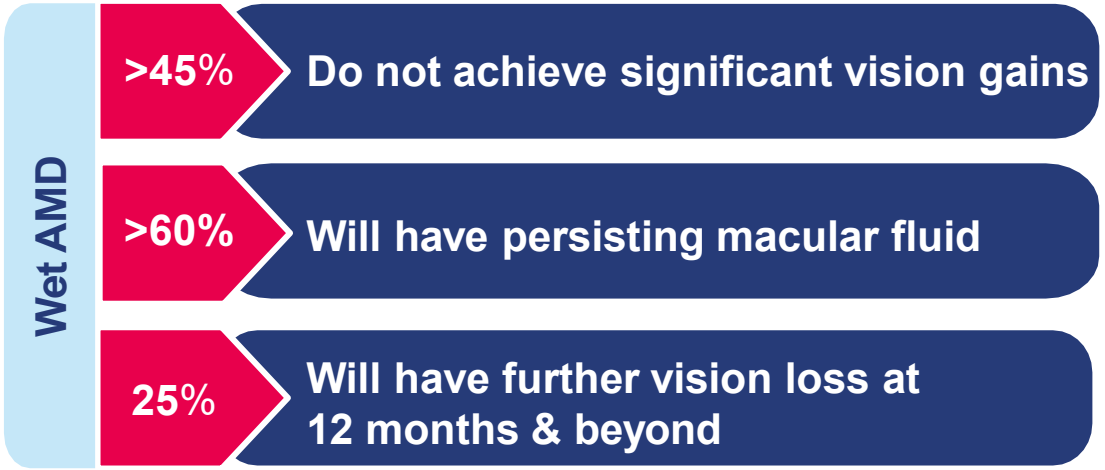
- Safety data from our completed OPT-302 trials show OPT-302 combination therapy has a safety and tolerability profile comparable to standard of care anti-VEGF-A monotherapy.

a There can be no assurance that the due diligence will be completed to the satisfaction of the co-investor of Carlyle and Abingworth, that the closing terms and conditions will be satisfied or that the company will ultimately receive the additional $50 million

The Unmet Medical Need for wet AMD

- Wet AMD is the leading cause of irreversible blindness
- Currently:
  - Impacts 3.5M patients[1]
  - 1.6M patients in U.S.A.
  - 200,000 new patients each year in U.S.A.
- 80% are diagnosed
- 80% of diagnosed patients are treated
- 99% receive anti-VEGF-A therapy

Despite treatment with anti-VEGF-A therapy[2]:

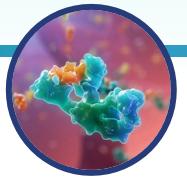


[1]U.S., EU. [2] Based on randomised, controlled clinical trial data; >45% Fail to achieve ≥ 2 lines improvement in Best Corrected Visual Acuity (BCVA); Persisting fluid: SD-OCT CST ≥ 300 µM or Time-Domain OCT CST ≥ 250 µM

Large and Growing Market Opportunity in Wet AMD

OPT-302 is Anti-VEGF-A and Durability Agnostic

New entrant trending to $2B* in revenues shows willingness to switch and impact of commercial investment



>$16B

>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

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

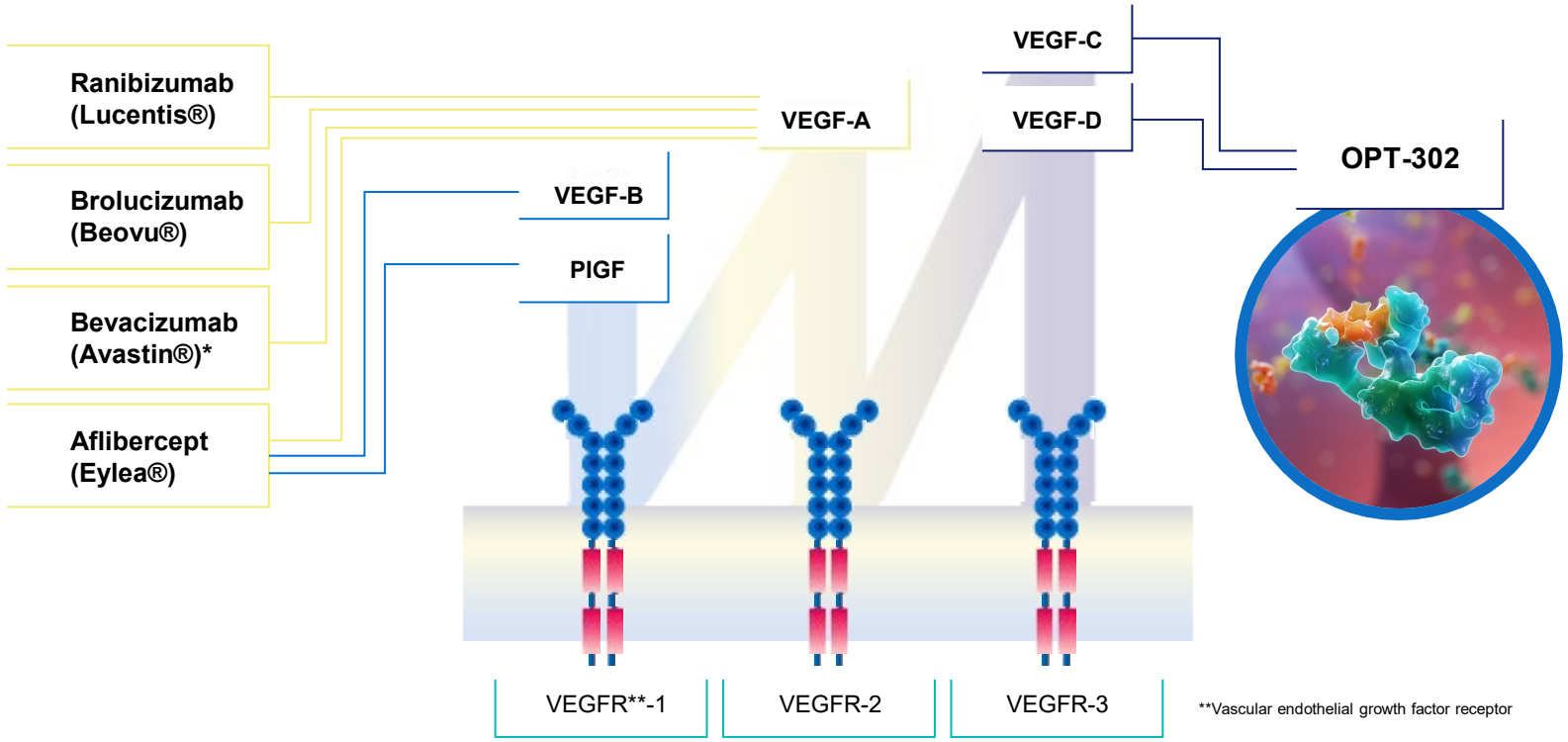
(Captures Lucentis, Eylea, and Avastin or biosimilar-treated patients worldwide)

