New approach in wet-AMD treatment: Efficacy and safety of dual inhibition of VEGF-C/-D and VEGF-A with OPT-302 combination therapy

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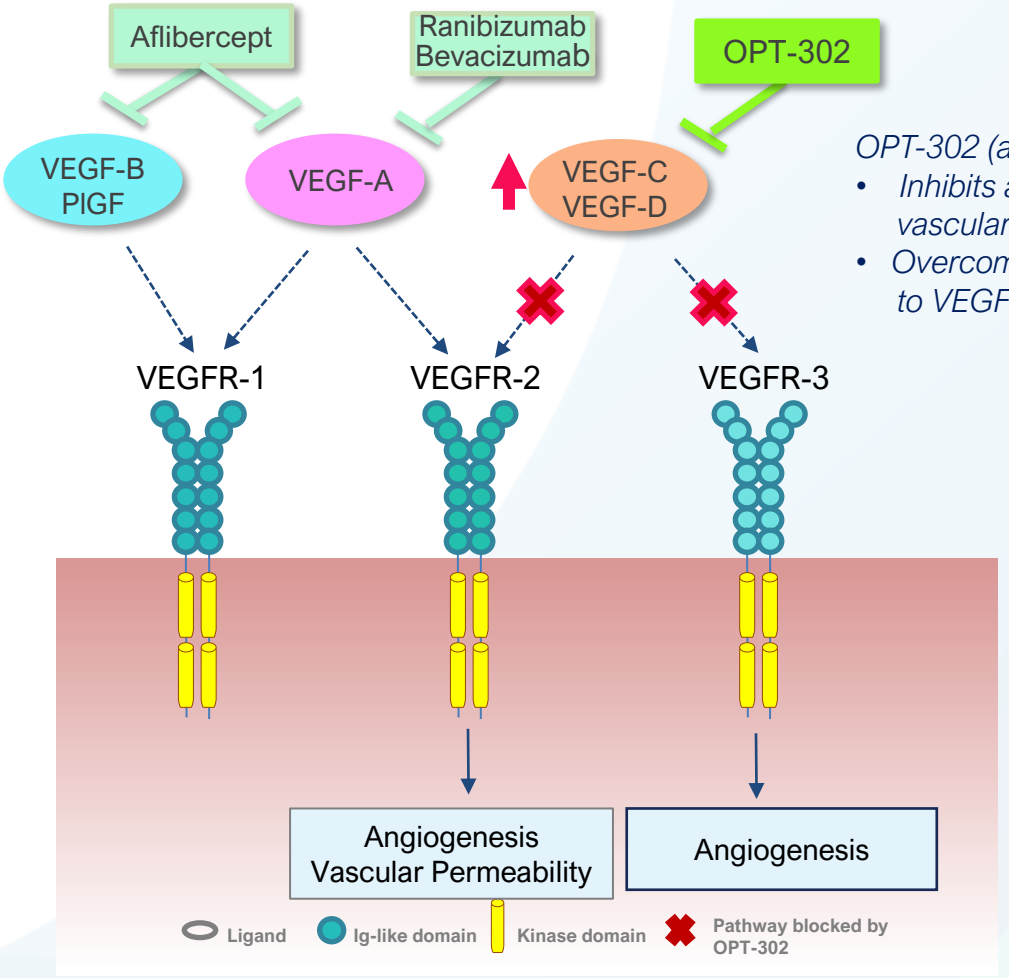
Disclosures

Consultant:

Alcon; Apellis Pharmaceuticals, Inc; Bayer Corporation; Genentech, Inc.; Ora, Inc.; Regeneron Pharmaceuticals Inc

OPT-302 combination therapy offers broader inhibition of VEGF receptor signaling by targeting VEGF-C /-D and VEGF-A

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



OPT-302 (anti-VEGF-C/-D):

- *Inhibits angiogenesis & vascular leakage*
- *Overcomes escape mechanism to VEGF-A suppression*

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

[a] *Bevacizumab is used 'off-label' for the treatment of nAMD*
Dugel PU, et al Ophthalmology Retina. 2020; 4: 250–263.

