

# OPT-302 Combination Therapy in Polypoidal Choroidal Vasculopathy

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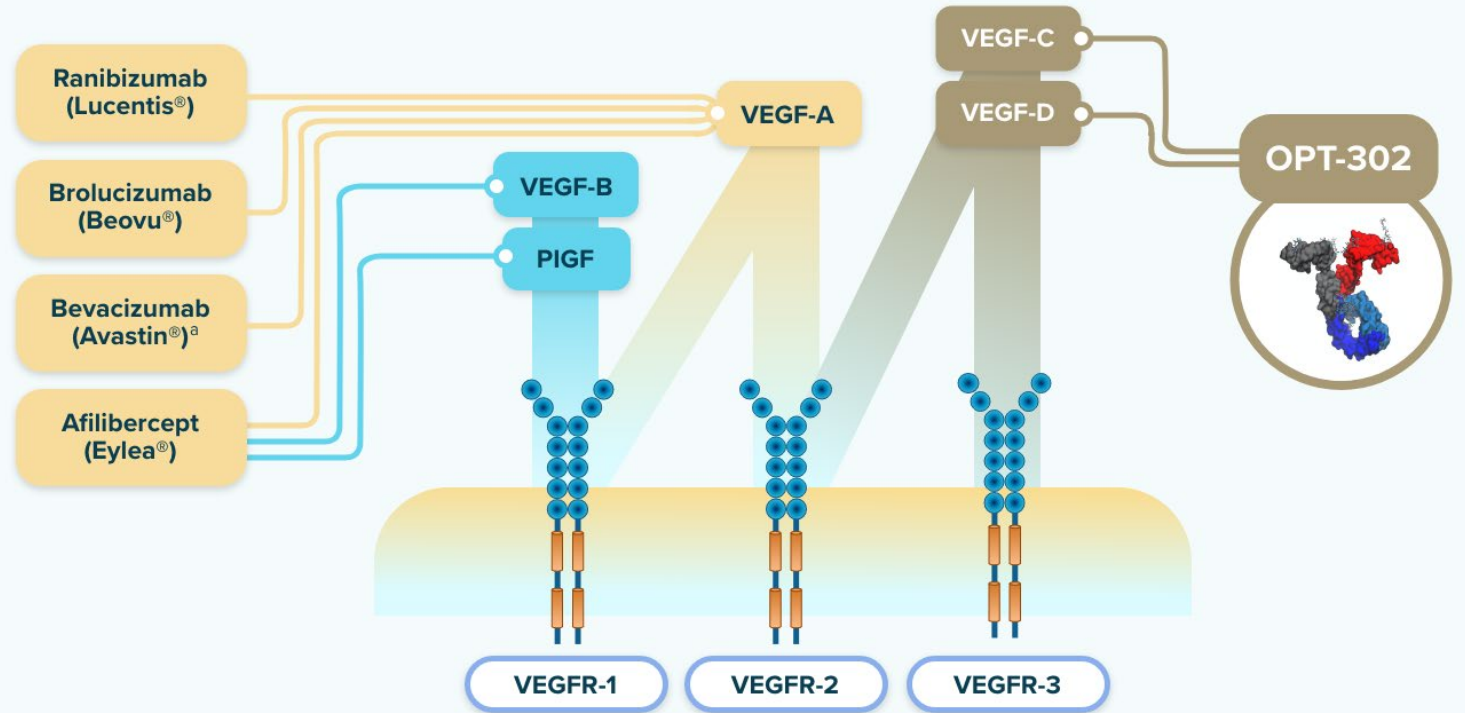
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# Key Take-Aways

- Opthea's OPT-302 combination therapy has the potential to improve visual acuity outcomes over standard of care in patients with PCV
- PCV is a subtype of wet AMD with variable response to current anti-VEGF therapy
- OPT-302 combination with ranibizumab achieved superior visual acuity gains and anatomical improvements compared to ranibizumab alone in PCV patients
- OPT-302 combination therapy safety profile is consistent with standard of care anti-VEGF-A therapy