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

*Eye drug Vabysmo blasts off as Roche's biggest growth driver (fiercepharma.com)

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

Used in combination with any VEGF-A inhibitor, OPT-302 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. [#] As assessed in cell-based bioassays.*
VEGF: Vascular Endothelial Growth Factor; VEGFR: Vascular Endothelial Growth Factor Receptor

OPT-302 Combination Therapy Clinical Program

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

Now Recruiting

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

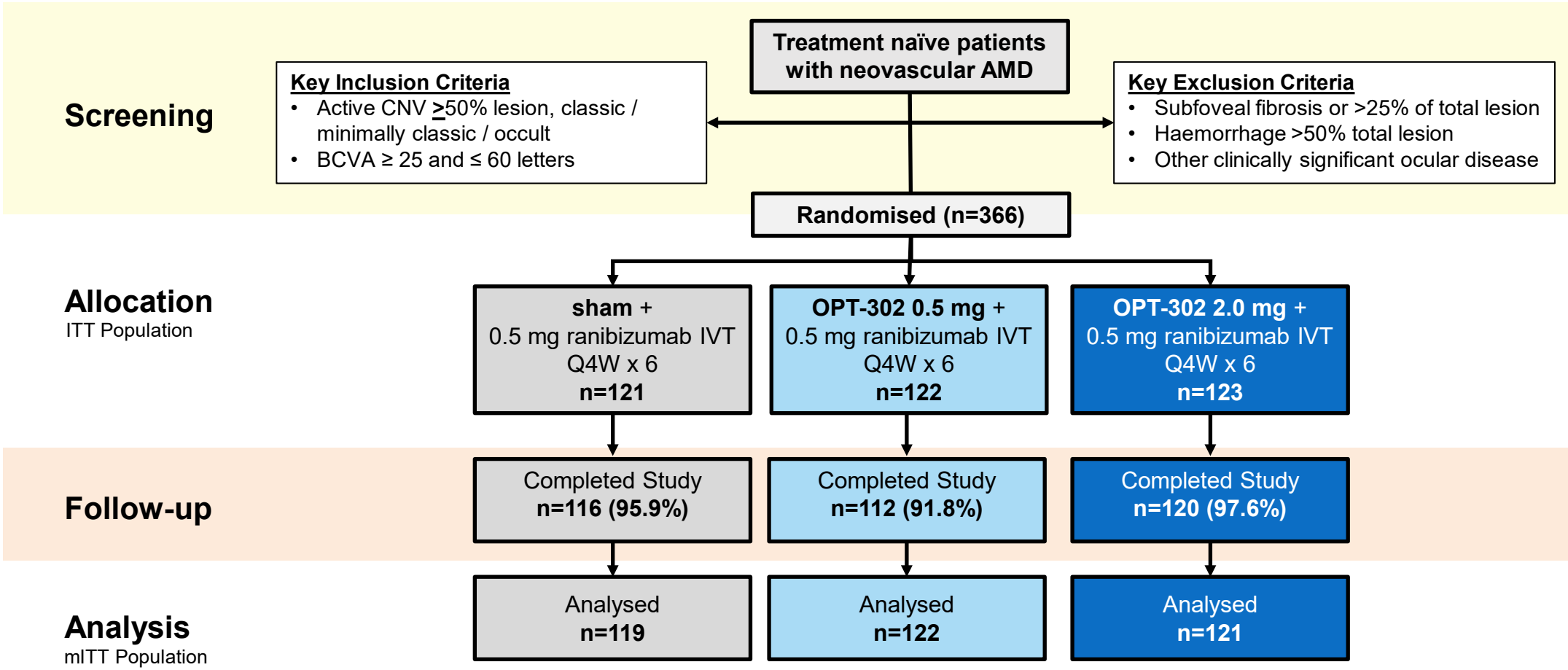
Standard Dosing	Extended Dosing
OPT-302 once every month	OPT-302 once every two months after three monthly doses
Monthly dosing	Every two months dosing

Treatment naïve patients

OPT-302 pivotal registrational Phase 3 wet AMD program designed to maximize outcomes with flexible standard of care dosing regimens

Note: Ranibizumab (Lucentis®); Aflibercept (Eylea®)

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 Visual Acuity score and/or any participant who did not return for at least one post-baseline visit