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 Arm	Extended Dosing Arm
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

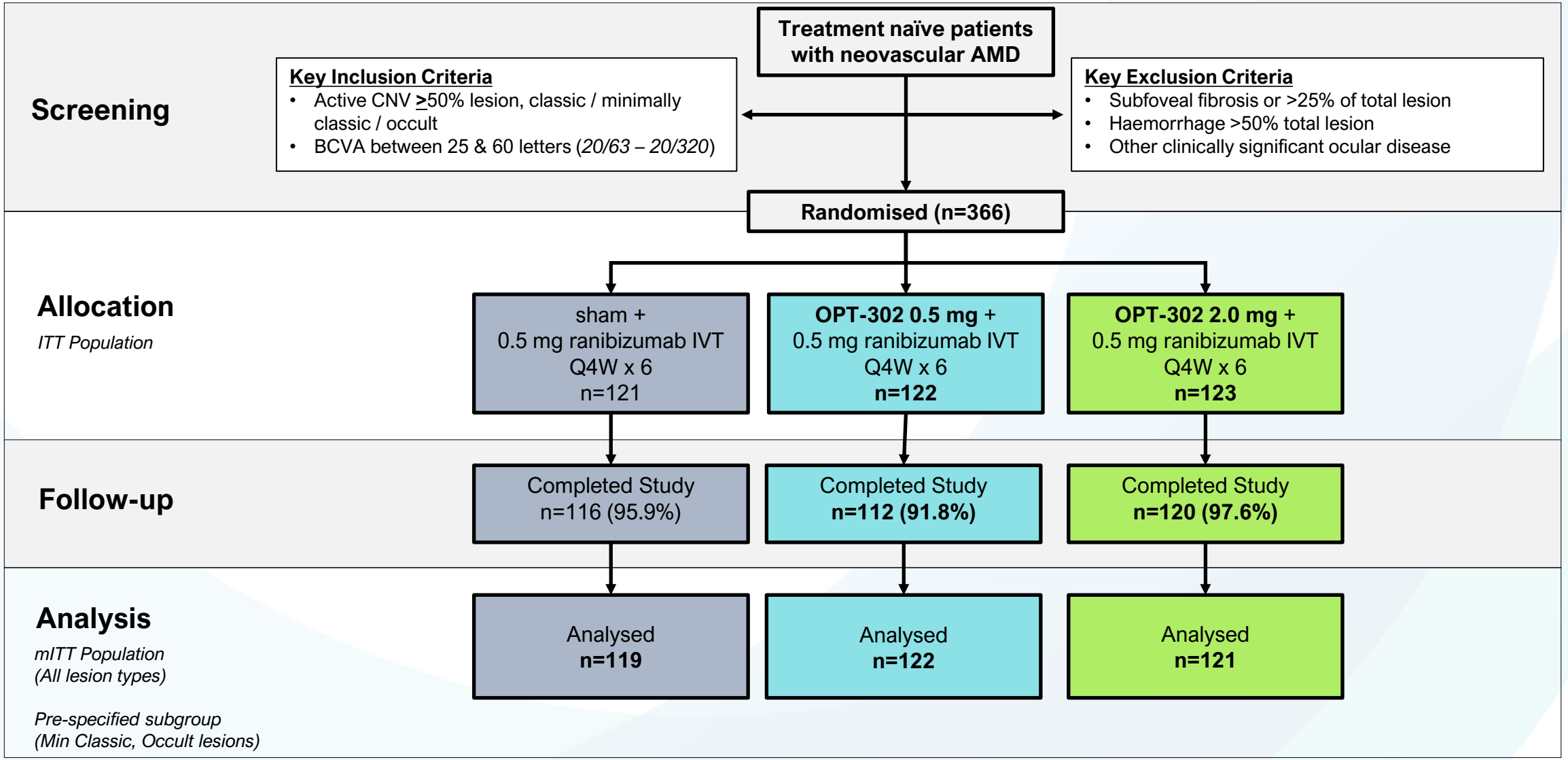
Standard Dosing Arm	Extended Dosing Arm
OPT-302 *once every month*	OPT-302 *once every 2 months after 3 monthly doses*
Monthly Dosing	Every Two Months Dosing