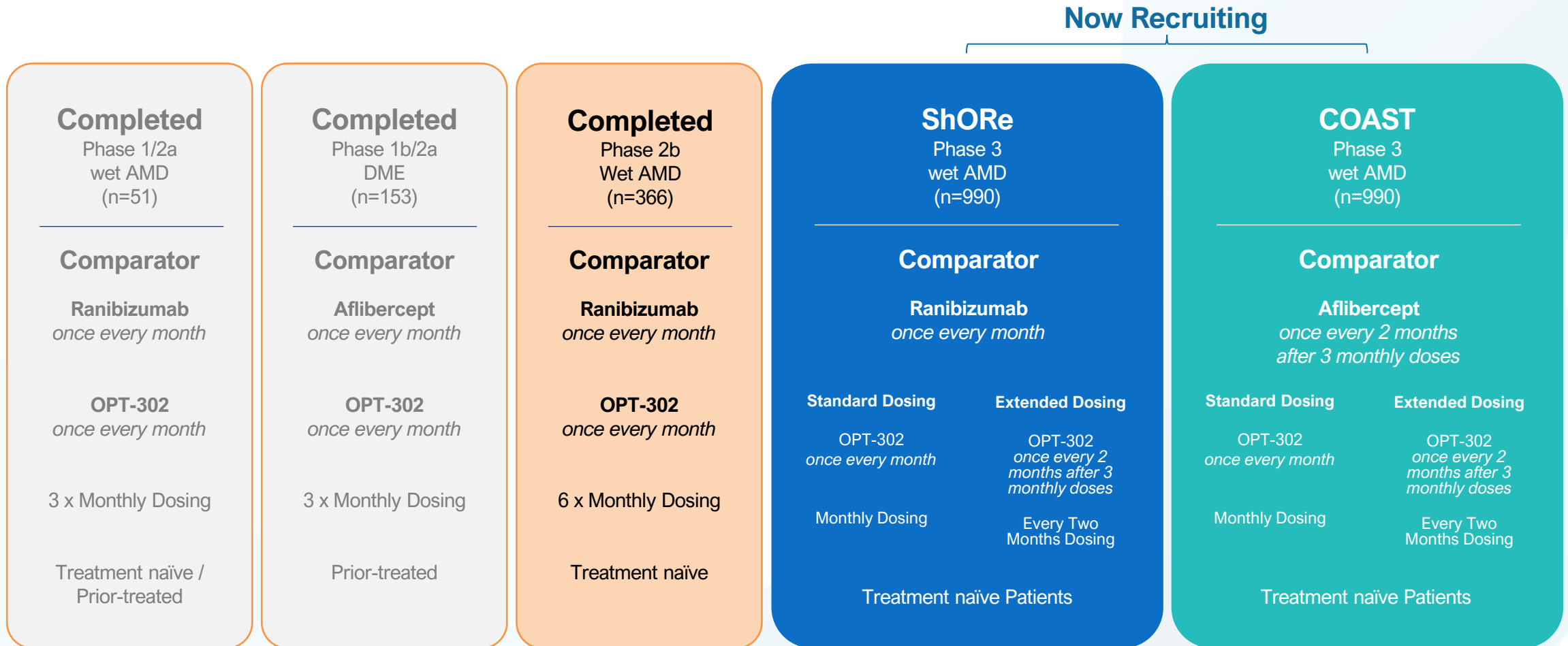
# OPT-302 Combination Therapy Enhances the Blockade of the Validated VEGF Pathways in wet AMD

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

# OPT-302 Combination Therapy – Clinical Program



# Polypoidal Choroidal Vasculopathy: Role of VEGF-C/-D

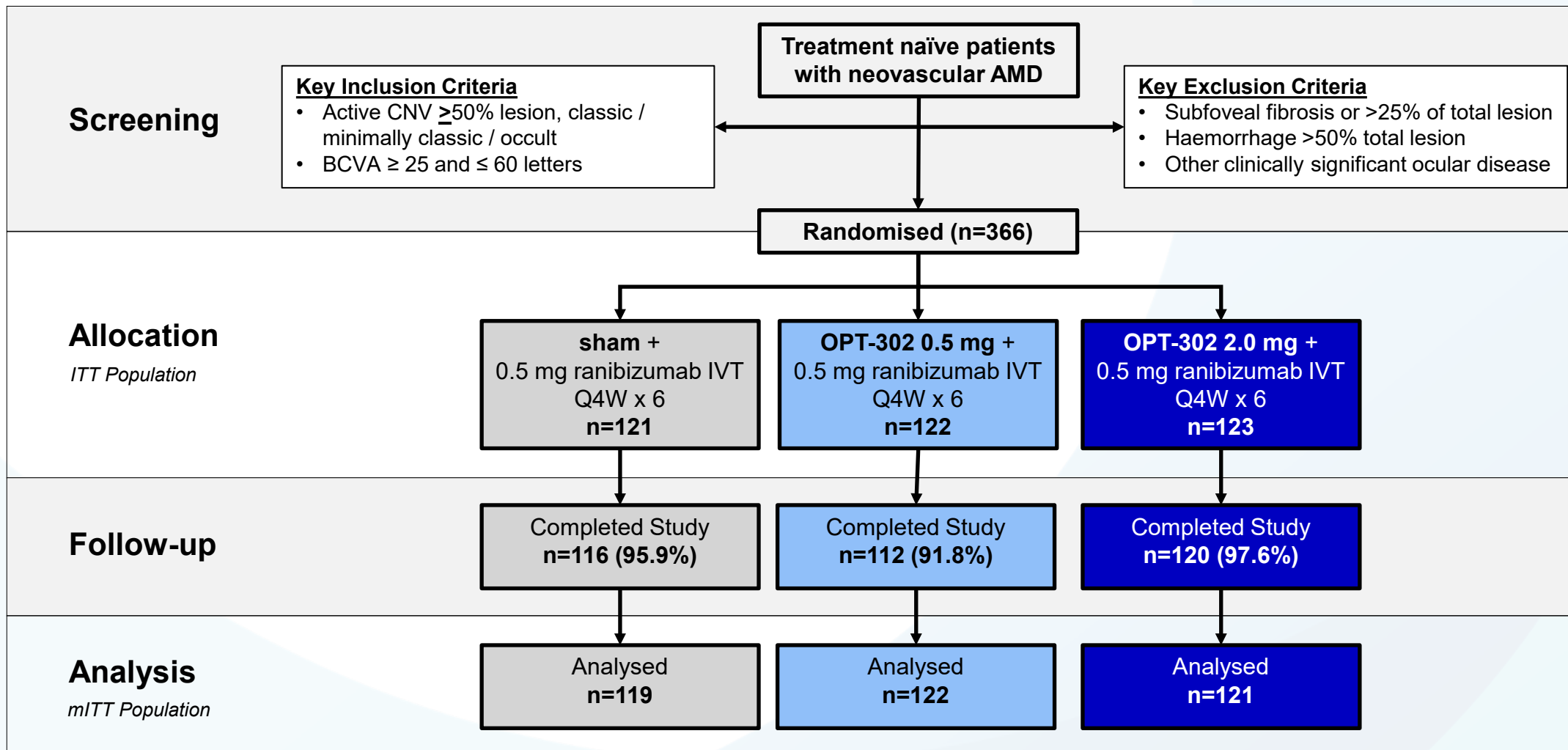
- **PCV is a common subtype of nAMD**
  - Distinct epidemiology, pathogenesis, natural history and treatment responses
- **PCV is more prevalent in the Asian population (up to 62%) than in the Caucasian population (8-13%)**
- **Role of VEGF-C/VEGF-D in wet AMD and PCV**
  - VEGF-C and VEGF-D are upregulated in response to VEGF-A suppression
  - Over-expression of VEGF-C disrupts retinal vasculature development and elevated levels are associated with wet AMD
  - Aqueous humor levels of VEGF-D are increased ~5 fold in PCV