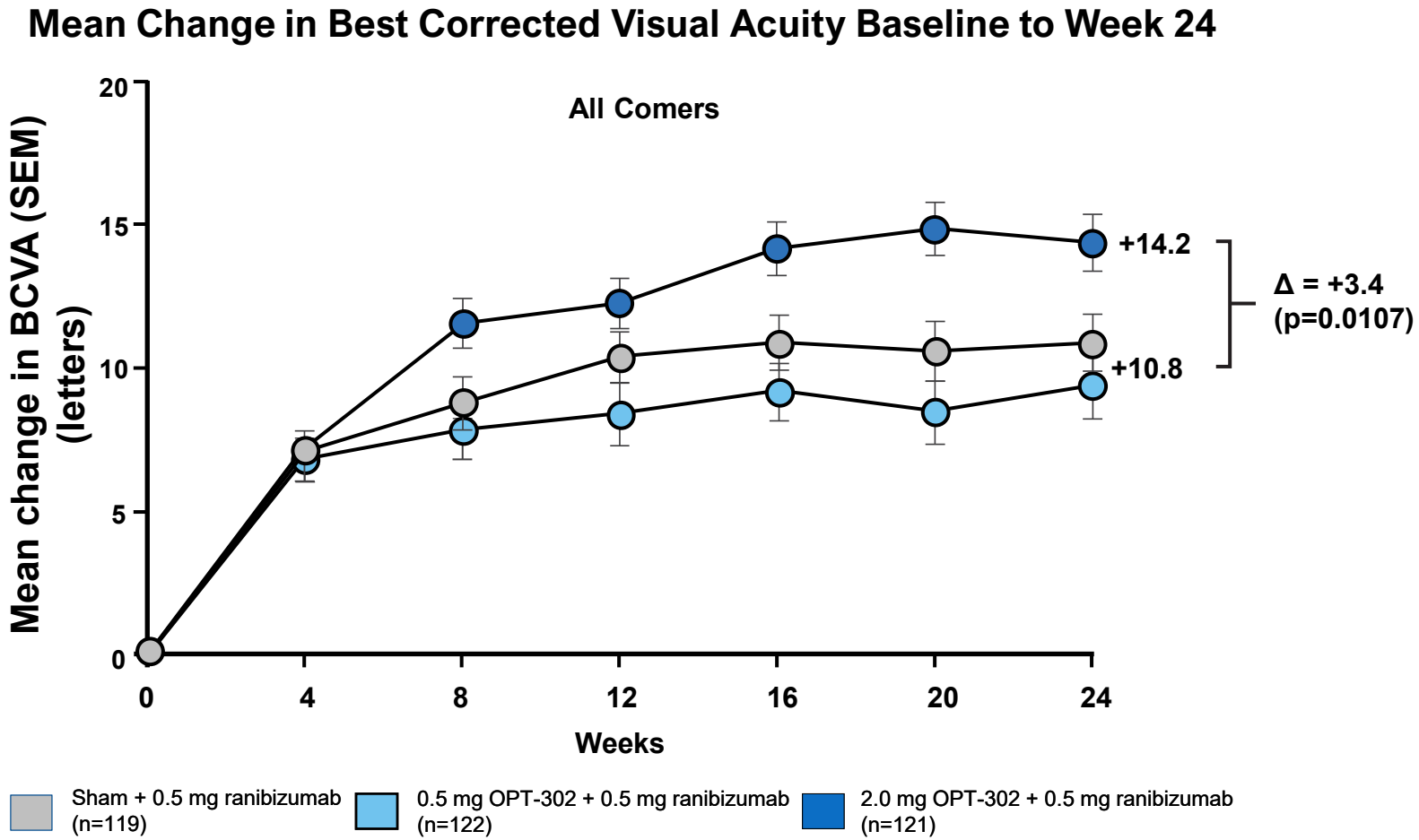
Phase 2b Study Demographics and Baseline Characteristics

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 - mm² ± 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

- Phase 2b primary endpoint achieved

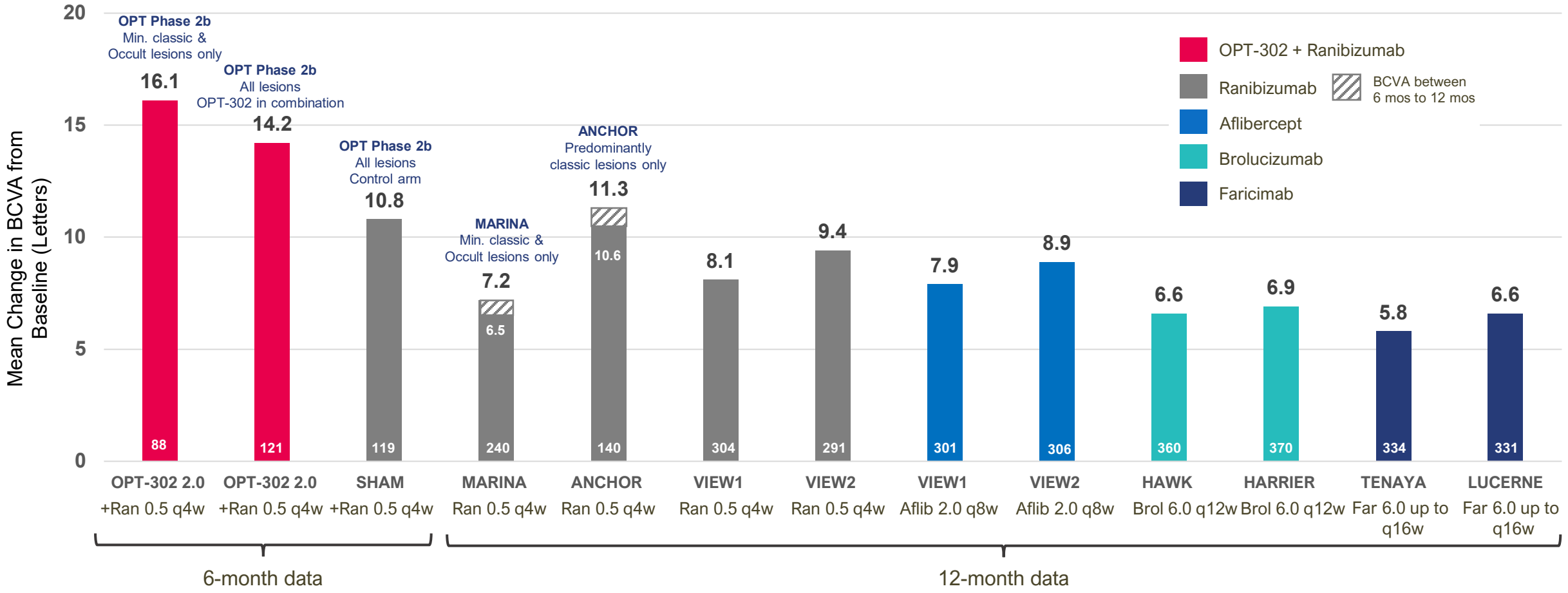


mITT, modified Intent to Treat population; BCVA – Best Corrected Visual Acuity.
Left: Difference in Least Square Means, using Model for Repeated Measures (MRM) analysis. Right: Graph represents "as observed" data and SEM (standard error of the mean).