Treatment naïve Patients

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

OPT-302 Phase 2b wet AMD Study Overview

A multicenter RCT of intravitreal OPT-302 in combination with ranibizumab



Study OPT-302-1002 (ClinicalTrials.gov Identifier: NCT0334508) conducted at 109 sites across 10 countries: US, EU, Israel

Jackson T. A multicenter, randomized, double-masked, sham-controlled clinical trial of intravitreal OPT-302, a novel anti-VEGF C and D drug for the treatment of neovascular age-related macular degeneration. EURETINA Congress; 2019; Paris, France.

Phase 2b wet AMD Study Demographics & Baseline Characteristics

The three treatment arms were well-balanced

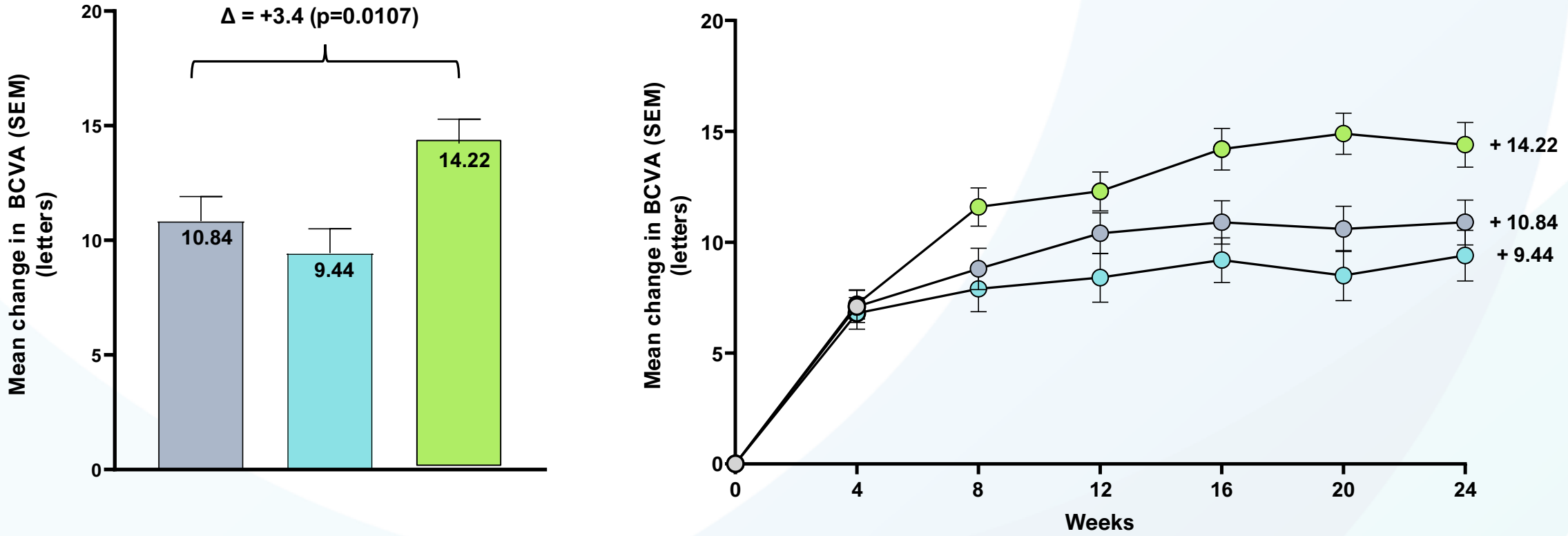
Demographic / Baseline Disease Characteristic		Sham + ranibizumab N=121	0.5 mg OPT-302 + ranibizumab N=122	2.0 mg OPT-302 + ranibizumab N=123
Mean Age – years ± SD		76.1 ± 9.48	78.8 ± 8.16	77.8 ± 8.82
Sex – n (%)	Male	48 (39.7%)	49 (40.2%)	45 (36.6%)
	Female	73 (60.3%)	73 (59.8%)	78 (63.4%)
Caucasian 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

