OPT-302 for wet AMD

VEGF-C/D ‘trap’ to improve wet AMD vision outcomes

Megan Baldwin, PhD
Chief Executive Officer

Timothy E. Morris
Chief Financial Officer

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

OPTHEA

Disclaimer

This presentation includes general background information about the activities of Opthea Limited (ABN 32 006 340 567, NASDAQ: OPT) ('Opthea' or 'Company') and its affiliates and subsidiaries (together, the 'Opthea Group'). The information contained in this presentation is in summary form and does not purport to be complete.

This presentation contains forward-looking statements within the meaning of the U.S. federal securities laws that involve substantial risks and uncertainties. All statements, other than statements of historical facts, contained in this presentation, including statements regarding our strategy, future operations, future financial position, future revenues, projected costs, prospects, plans and objectives of management, are forward-looking statements. The words "anticipate," "believe," "estimate," "expect," "intend," "may," "might," "plan," "predict," "project," "target," "potential," "will," "would," "could," "should," "continue," and similar expressions are intended to identify forward-looking statements, although not all forward-looking statements contain these identifying words. We may not actually achieve the plans, intentions or expectations disclosed in our forward-looking statements, and you should not place undue reliance on our forward-looking statements as predictions of future events. Actual results or events could differ materially from the plans, intentions and expectations disclosed in the forward-looking statements we make. The forward-looking statements contained in this presentation reflect our current views with respect to future events, and we assume no obligation to update any forward-looking statements except as required by applicable law. Please refer to information, including risk factors, set forth in Opthea's filings with the U.S. Securities and Exchange Commission for key factors that could cause actual results to differ materially from those projected in the forward-looking statements contained herein.

This presentation includes statistical and other industry and market data that we obtained from industry publications and research, surveys and studies conducted by third parties as well as our own estimates of potential market opportunities. All of the market data used in this presentation involves a number of assumptions and limitations, and you are cautioned not to give undue weight to such data. Industry publications and third-party research, surveys and studies generally indicate that their information has been obtained from sources believed to be reliable, although they do not guarantee the accuracy or completeness of such information. Our estimates of the potential market opportunities for our product candidates include several key assumptions based on our industry knowledge, industry publications, third-party research and other surveys, which may be based on a small sample size and may fail to accurately reflect market opportunities. While we believe that our internal assumptions are reasonable, no independent source has verified such assumptions.

The information contained in this presentation does not constitute investment or financial product advice (nor taxation or legal advice) and is not intended to be used as the basis for making an investment decision. It does not take into account the investment objectives, financial situation, taxation position or needs of any particular investor, which should be considered when deciding if an investment is appropriate. You must consider your own investment objectives, financial situation and needs and conduct your own independent investigations and enquiries, including obtaining taxation, legal, financial or other professional advice in relation to the information contained in this presentation as appropriate to your jurisdiction. This presentation should not be relied upon by the Recipient in considering the merits of any particular transaction.

This presentation may contain trademarks and trade names of third parties, which are the property of their respective owners. Third party trademarks and trade names used in this presentation belong to the relevant owners and use is not intended to represent sponsorship, approval or association by or with any of Opthea.

OPT-302 has the potential to improve vision for millions of patients with wet AMD

We are developing OPT-302, a first-in-class VEGF-C/D ‘trap’, to be used in combination with standard of care anti-VEGF-A therapies

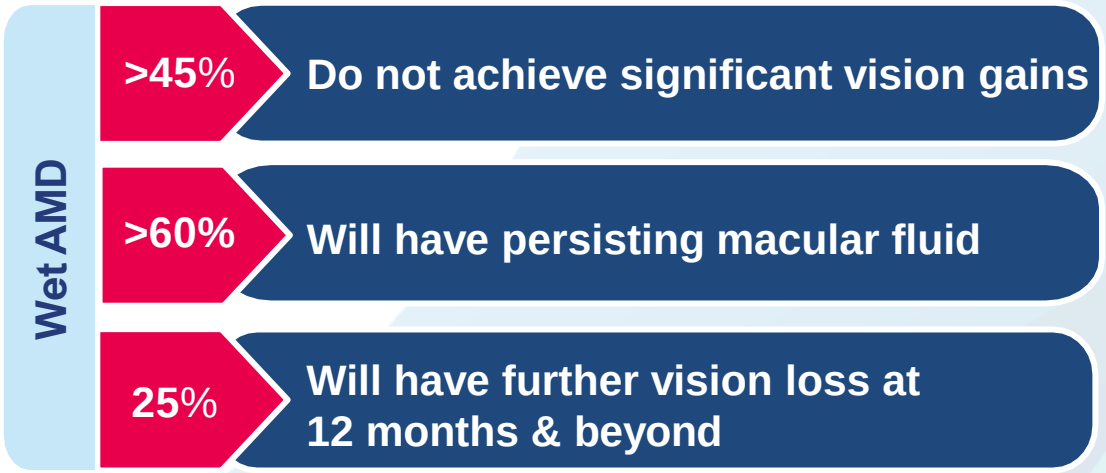
- First and **only** retina asset with strong clinical evidence of **better visual outcomes** over anti-VEGF-A therapy for wet AMD, with well tolerated safety profile
- Currently available treatment options and those in development focus only on reducing burden of care, **OPT-302 is designed to transform patient outcomes by improving vision**
- OPT-302 expected to be **rapidly adopted** by patients, physicians and payers globally due to:
  - High unmet need
  - Established wet AMD market and clinical practice
  - Favorable physician and health system economics
- FDA granted **Fast-Track** designation based on superior Phase 2b results
- Pivotal Phase 3 trials ongoing, ShORe and COAST
- OPT-302 represents a **multi-billion dollar** commercial opportunity
- **Long-term value** opportunity substantial:
  - Composition of Matter and Methods of Use Patents through 2034
  - Further opportunity for Patent Term Extension (PTE), Data and Market Exclusivity periods beyond 2034
  - Expansion in to DME, RVO and PCV represent blockbuster upside opportunity

OPTHEA

The Unmet Medical Need for wet AMD

- Wet AMD is the leading cause of irreversible blindness
- Currently:
  - Impacts 4.2M 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]:

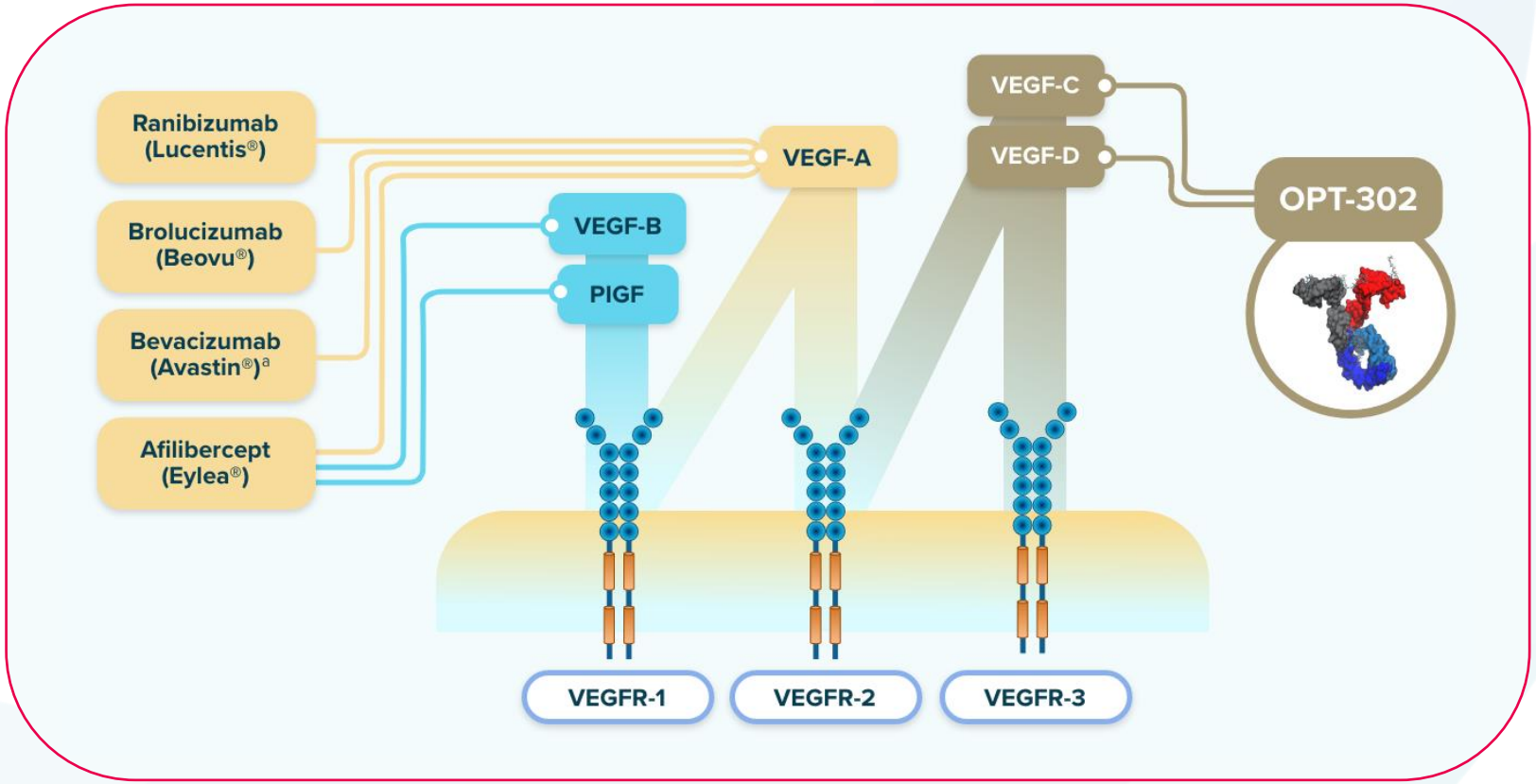


OPTHEA

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

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 can contribute to sub-optimal clinical efficacy of anti-VEGF-A treatments

OPTHEA

[a] *Bevacizumab is used 'off-label' for the treatment of nAMD*

Large & 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 & Avastin or biosimilar treated patients WW)

>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 & Eylea

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

OPTHEA

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 2 months after 3 monthly doses*
Monthly Dosing	Every Two Months Dosing

Treatment naïve Patients

COAST
Phase 3
wet AMD
(n=990)

Comparator

Aflibercept
once every 2 months after 3 monthly doses

Standard Dosing	Extended Dosing
OPT-302 *once every month*	OPT-302 *once every 2 months after 3 monthly doses*
Monthly Dosing	Every Two Months Dosing