Investigation of 34 cytokines in aqueous humor of treatment naïve patients show a > 5 fold increase in VEGF-D levels in nAMD and PCV compared to controls

Cytokine	nAMD (pg/mL)	PCV (pg/mL)	Control (pg/mL)	nAMD v control (p value)	PCV v control (p value)	nAMD v PCV (p value)
VEGF-D	242.49 ± 28.96	221.50 ± 96.24	43.66 ± 23.61	< 0.0001	< 0.0001	0.459
VEGF-A	175.71 ± 36.29	154.43 ± 87.56	38.69 ± 17.26	< 0.0001	< 0.0001	0.483
PIGF	0.28 ± 0.20	0.25 ± 0.14	0.26 ± 0.14	0.806	0.852	0.657
PDGF-BB	1.90 ± 0.77	1.68 ± 0.88	1.62 ± 0.90	0.426	0.845	0.482

Lashkari et al, 2013 ARVO Annual Meeting, 4999-A0128. Schepens Eye Research Institute, Department of Ophthalmology, Harvard Medical School  
 Zhou et al. BMC Ophthalmology (2020) 20:15

# Phase 2b Wet AMD Study Overview



CNV – choroidal neovascularisation; IVT – intravitreal; Q4W – once every 4 weeks

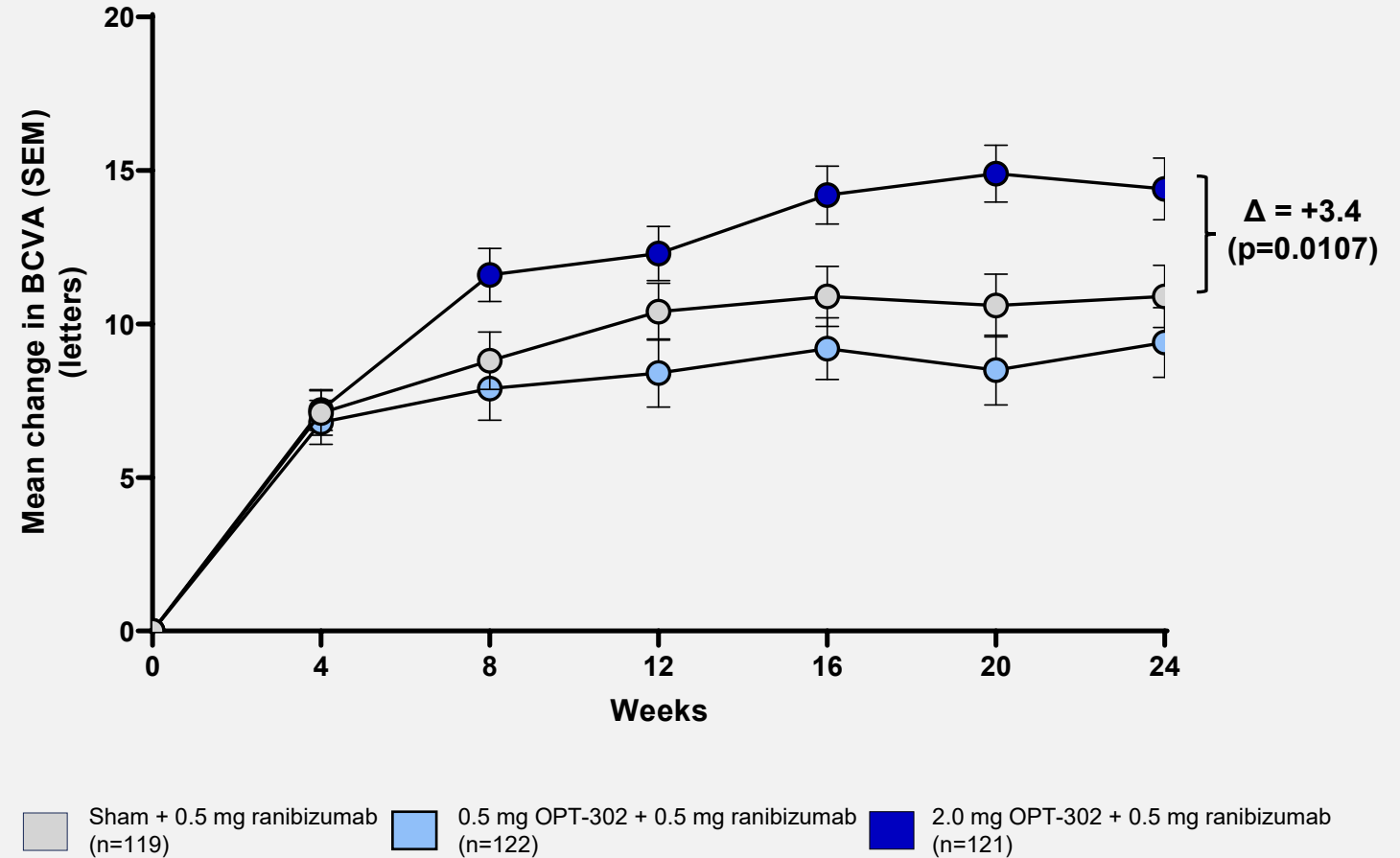
ITT – Intent to Treat Population, all participants who were randomised into the study irrespective of whether study medication was administered or not