OPT-302 Combination Therapy

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

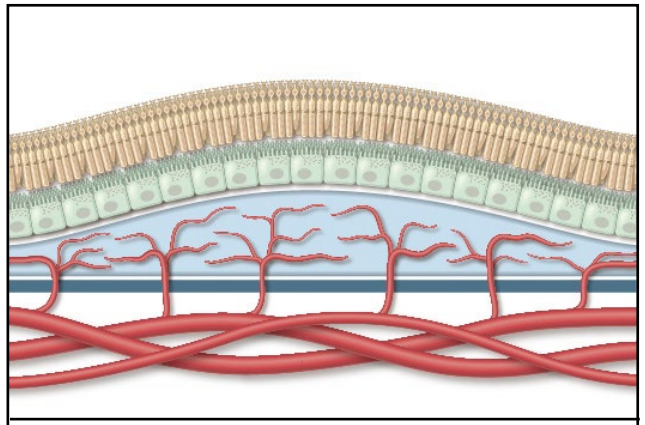
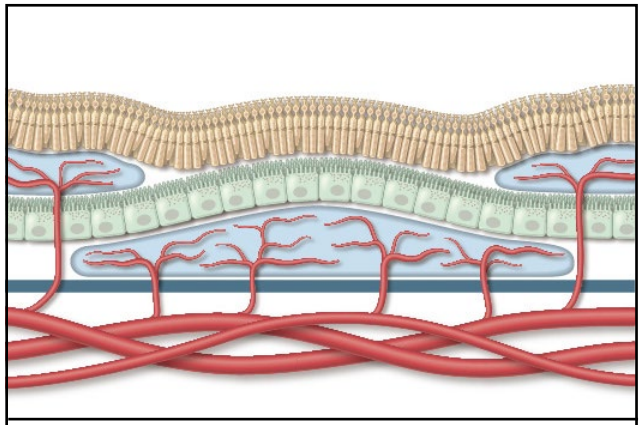
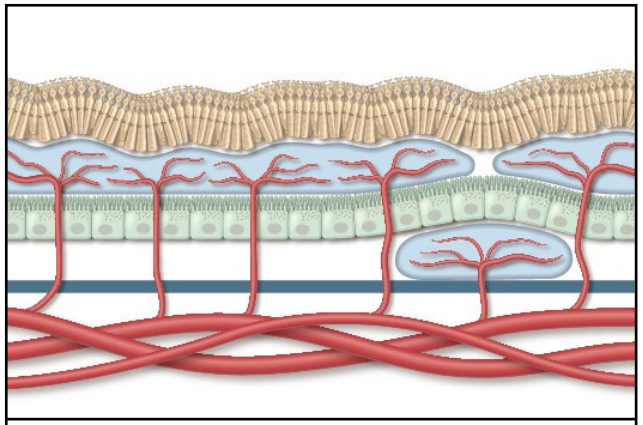
BCVA at 6 months is typically maintained or greater at 12 months in Phase 3 trials with VEGF-A inhibitors



All trials shown, excluding Opthea's Phase 2b data, are Phase 3 registrational studies. Baseline BCVA values in the Phase 3 registrational studies vary. 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

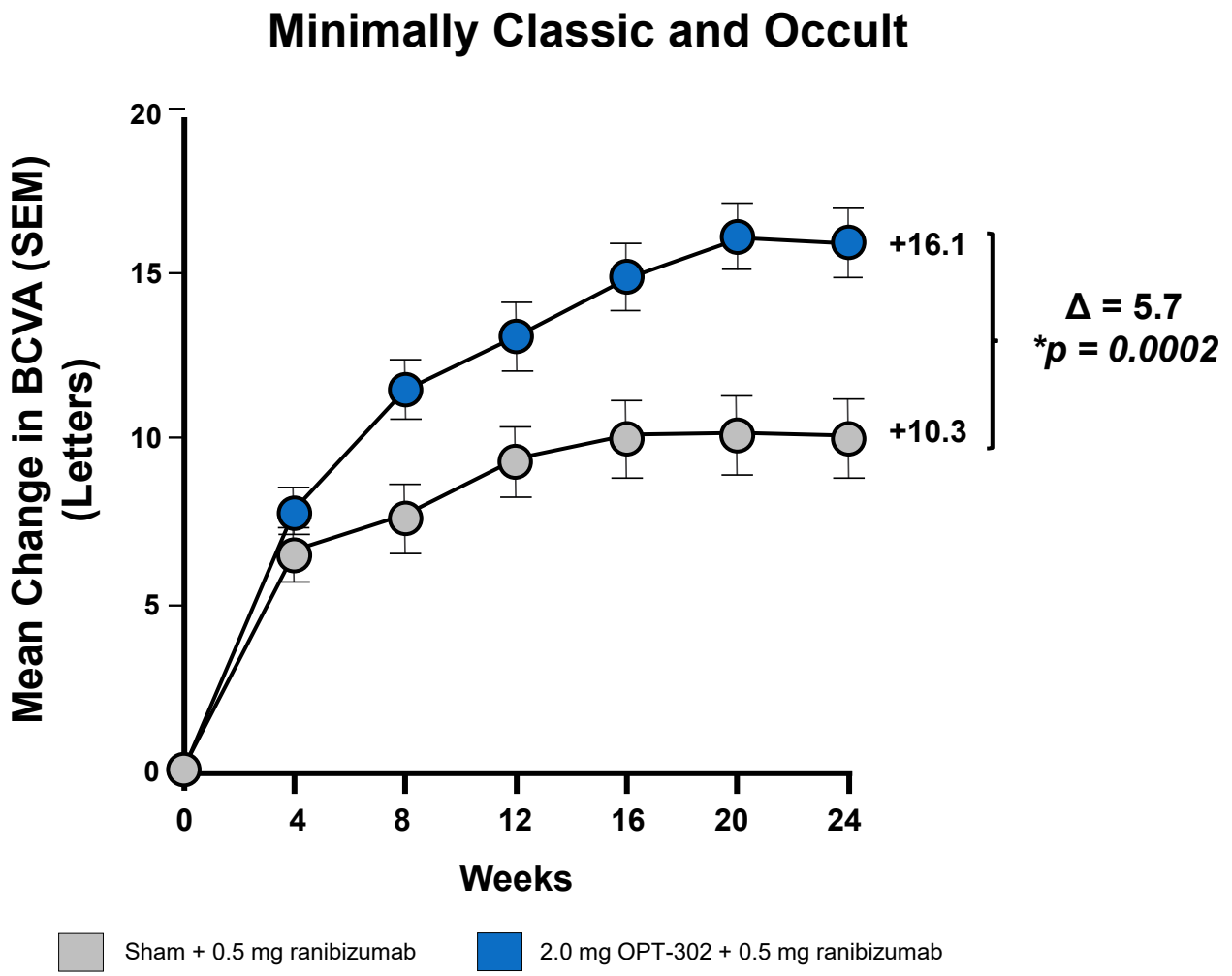
Differ in Vessel Location, Leakiness, and Responsiveness to VEGF-A Inhibitors

OCCULT	MINIMALLY CLASSIC	PREDOMINANTLY CLASSIC
		
LEAST RESPONSIVE to VEGF-A inhibition	**MODERATELY RESPONSIVE** to VEGF-A inhibition	**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