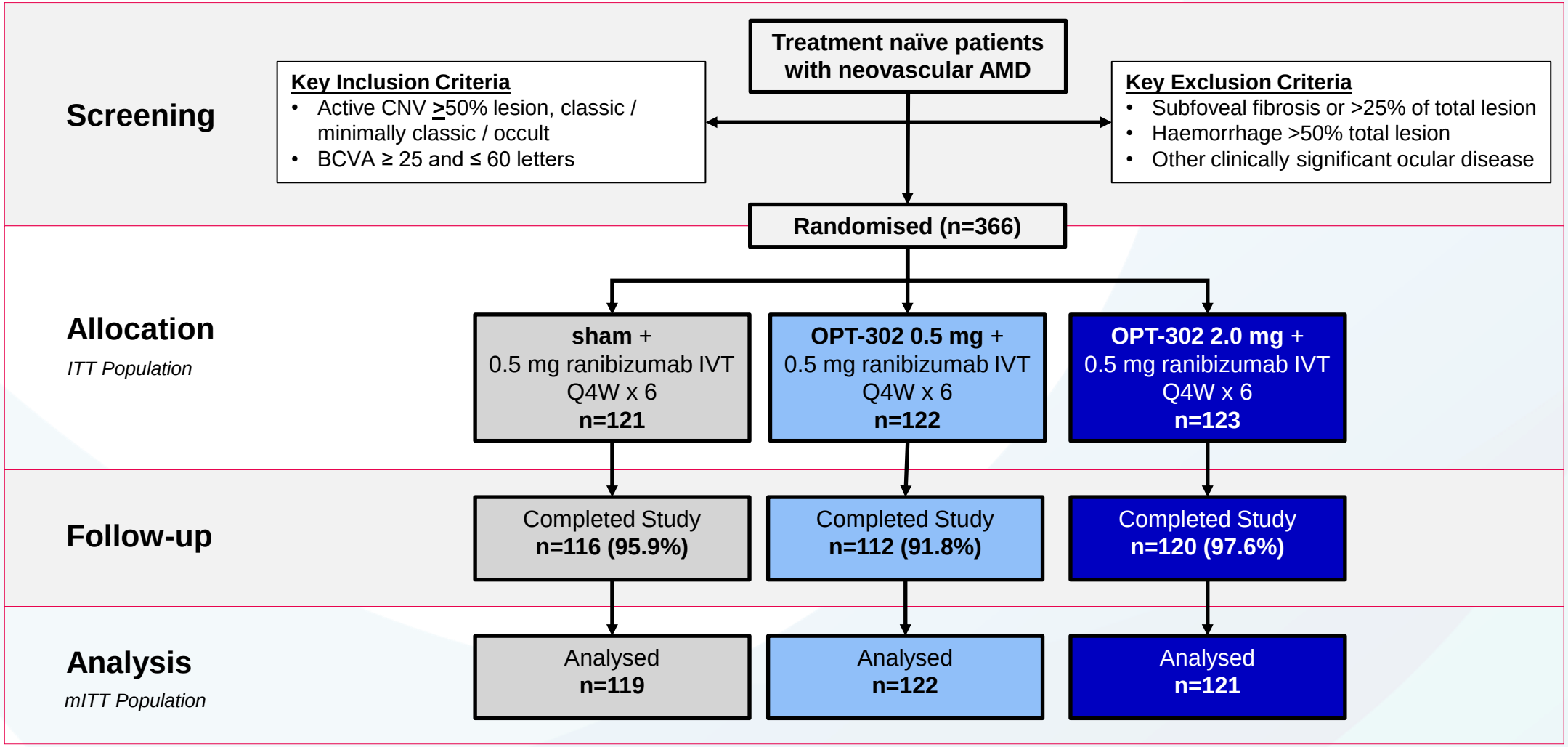
Treatment naïve Patients

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

OPTHEA

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 our OPT-302 development program.

Study Overview



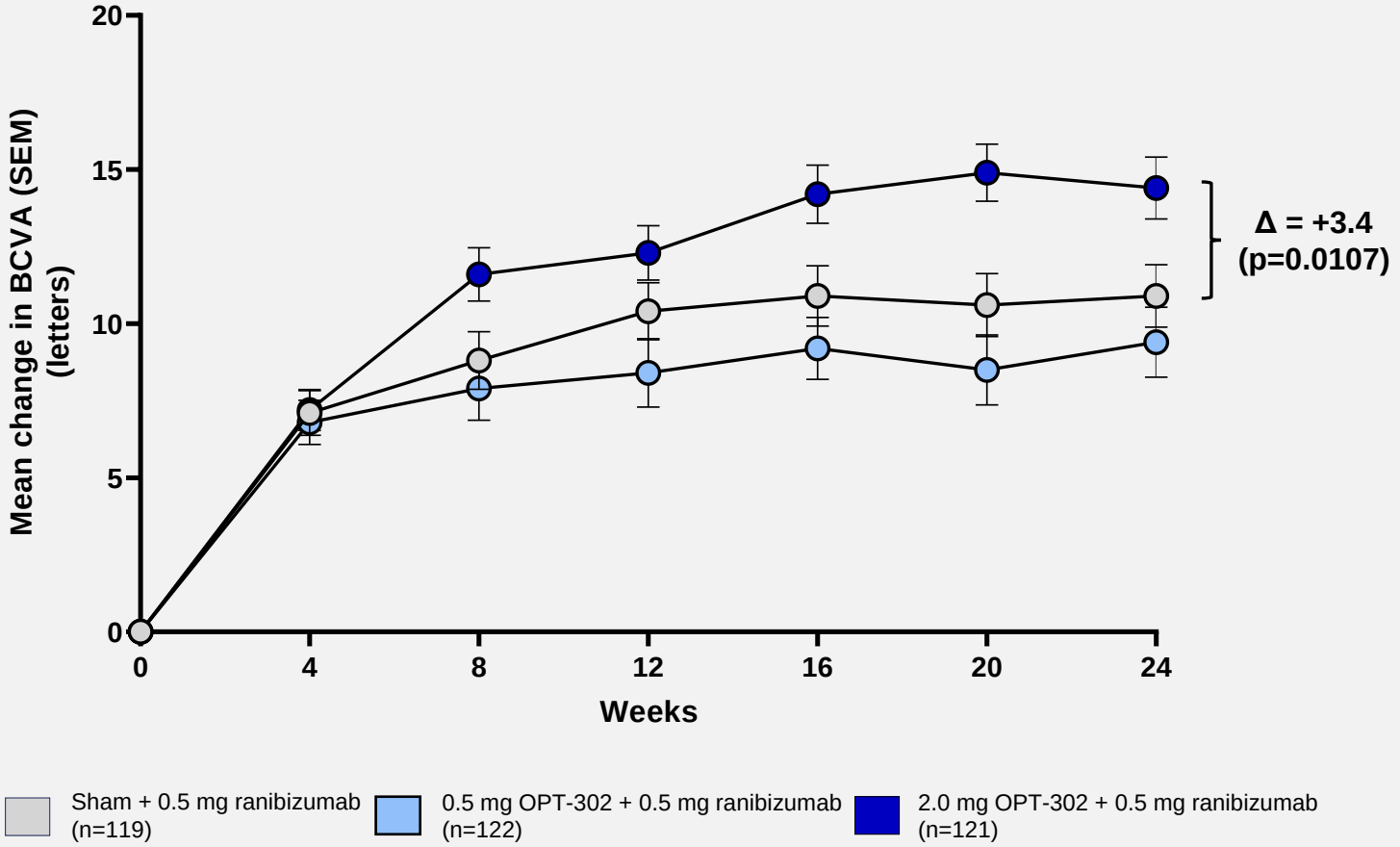
CNV – choroidal neovascularisation; IVT – intravitreal; Q4W – once very 4 weeks
ITT – Intent to Treat Population, all participants who were randomised into the study irrespective of whether study medication was administered or not
Safety Population - all participants in the ITT but excluding those who 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

OPT-302 (2.0 mg) Combination Therapy:

Superiority in Visual Acuity over Ranibizumab

Primary endpoint achieved

Mean Change in Best Corrected Visual Acuity Baseline to Week 24

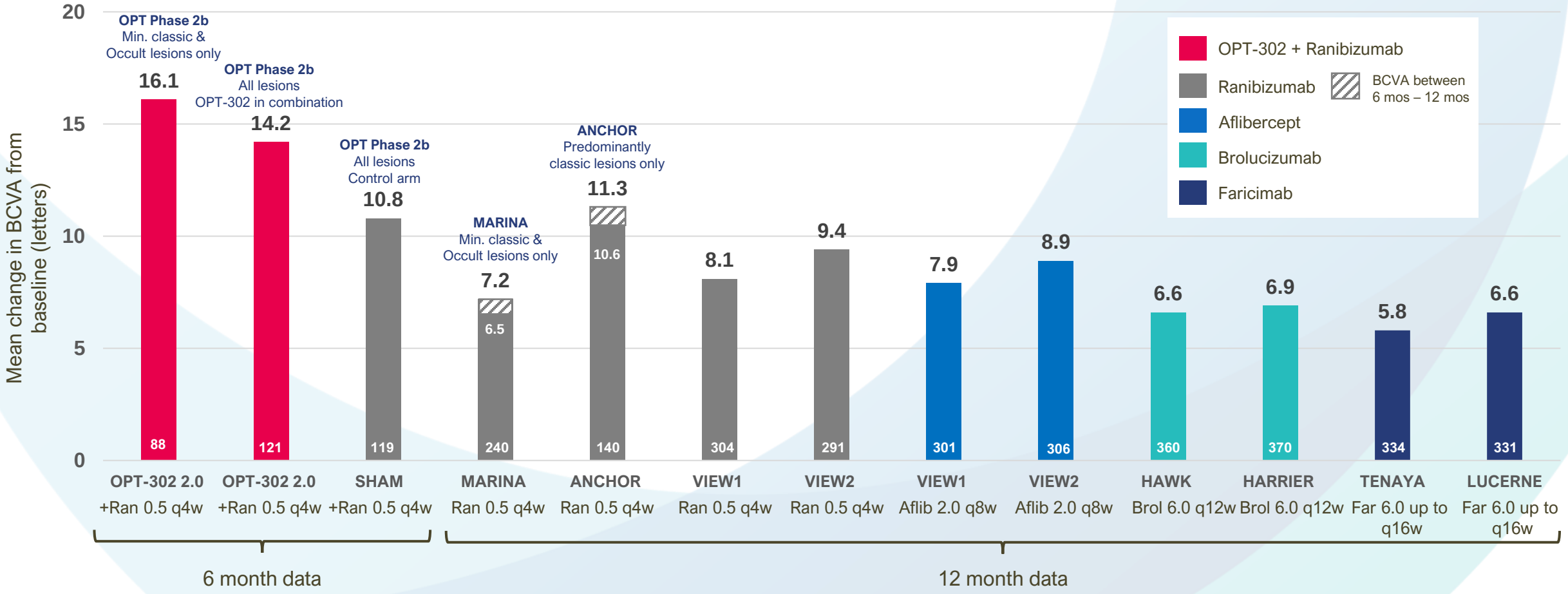


mITT; BCVA – Best Corrected Visual Acuity
Left: Difference in Least Square Means, using Model for Repeated Measures (MRM) analysis. Right: Graph represents "as observed" data and SEM

Comparison with Other Trials

Mean visual acuity higher vs previous VEGF-A inhibitor trials

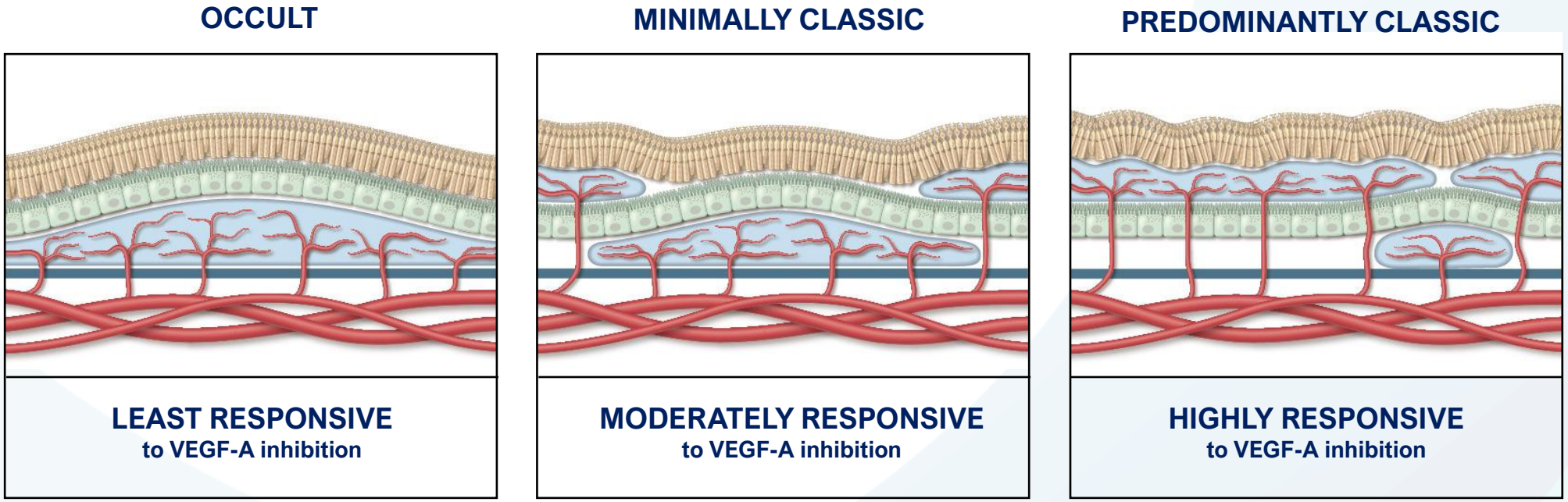
Efficacy at 6 months is typically maintained or greater at 12 months in Phase 3 trials with VEGF-A inhibitors



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; 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