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



## 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

OPT-302 (2.0 mg)  
 Combination Therapy:

# Superiority in Visual Acuity over Ranibizumab

Primary endpoint achieved

# 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 <sup>2</sup> ± SD		6.08 ± 3.21	6.48 ± 3.30	6.62 ± 3.39
FA subtype	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%)
Lesion Subtype	PCV detected <sup>1</sup> – n (%)	20 (16.5%)	24 (19.7%)	22 (17.9%)
	RAP detected <sup>2</sup> – 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

<sup>1</sup>PCV - polypoidal choroidal vasculopathy, detected by SD-OCT, FA and fundus photography

<sup>2</sup>RAP - retinal angiomatous proliferation, detected by SD-OCT, FA and fundus photography

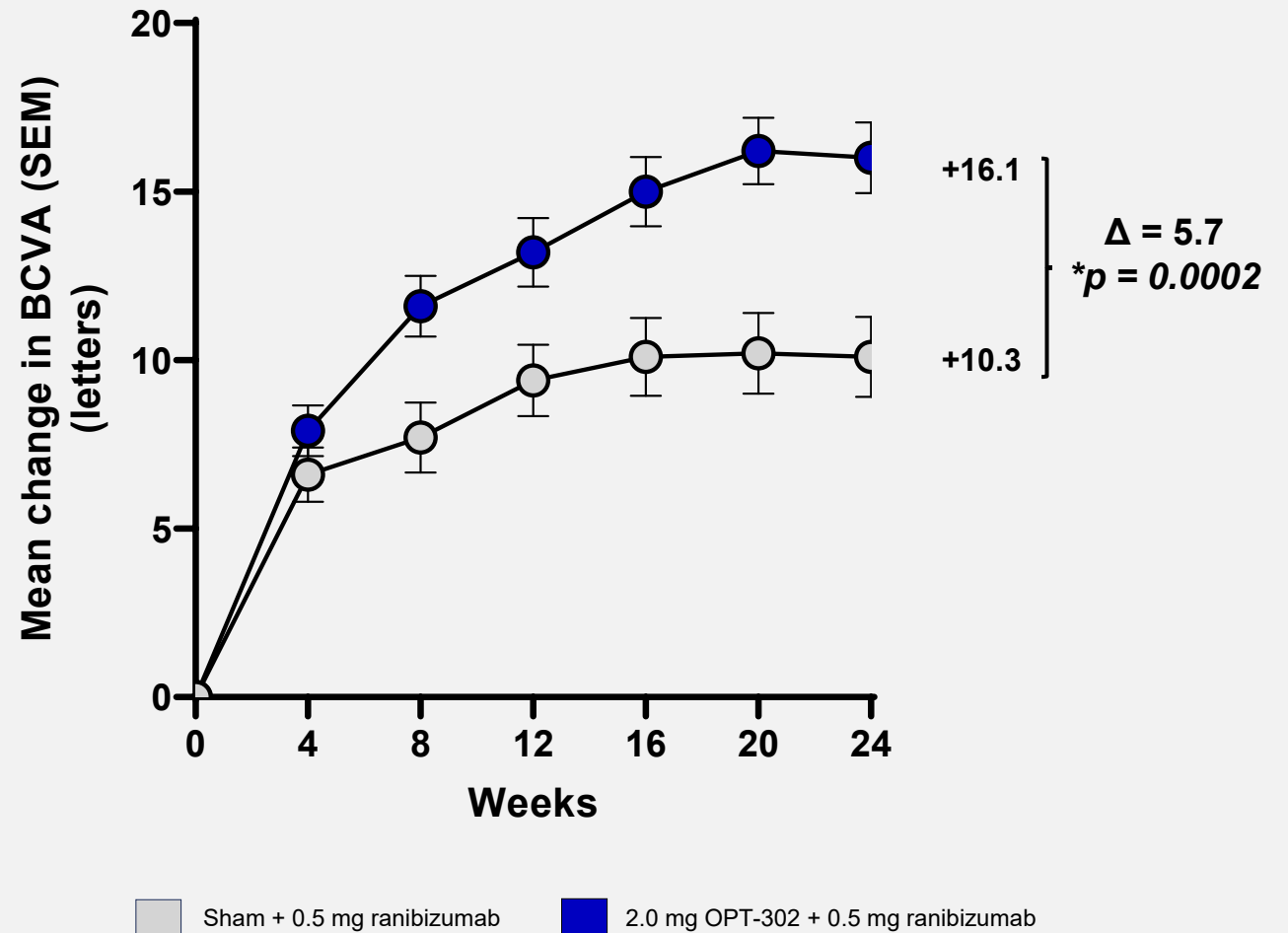
Best Responders:

# Minimally Classic & Occult lesions

Represents primary analysis population in OPT-302 phase 3 program

\* Unadjusted p-value;  
RAP absent patients

## Minimally Classic & Occult (>80% of study population)



# Pre-specified subgroup analysis of Phase 2b PCV Sub-Group

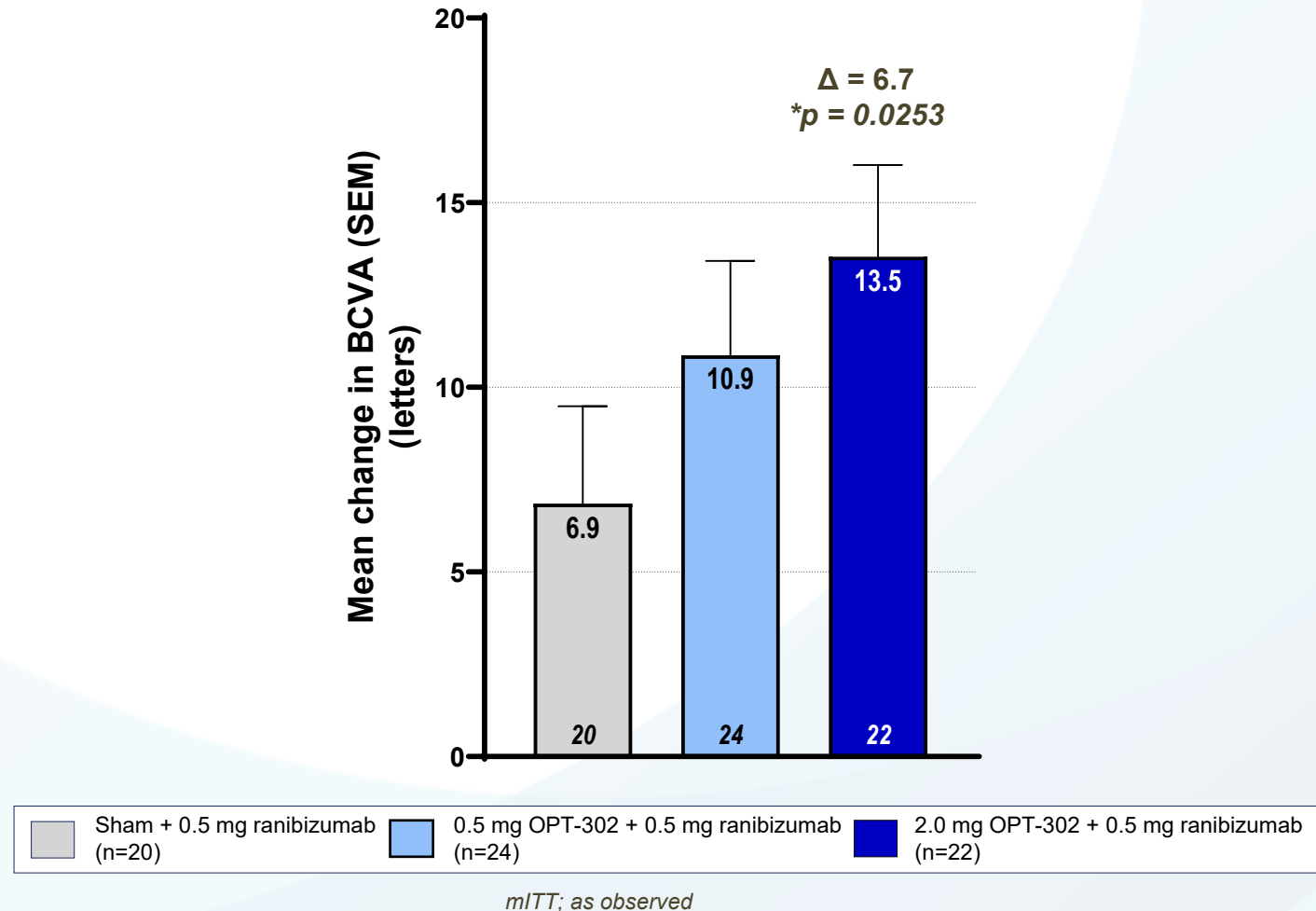
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- In the **Phase 2b clinical trial** PCV was detected in 18% of patients
  - Independent Reading Center (DARC, NY) grading of possible PCV lesions at baseline
    - Evaluated by color FP, FA and SD-OCT
    - *(note: ICGA was not used in the trial)*
  - **Polyps were presumed to be present by OCT**
    - **when notched, sharply peaked or multi-lobular PED were noted**
      - with or without a ring of hyperreflectivity along the inner border
  - FP and FA images were assessed to determine the degree of activity of the presumed polyps
    - specific attention paid to presence of subretinal orange nodules on FP and
    - appearance of multifocal lesions with typically primarily occult characteristics on FA