Superiority in visual acuity for OPT-302 (2 mg) combination therapy versus ranibizumab monotherapy

Primary endpoint met in Phase 2b wet AMD study

Mean Change in BCVA Baseline to Week 24



mITT; BCVA – Best Corrected Visual Acuity

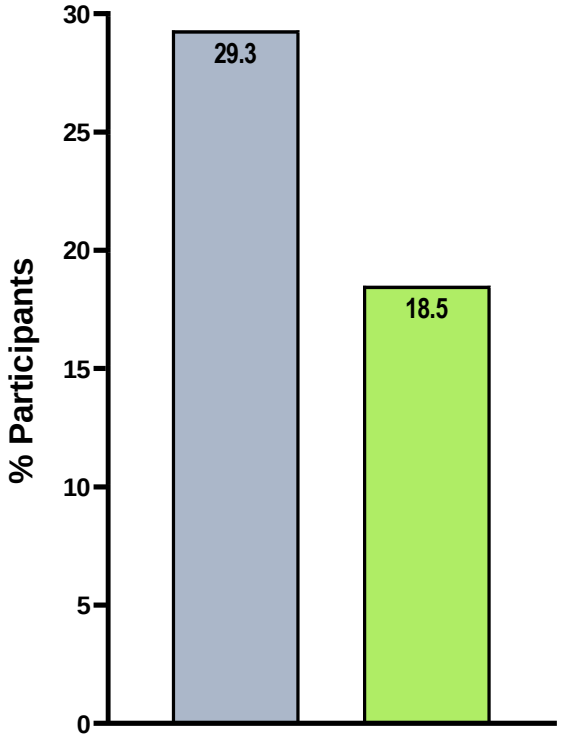
Left: Difference in Least Square Means, using Model for Repeated Measures (MRM) analysis. Right: Graph represents "as observed" data and SEM

Improved anatomy for OPT-302 (2 mg) combination therapy versus ranibizumab monotherapy