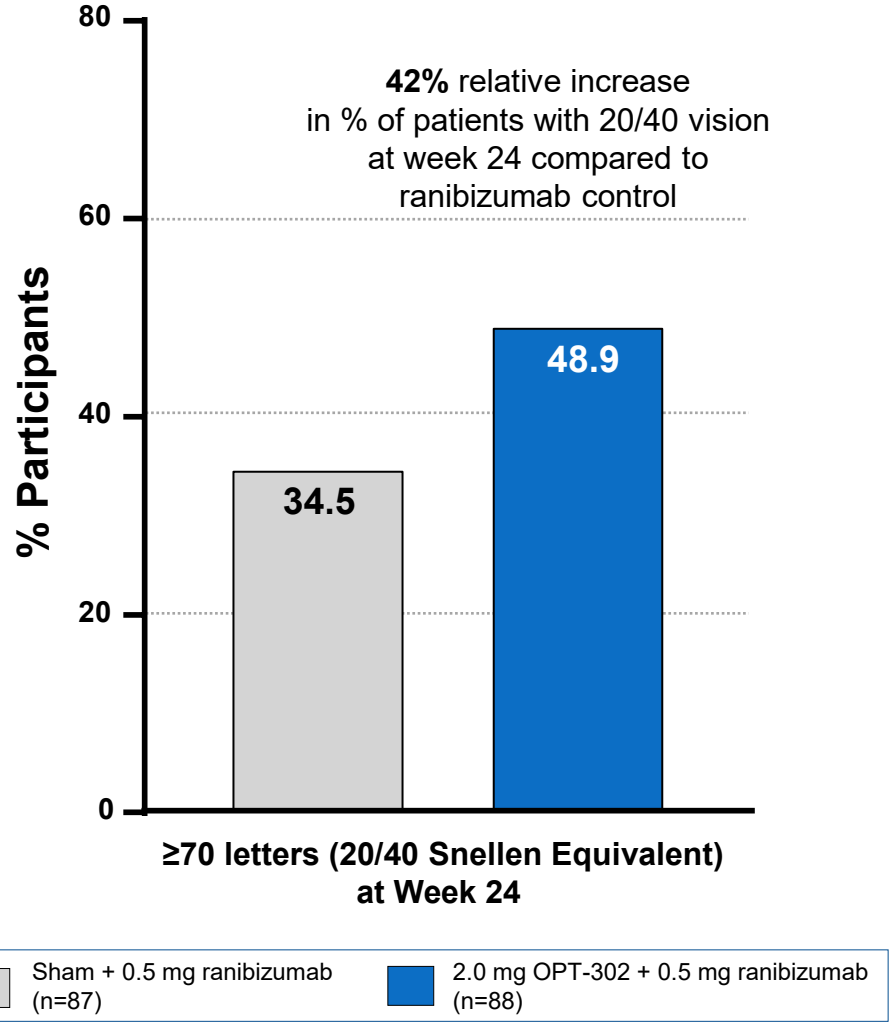
- Achieved greatest vision benefit
- Represents primary analysis population in OPT-302 Phase 3 program



* 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

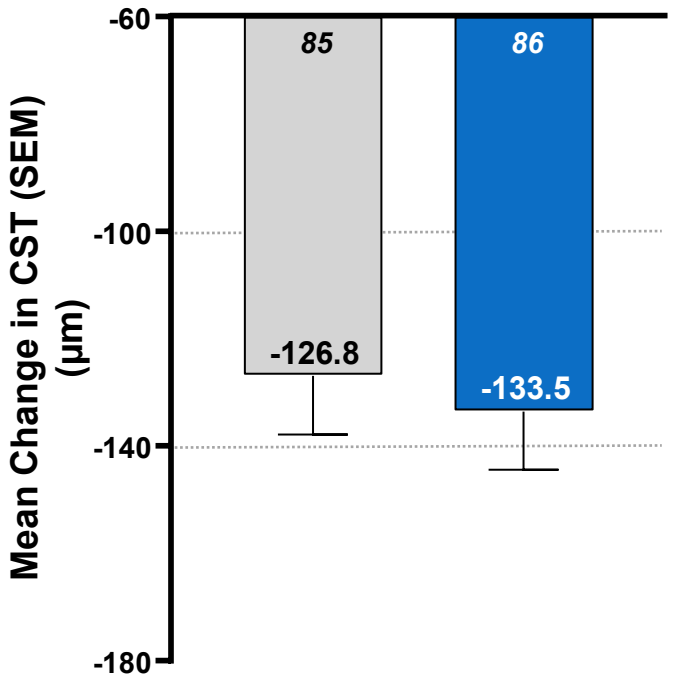


BCVA: Best Corrected Visual Acuity. Modified Intent-to-Treat (mITT) population; as observed.

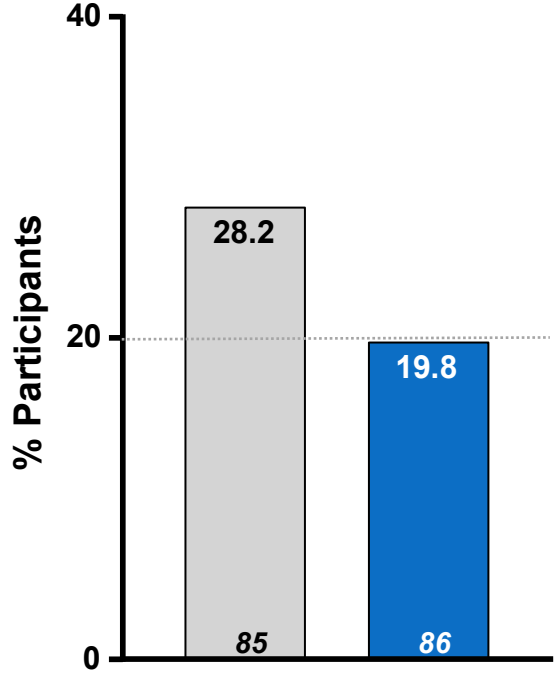
Reduced Retinal Thickness and Better ‘Retinal Drying’