Neovascular (wet) AMD Lesion Types

Differ in vessel location, leakiness and responsiveness to VEGF-A inhibitors



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

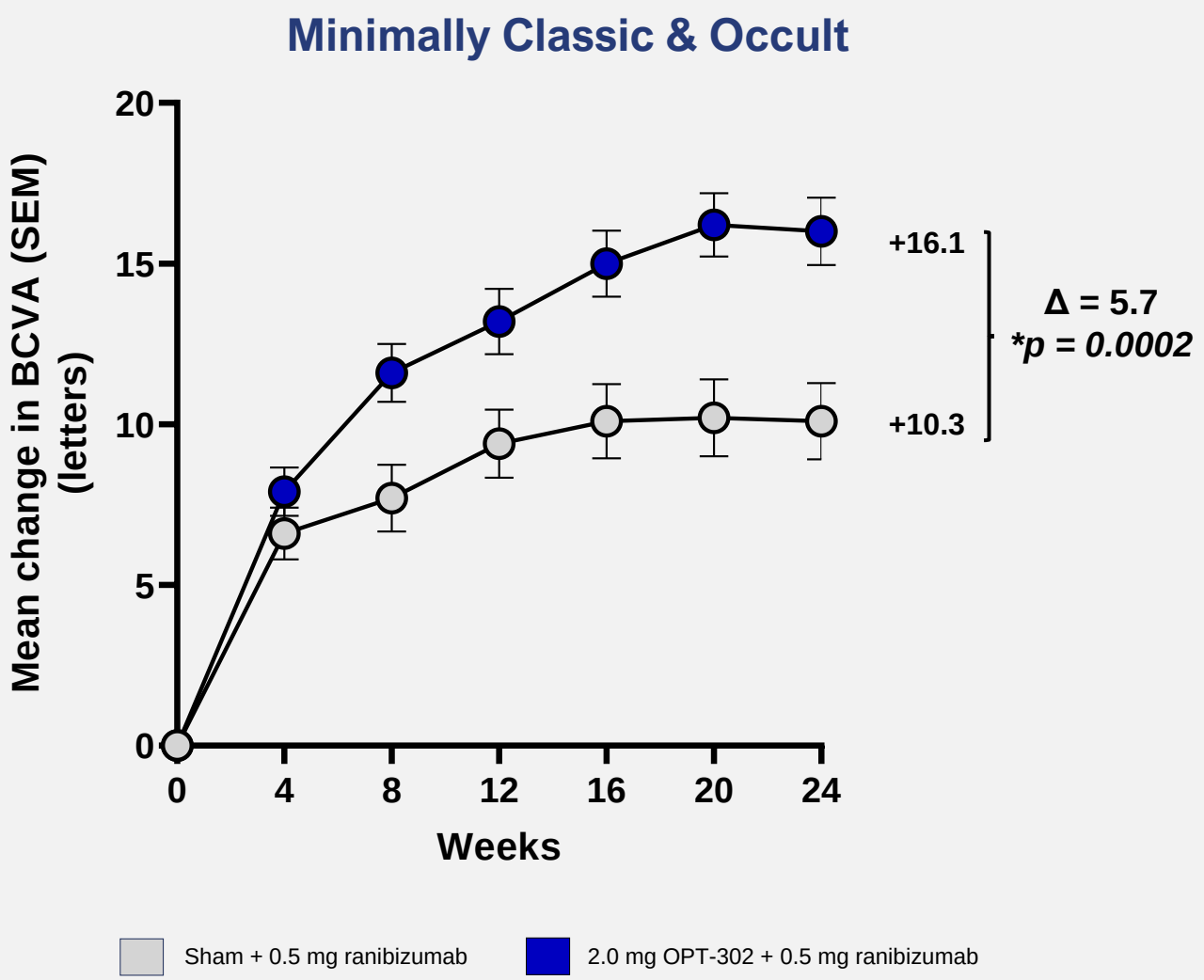
OPTHEA

Best Responders:

Minimally Classic & Occult lesions
(RAP Absent)