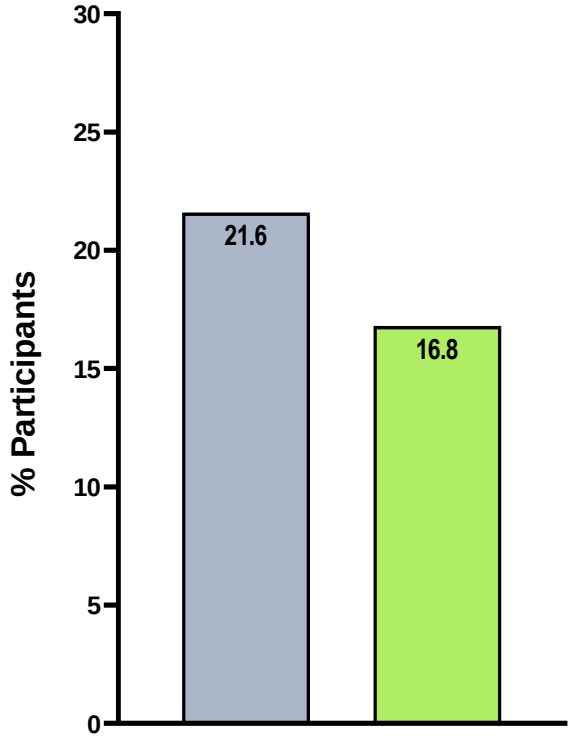
Phase 2b wet AMD study

SD-OCT at Week 24

↓ Presence of sub-retinal fluid

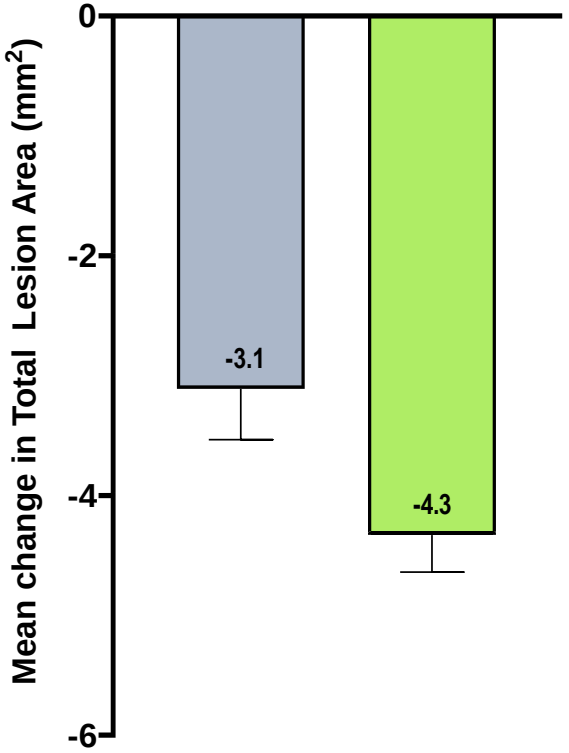


↓ Presence of Intraretinal cysts

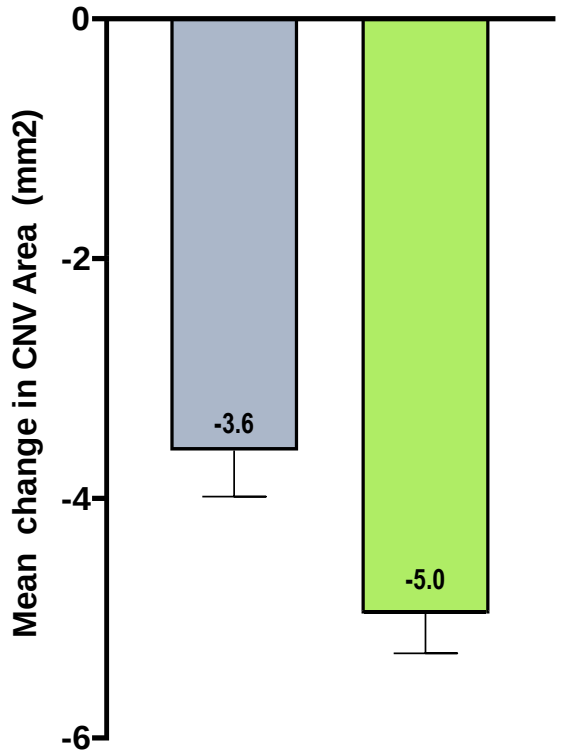


FA at Week 24

↓ Total Lesion Area



↓ CNV Area

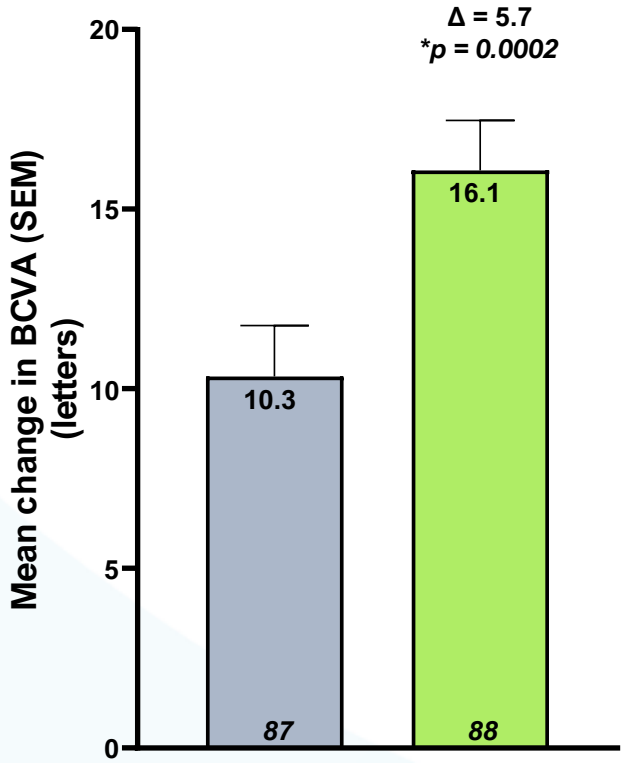


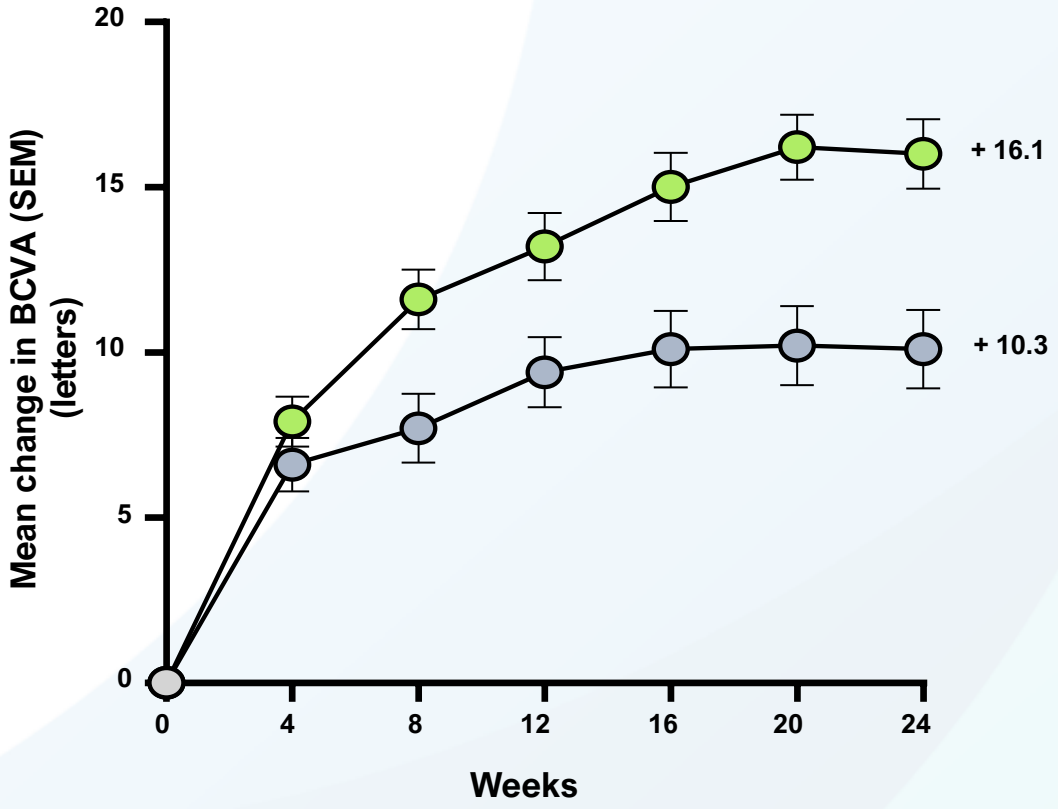
Sham + 0.5 mg ranibizumab (n=116)

2.0 mg OPT-302 + 0.5 mg ranibizumab (n=120)

Improved BCVA in occult & minimally-classic lesions subgroup for OPT-302 (2 mg) combination therapy versus ranibizumab monotherapy

Mean Change in BCVA Baseline to Week 24





Sham + 0.5 mg ranibizumab (n=87)

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

p-value unadjusted
**RAP lesions absent*

Safety: Phase 2b wet AMD study

OPT-302 combination therapy well-tolerated and comparable to ranibizumab monotherapy

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 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)*