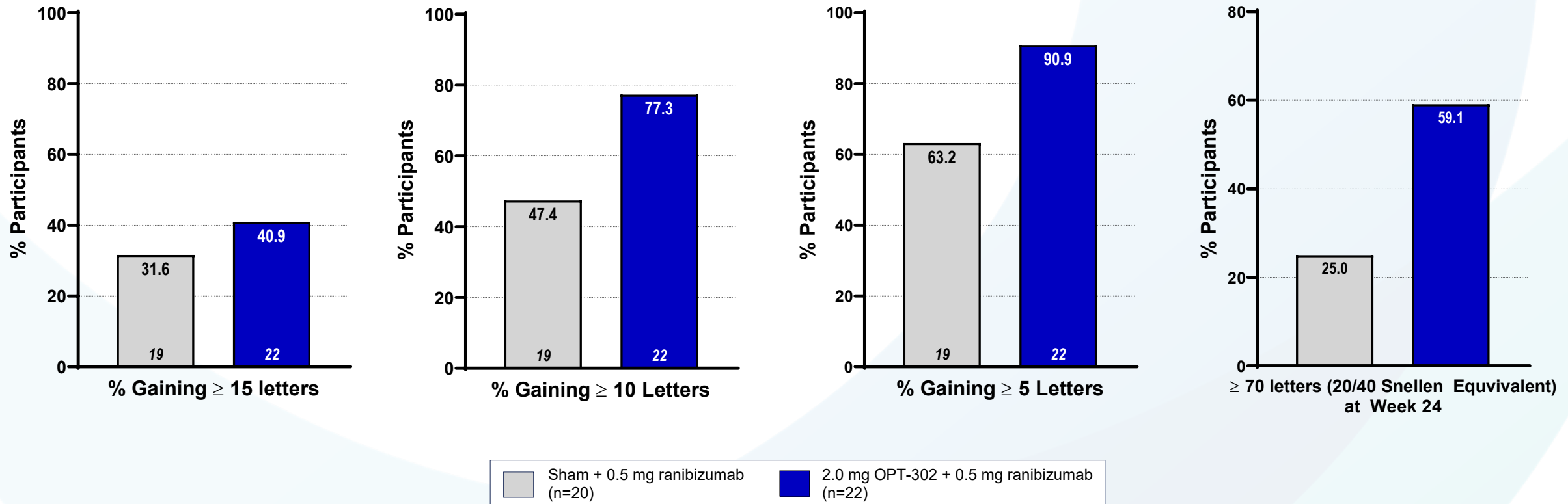
# PCV Baseline Disease Characteristics

Characteristic	0.5 mg ranibizumab + Sham N=20	0.5 mg ranibizumab + 0.5 mg OPT-302 N=24	0.5 mg ranibizumab + 2.0 mg OPT-302 N=22
<b>Vision</b>			
Mean visual acuity (VA) – letters (±SD)	52.5 (±9.51)	54.8 (±5.45)	54.7 (±6.02)
<b>Anatomic</b>			
Mean lesion area - mm <sup>2</sup> (±SD)	6.71 (±3.66)	6.19 (±2.46)	5.92 (±2.89)
Mean CNV Area - mm <sup>2</sup> (±SD)	6.24 (±2.65)	6.11 (±2.44)	5.90 (±2.93)
Mean % CNV of lesion (±SD)	96.8 (±9.6)	98.2 (±5.4)	99.0 (±4.8)
Lesion type			
Predominantly classic – n (%)	0 (0.0%)	1 (4.2%)	0 (0.0%)
Minimally classic – n (%)	9 (45.0%)	8 (33.3%)	13 (59.1%)
Occult - n (%)	11 (55.0%)	15 (62.5%)	9 (40.9%)
Mean central subfield thickness (CST) - μm (±SD)	407.20 (±144.76)	388.38 (±70.35)	436.09 (±132.61)
Subretinal fluid (SRF) – % pats	80.0%	83.3%	95.5%
Mean SRF thickness - μm (±SD)	112.7 (±59.4)	149.7 (±75.6)	143.4 (±88.6)
Intra-retinal cysts – % pats	40.0%	45.8%	40.9%