Achieved greatest vision benefit

Represents primary analysis population in OPT-302 phase 3 program

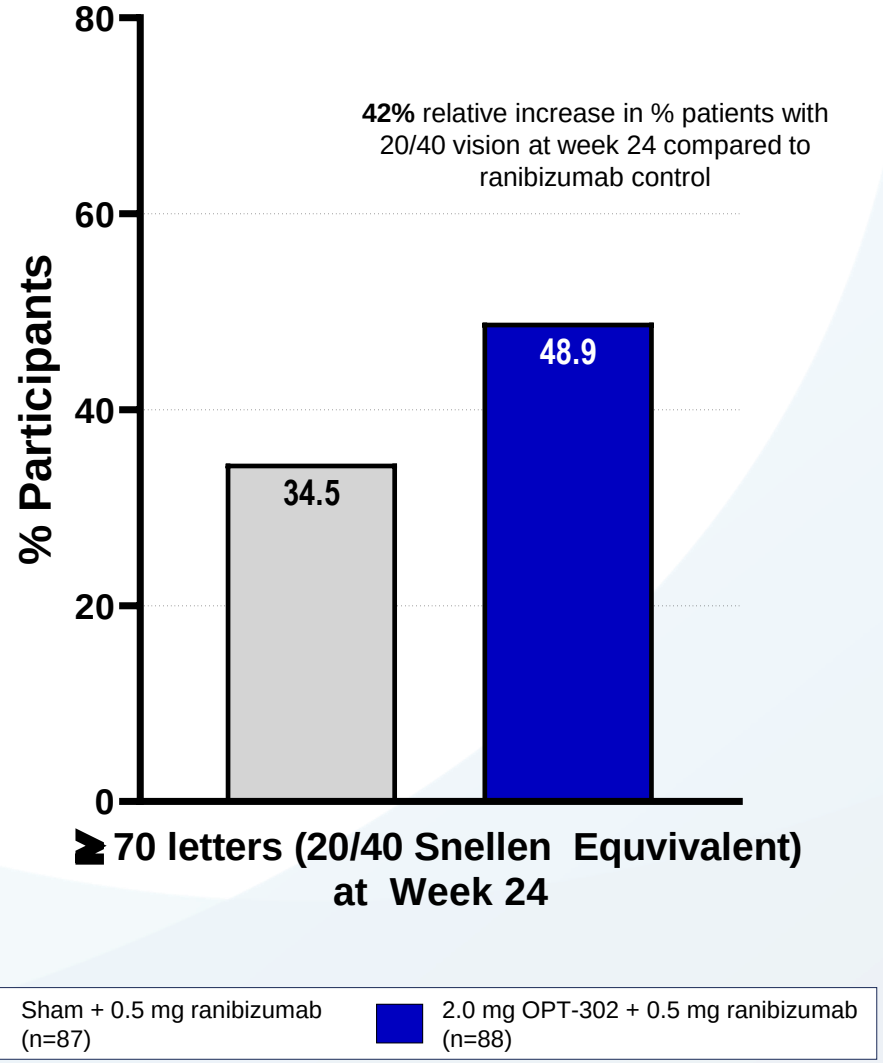


OPTHEA

* *Unadjusted p-value*

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

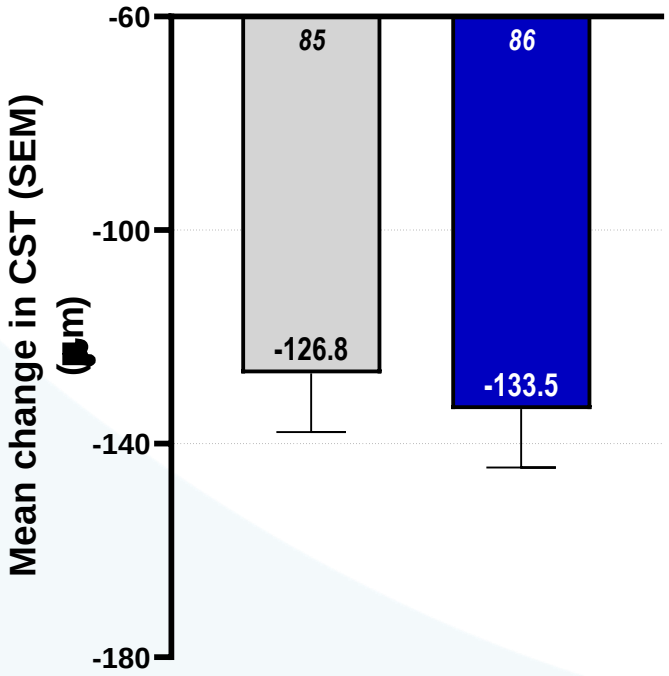


Modified Intent-to-Treat (mITT) population; as observed

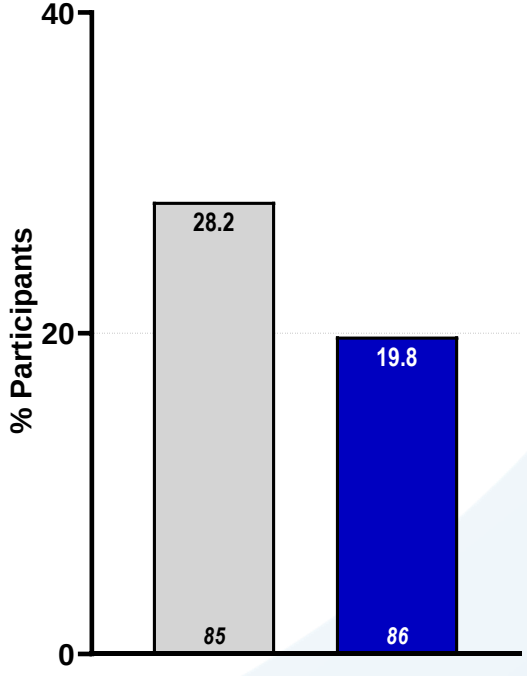
Reduced Retinal Thickness & Better ‘Retinal Drying’

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

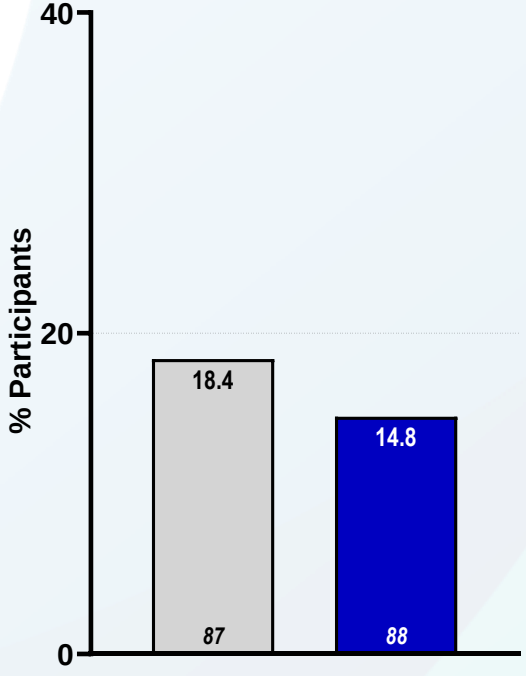
Mean Change in CST Baseline to Week 24



% Participants with SRF at Week 24



% Participants with IR Cysts at Week 24



Sham + 0.5 mg ranibizumab (n=87)