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

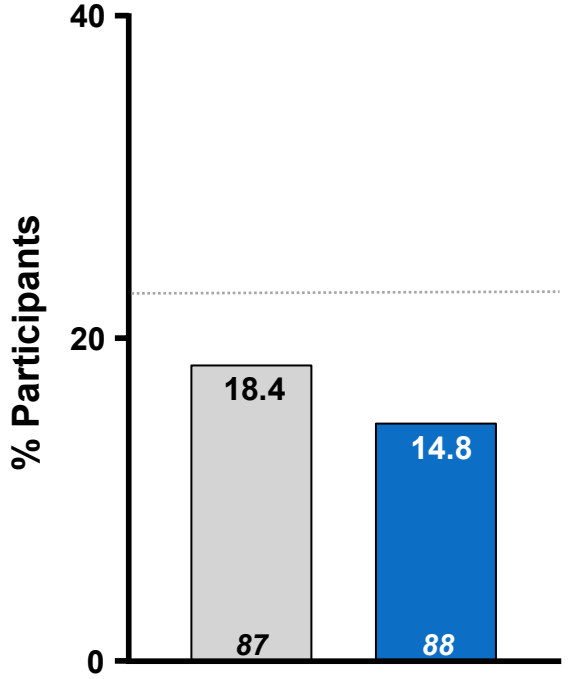
Mean Change in CST Baseline to Week 24



% of Participants with SRF at Week 24



% of Participants with IR Cysts at Week 24



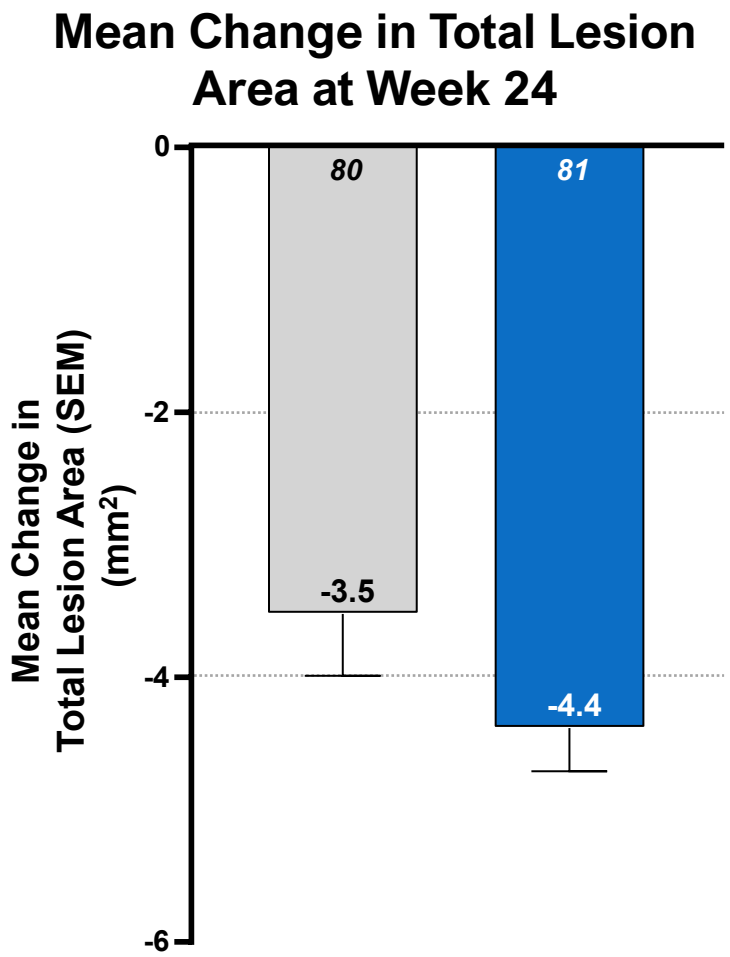
Sham + 0.5 mg ranibizumab (n=87)

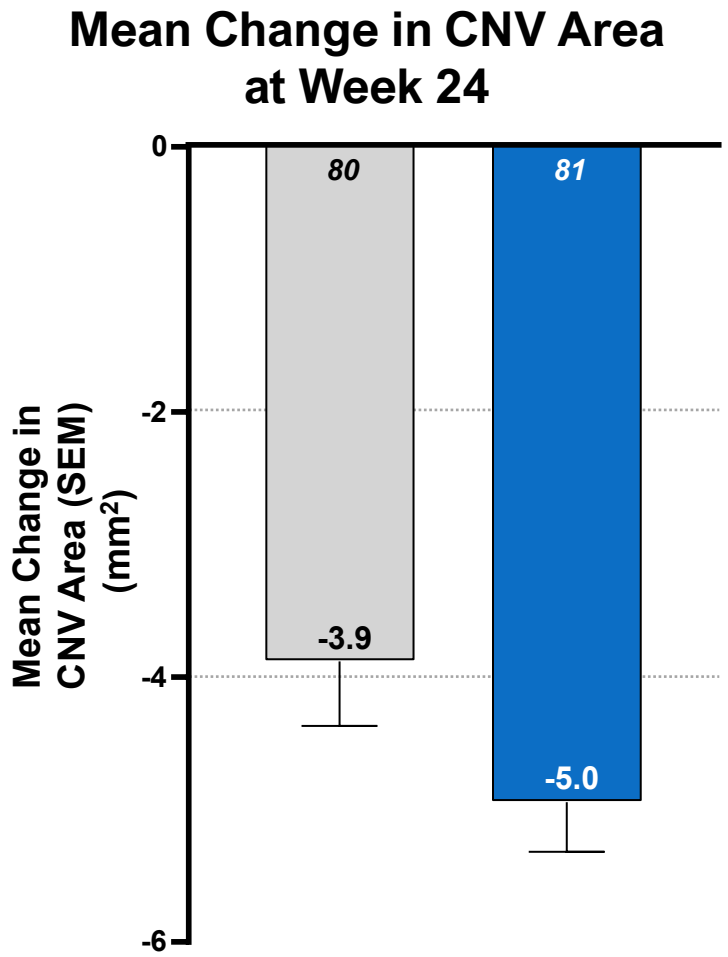
2.0 mg OPT-302 + 0.5 mg ranibizumab (n=88)

mITT; as observed; top of bar – statistic, bottom of bar - n.
CST: Central Subfield Thickness; SRF: Subretinal fluid; IR: Intra-retinal.