# Superior visual acuity at week 24 following OPT-302 combination therapy in patients with PCV

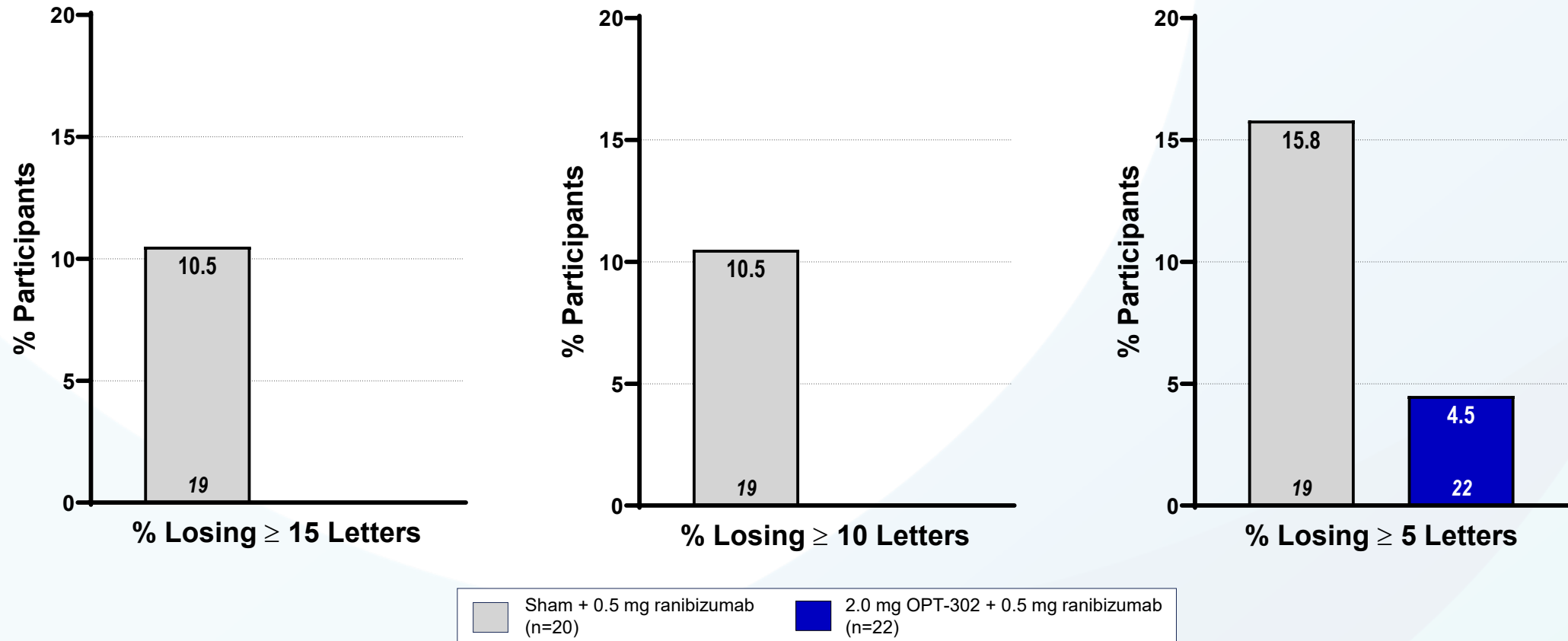


# Higher proportion of PCV patients receiving OPT-302 combination therapy in multiple categories of vision gain



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

# Fewer PCV patients receiving OPT-302 combination therapy lost vision

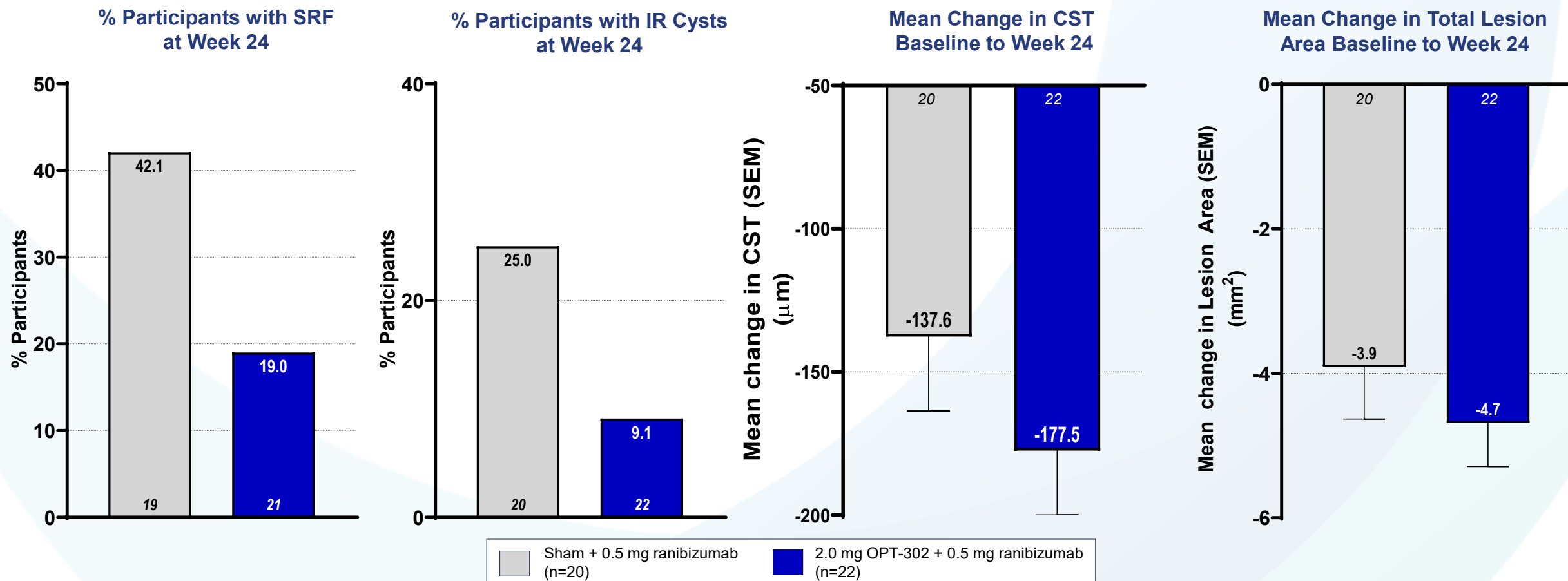


Modified Intent-to-Treat (mITT) population; as observed



# Greater anatomic improvements in PCV patients following OPT-302 combination therapy

Greater reductions in retinal fluid and lesion area



MITT; as observed; SRF: Sub-retinal Fluid; IR: Intra-retinal; CST: Central Subfield Thickness