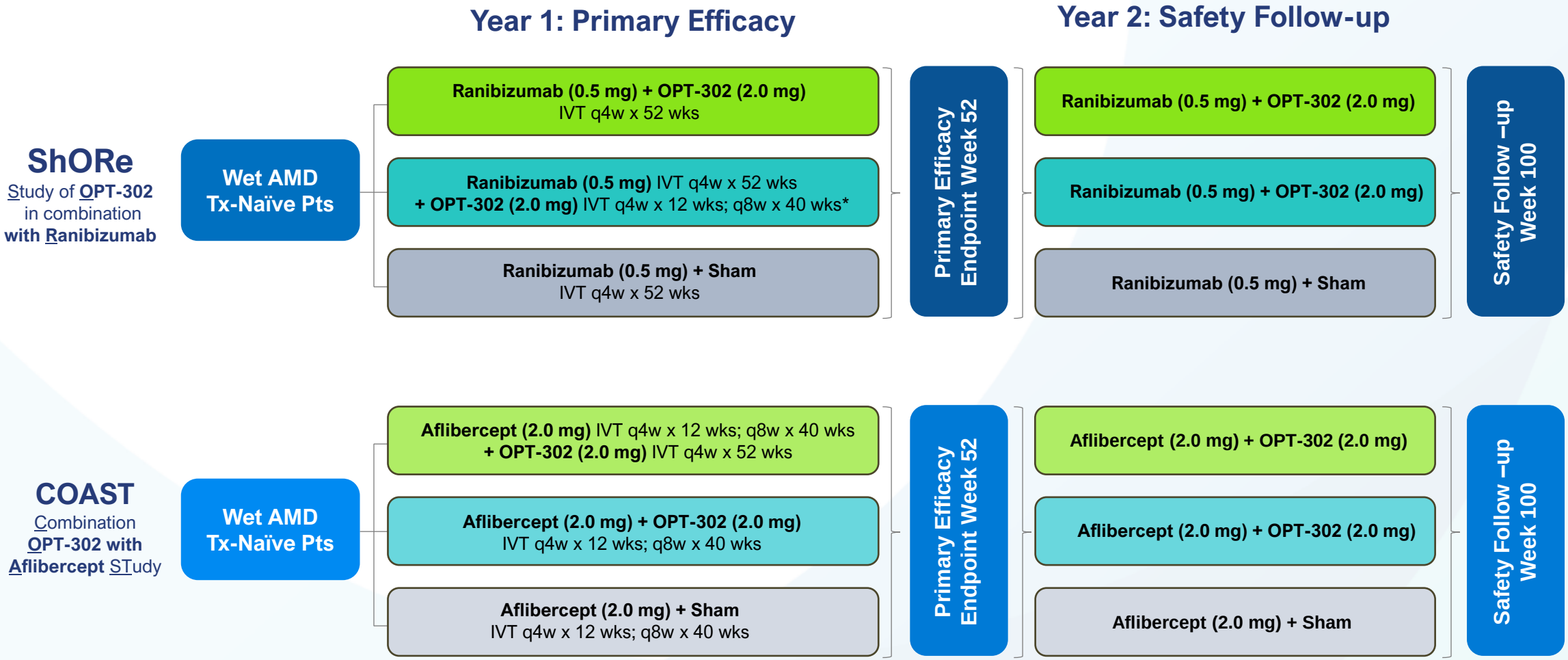
[6] *Not reported as a TEAE*

[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)*

Current Phase 3 studies in wet AMD for OPT-302 in combination with ranibizumab or aflibercept



- **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*

Conclusions: OPT-302 combination therapy for wet AMD

- **OPT-302 selectively targets the angiogenic ligands VEGF-C and –D**
  - two ligand mediators of the validated VEGF/VEGFR signaling pathway contributing to angiogenesis and vascular leakage
- **OPT-302 combination therapy has broader inhibition (VEGF-A, VEGF-C and VEGF-D) that may offer benefits that exceed the inhibition of VEGF-A alone**
- **Phase 2b wet AMD trial met primary endpoint**
  - OPT-302 (2 mg) combination therapy demonstrated superiority in visual acuity over ranibizumab + sham
  - Additional +3.4 letter gain (p=0.0107) over ranibizumab in total patient population
  - Additional +5.7 letter gain observed in high responder subgroup (minimally classic & occult lesions, RAP absent, >70% study population), represents Phase 3 primary analysis population
- **Phase 2b secondary visual function and anatomic outcomes were supportive of the primary endpoint**
- **OPT-302 has a favourable tolerability profile similar to SoC anti-VEGF-A monotherapy**
- **Promising treatment option for wet AMD currently in two pivotal registrational Phase 3 studies**