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





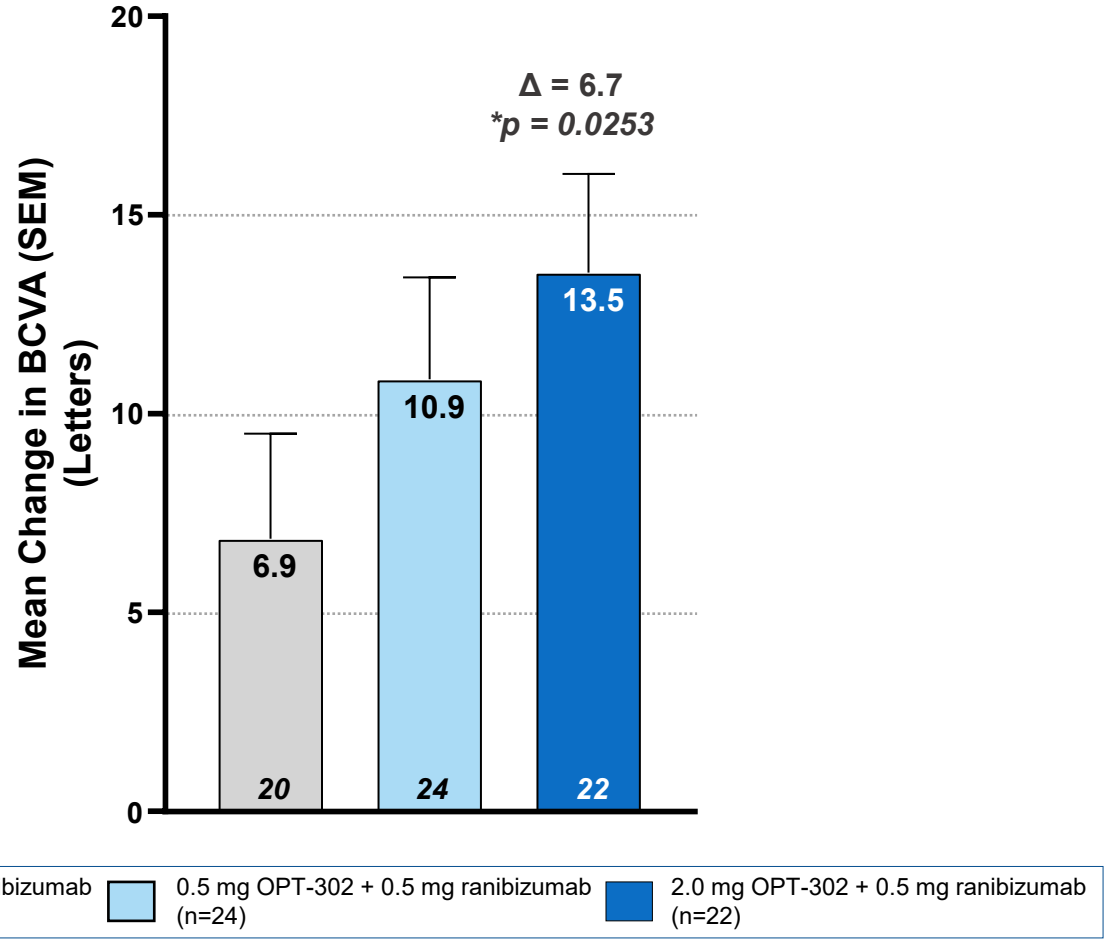
mITT; as observed; top of bar – statistic, bottom of bar – n.
CNV: Choroidal Neovascular.

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

Pooled Safety for Completed OPT-302 Trials

Combination therapy well-tolerated and comparable to standard of care monotherapy

N Participants (%)	OPT-302 Any dose* N=399 (N=1,842 injections)	OPT-302 2.0 mg N=263 (N=1,121 injections)	Sham + anti-VEGF-A control N=169 (N=854 injections)
Ocular TEAEs - Study Eye – related to study product(s)	41 (10.2%)	22 (8.4%)	20 (11.8%)
Ocular TEAEs - Study Eye – Severe	4 (1.0%)	2 (0.8%)	2 (1.2%)
Intraocular inflammation – Study Eye	7[1,2,3] (1.8%)	3[1] (1.1%)	3[1] (1.8%)
Participants with AEs leading to treatment discontinuation	4[2,4-6] (1.0%)	1[4] (0.4%)	2[7,8] (1.2%)
Any APTC event	4[4,5,9,10] (1.0%)	3[5,9,10](1.1%)	2[11,12] (1.2%)
Deaths	2[10,13] (0.5%)	2[10,13] (0.8%)	2[14,15] (1.2%)

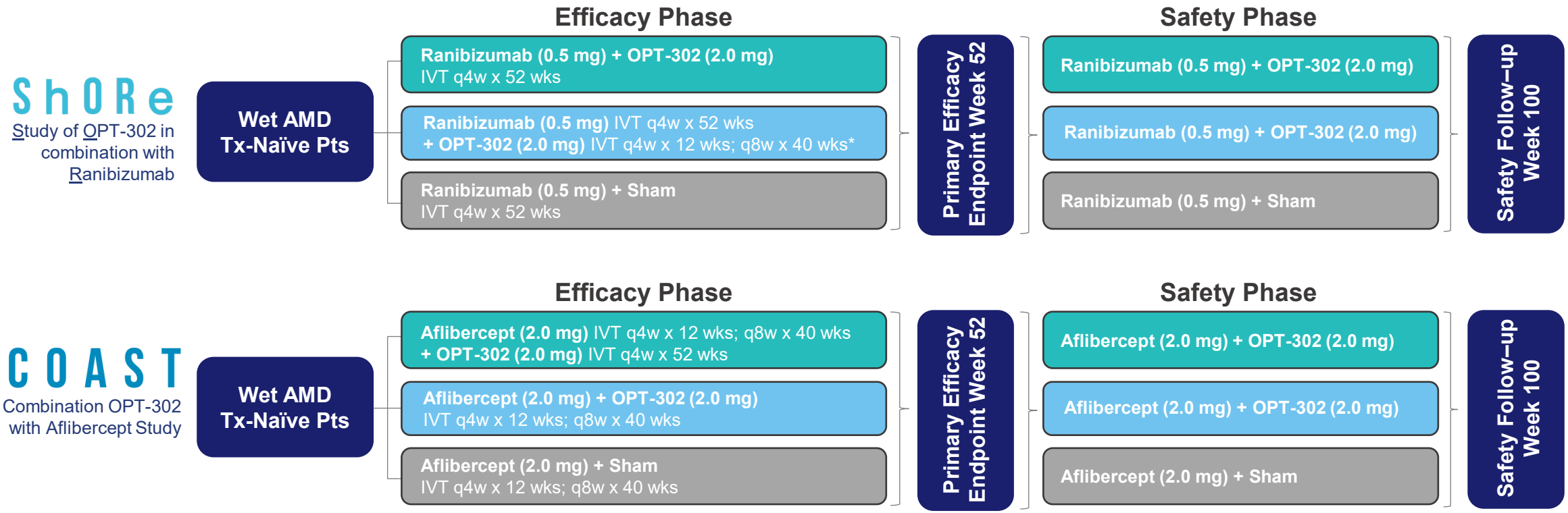
- Pooled safety analysis of 399 patients for completed OPT-302 trials
- Data Monitoring Committee (“DMC”) regularly reviews data from ongoing Phase 3 COAST and ShORe studies
- Safety data from our completed OPT-302 trials show OPT-302 combination therapy has a safety and tolerability profile comparable to standard of care anti-VEGF-A monotherapy.