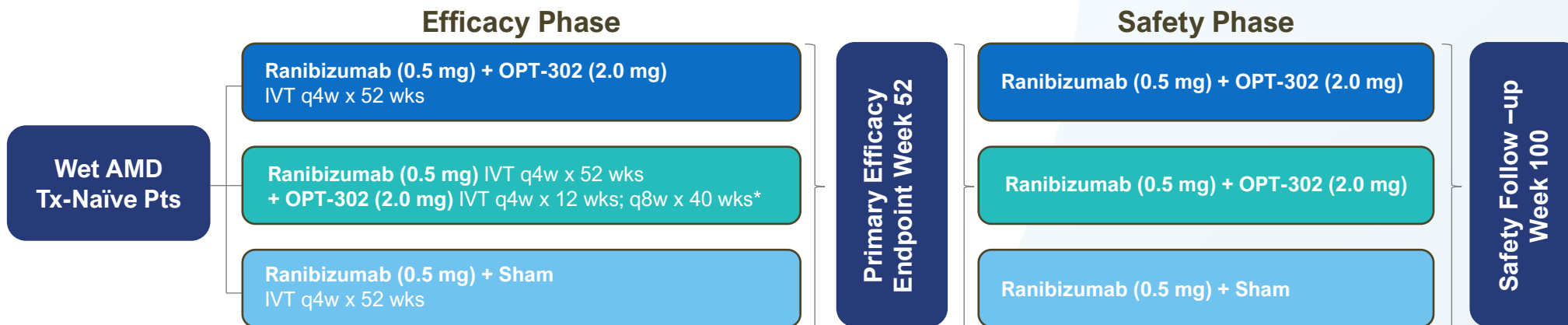
# Key Take-Aways

- OPT-302 combination therapy has the potential to improve visual acuity outcomes over standard of care in patients with PCV
- Following OPT-302 combination therapy in PCV patients:
  - Additional **+6.7 letter gain** ( $p=0.025$ )\* over ranibizumab alone
  - Greater proportion of patients gained  $\geq 15$ ,  $\geq 10$  or  $\geq 5$  letters
  - More patients achieved 20/40 or better vision
  - Fewer patients lost  $\geq 5$  letters
  - Improved anatomic measures observed, including less fluid and decreases in CST and total lesion area
- OPT-302 combination therapy safety profile is consistent with standard of care anti-VEGF-A therapy
- Further studies of dual inhibition of VEGF-C/-D and VEGF-A for the treatment of PCV are warranted
  - Generate PCV-specific data in Asian population
  - Additional data on treatment naïve patients with PCV lesions will be obtained from the ongoing OPT-302 Phase 3 ShORe and COAST trials

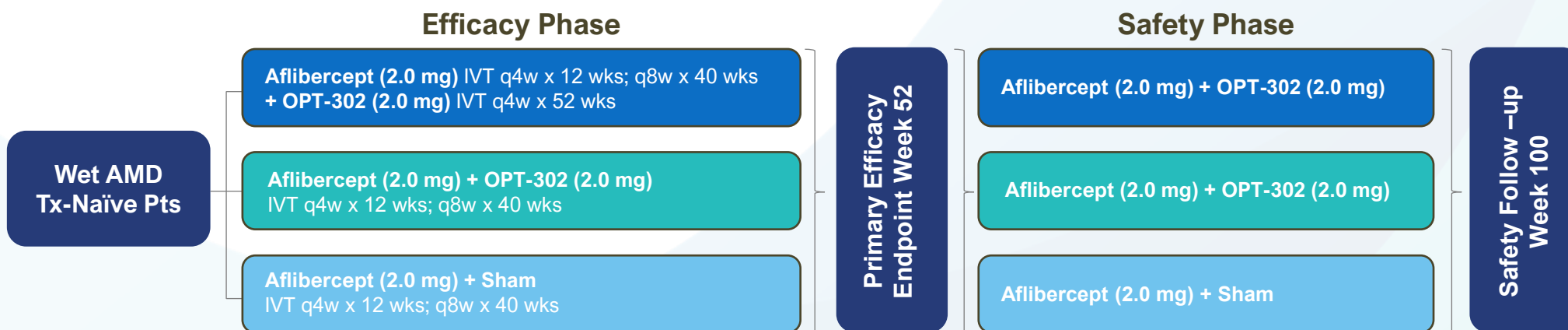
# OPT-302 Phase 3 Pivotal Program

Opthea intends to submit Biologics License and Marketing Authorization Applications with the FDA and EMA, respectively, following Primary Efficacy Phase of the trials

**ShORe**  
Study of OPT-302 in combination with Ranibizumab



**COAST**  
Combination OPT-302 with Aflibercept Study



• **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

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