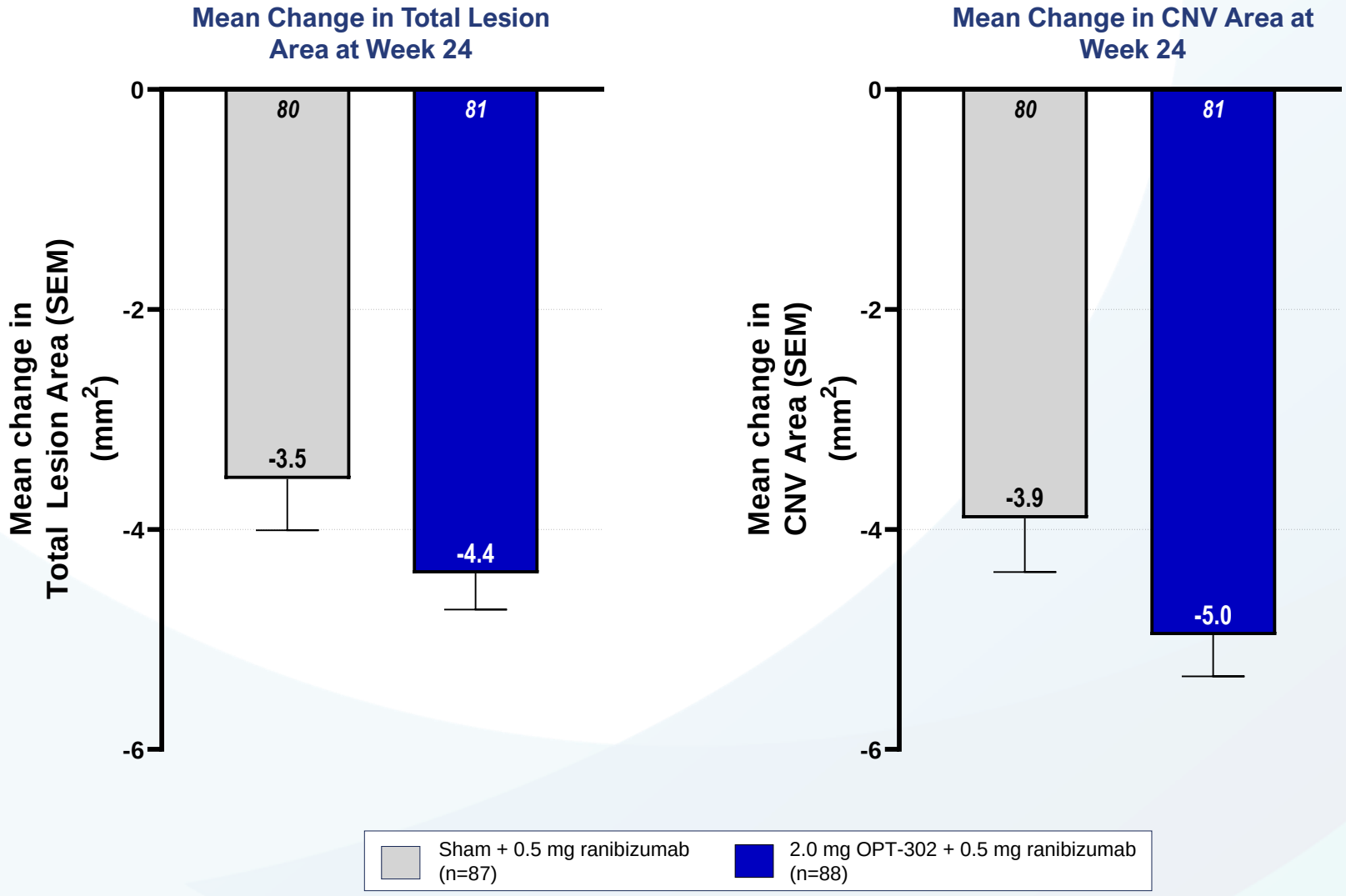
2.0 mg OPT-302 + 0.5 mg ranibizumab (n=88)

OPTHEA

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



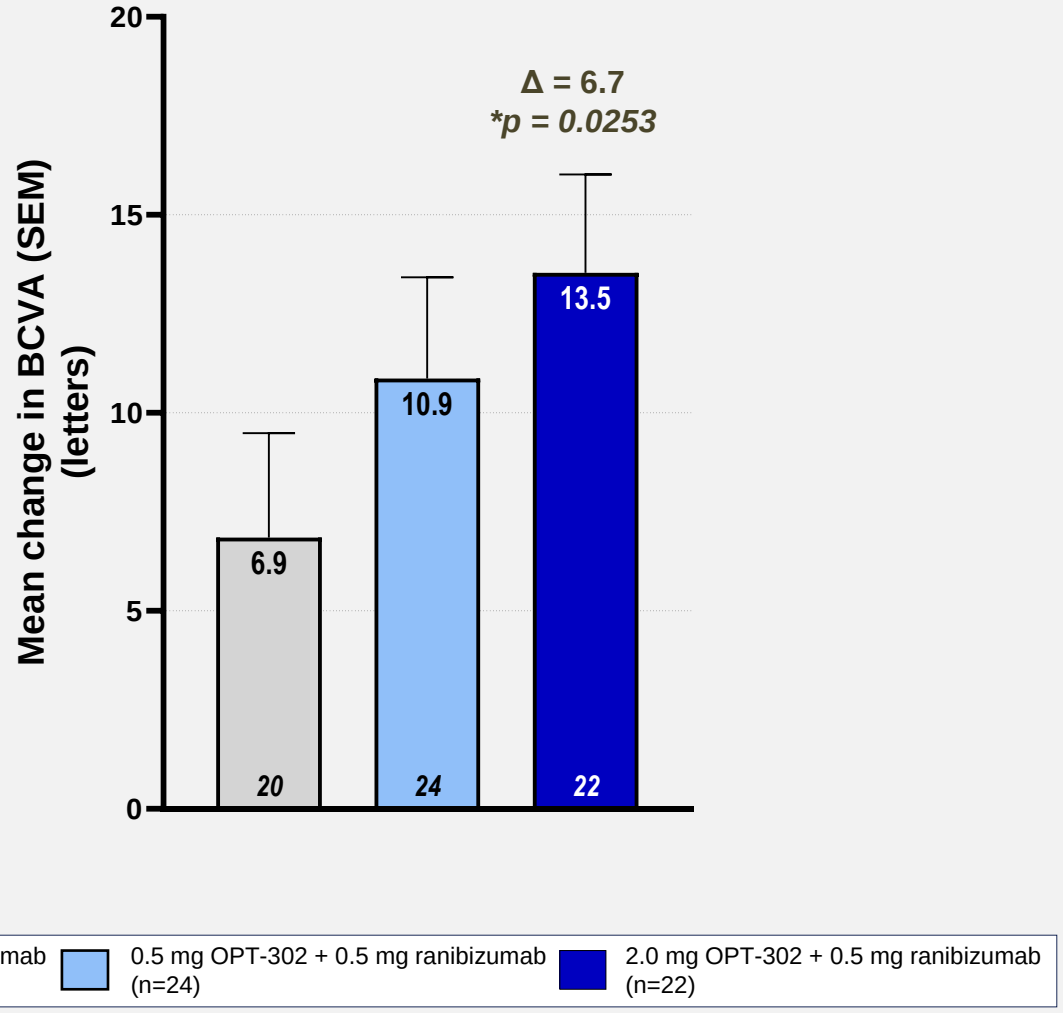
mITT; as observed; top of bar – statistic, bottom of bar - n

Polypoidal Choroidal Vasculopathy (PCV)

PCV is a difficult-to-treat wet AMD subtype, with large unmet need

OPT-302 combination therapy has 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**



OPTHEA

* Unadjusted p-value

Safety

OPT-302 well-tolerated with very low incidence of ocular inflammation, comparable to SoC 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*