*[1]Transient anterior chamber cell (trace 1-4 cells); [2] SAE of endophthalmitis, with AE’s of hypopyon and anterior chamber cell (n=1; 0.5 mg); [3] SAE of vitritis (n=1; 0.5 mg); [4]Non-fatal myocardial infarction; [5]Cerebrovascular accident; [6]Enteritis; [7]Abdominal pain; [8]Increased IOP; [9] Non-fatal angina pectoris; [10]Fatal congestive heart failure/myocardial infarction; [11]Non-fatal arterial embolism; [12]Embolic stroke; [13]Metatstaic ovarian cancer; [14] Pneumonia; [15] infective endocarditis. * Any dose (OPT-302 0.3 mg, 0.5 mg, 1 mg or 2 mg)*

OPT-302 Phase 3 Pivotal Program

Topline Primary Data Analysis at Week 52

- 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.*

Current Focus is on Phase 3 Recruitment

BLA preparation and pre-commercial activities continue

Phase 3 Execution

- Two trials concurrently recruiting across ~400 sites globally
- Key focus areas:
  - CRO oversight
  - Site data entry, data cleaning
  - Site engagement

Key Dates

- Expect to complete patient recruitment
  - COAST Q1 CY 2024
  - ShORe Q2 CY 2024
- Treatment period is 12 months
- Pre BLA meeting to be scheduled following topline data and sufficient safety period

Timeline

- Topline data results to follow data cleaning and database lock asap following completion patient enrollment
- All patients remain on study for a further 12 months for safety follow-up
- Intend to file BLA/MAA on basis of topline data & supplementally file safety follow-up

Pre-Commercial Activities

Building full commercial launch plan & initiating activities that are required to file BLA

- Commercial manufacturing (PPQ)
- Market shaping, physician mindshare
- Payer/pricing research
- Competitive landscape, OPT-302 positioning
- Initial focus – US, then EU/ROW

BLA: Biologics License Application
MAA: Marketing Authorisation Application

Opthea Limited and OPT-302 for Wet AMD
Positioned for Clinical and Commercial Success

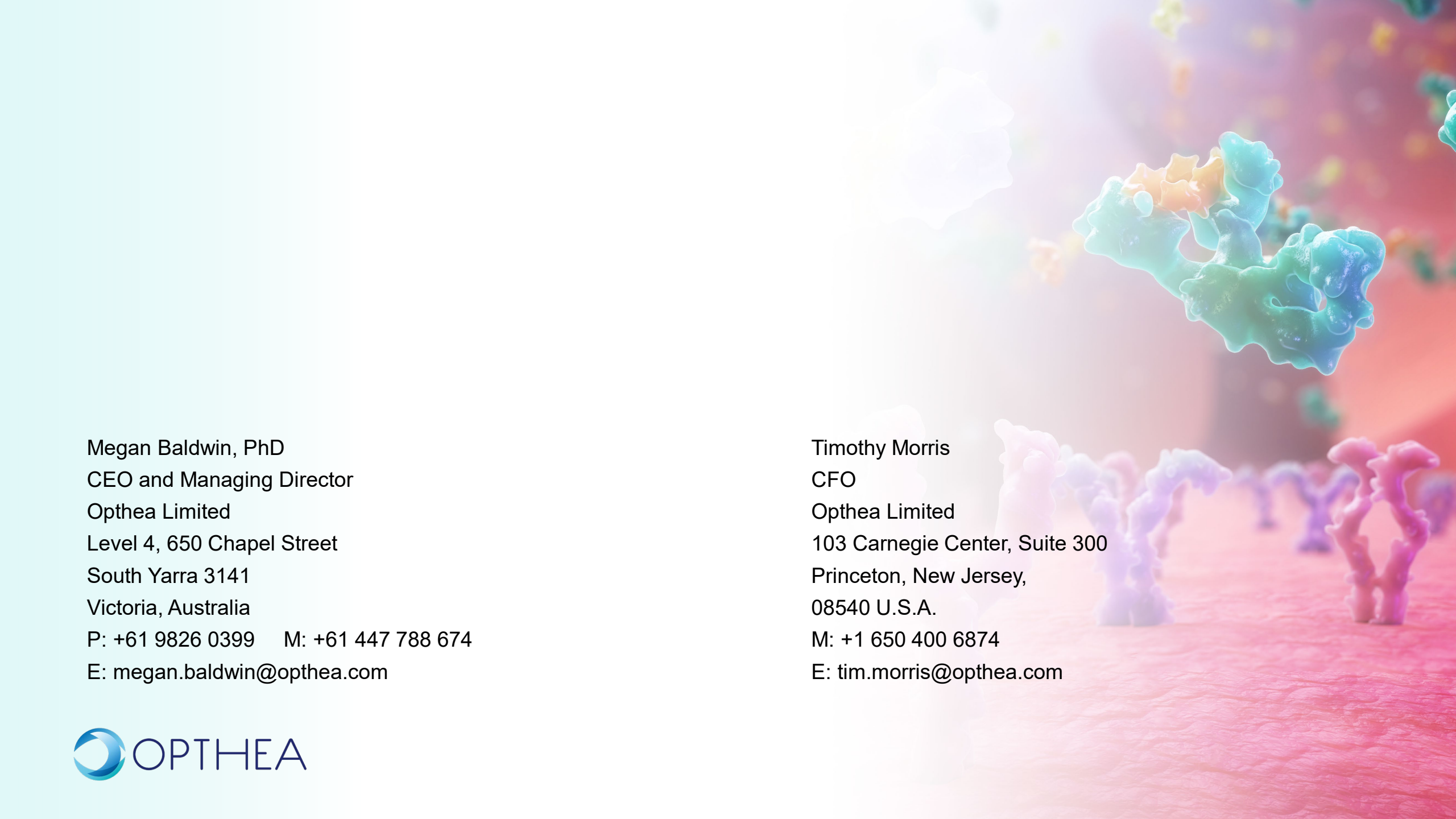
✓ Differentiated MOA to improve efficacy
- OPT-302 is a biologic VEGF-C/D “trap” with no viable threat in competitive pipelines
- The first therapy directly targeting VEGF-C & VEGF-D inhibiting angiogenic signaling through VEGFR-2 and VEGFR-3

✓ 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 in our trials to date

✓ Pivotal Phase 3 trials
- Informed by Phase 2b data to maximize probability of success
- Aligned with FDA and EMA review of protocols
- Granted FDA Fast Track designation

✓ Multi-billion dollar commercial opportunity
- Existing > US$8 billion p.a. global market for wet AMD alone. DME, RVO, PCV provide additional clinical opportunities
- Coformulation with approved therapies possible, exploration underway
- Most advanced product in clinical development to address #1 unmet need for wet AMD patients – improvement in vision outcomes

MOA: Mechanism of Action



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