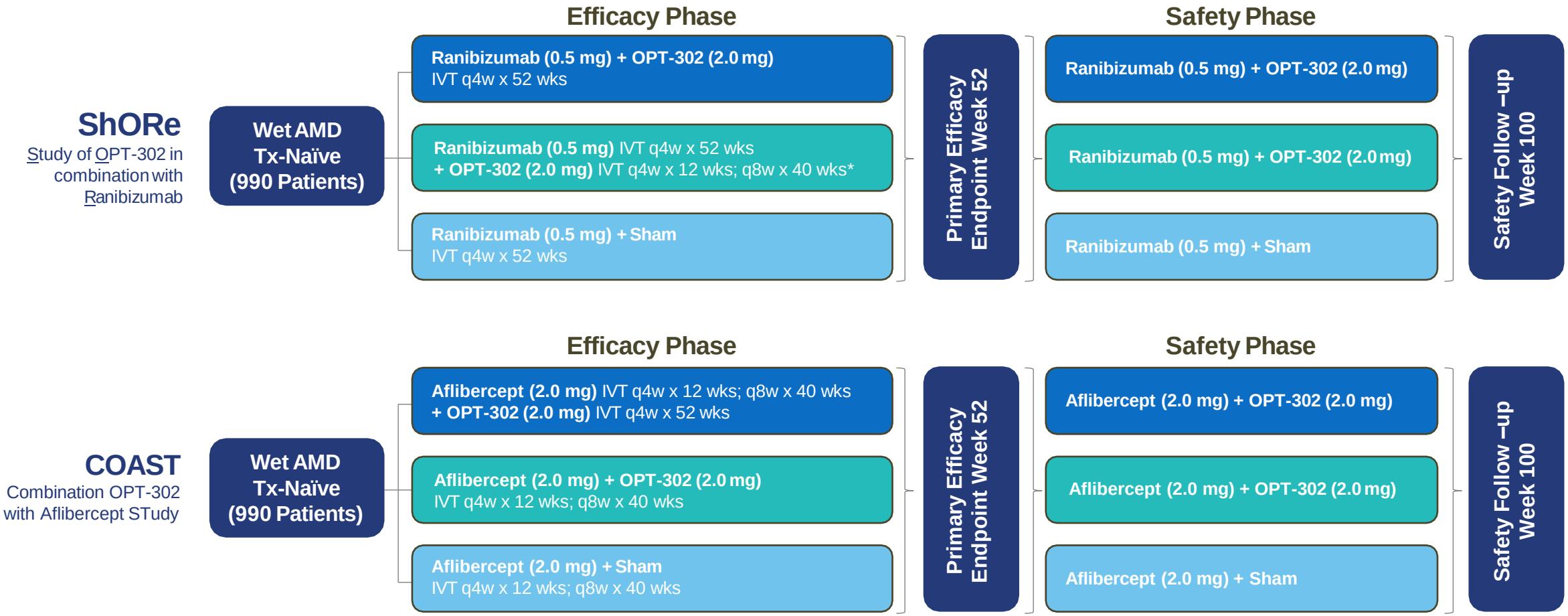
[9] *Pneumonia (n=1), infective endocarditis (n=1)*

OPTHEA

OPT-302 Phase 3 Pivotal Program

Topline primary data analysis end 2024 – early 2025

Opthea intends to submit Biologics License and Marketing Authorization Applications 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*

The Company's focus is on Phase 3 execution

CRO oversight, driving patient recruitment through site engagement, increasing physician & investor awareness

Phase 3 Execution

- *Two trials concurrently recruiting across ~400 sites globally*
- *Each site may only recruit for one trial at a time, only a limited number of high recruiting sites will switch to the second trial and recruit for both*
- *Similar rates of recruitment in both ShORe (Lucentis) & COAST (Eylea) trials*
- *Key focus areas:*
  - *CRO oversight*
  - *Site data entry, data cleaning, topline prep*
  - *Site engagement*

Key Dates

- *Aim to complete patient recruitment as early as Dec 2023*
- *Rolling lock & data cleaning to expedite topline data reporting*
- *Topline data – end 2024, early CY 2025*

Pre-Commercial Activities

Objective – to build full commercial launch plan & initiate those activities that are required to file for marketing approval to ensure expeditious launch timelines

Immediate Priorities:

- *Commercial manufacturing (multiple batches to demonstrate consistency, reproduceability of process & quality at scale)*
- *Market shaping, physician mindshare – how will OPT-302 be used?*
- *Preliminary – payer/pricing*
- *Competitive landscape, OPT-302 positioning*
- *Initial focus – US, then EU/ROW*

Timeline

- *All patients must complete 12 mos dosing for topline data*
- *Topline data to follow data cleaning and database lock asap following LPI completing 12 mos dosing*
- *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*

OPTHEA

Key Messages

- Potential for improved vision outcomes (improved treatment efficacy)
- Better efficacy may also lead to prolonged vision responses (durability)

- Our Phase 3 trials are designed to support a label for all neovascular (wet) AMD pts
- Treatment naïve and large population of patients who have received prior Tx
- 50% pts WW receive branded agents generating revenues ~USD 9BN p.a. for wet AMD

- Broad utility – for use with any anti-VEGF-A standard of care treatment
- Phase 3 designed to withstand new SoC entries to market with different delivery profiles

Financials & Corporate Activities

- Dec 31 2022: USD142m
- Project funding agreement up to USD170m completed with Carlyle/Abingworth:
  - USD120m (USD 85m received)
  - Third tranche of USD35m by end CY 2023
  - Additional USD50m option
- Investment took on clinical, regulatory & commercial risk, 4x capped ROI only if successful (approved)
- Engaged investment team & oversight

- Optimizing commercial opportunity for asset
- Co-formulation & life-cycle management
- Regional licenses

- Expanded team, increased investor engagement & investor events
- Increased clinical community engagement – conferences, sites, physician & market awareness

Summary

Opthea's 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 std 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 for up to $170M in place

OPTHEA

Megan Baldwin, PhD
CEO & Managing Director
Opthea Limited
Level 4, 650 Chapel Street
South Yarra 3141
Victoria Australia
P: +61 9826 0399 M: +61 447 788 674
E: megan.baldwin@opthea.com

Timothy Morris
CFO
Opthea Limited
103 Carnegie Center, Suite 300
Princeton, New Jersey, 08540 U.S.A.
M: +1 650 400 6874
E: tim.morris@opthea.com