OPT-302 Combination Therapy in Polypoidal Choroidal Vasculopathy

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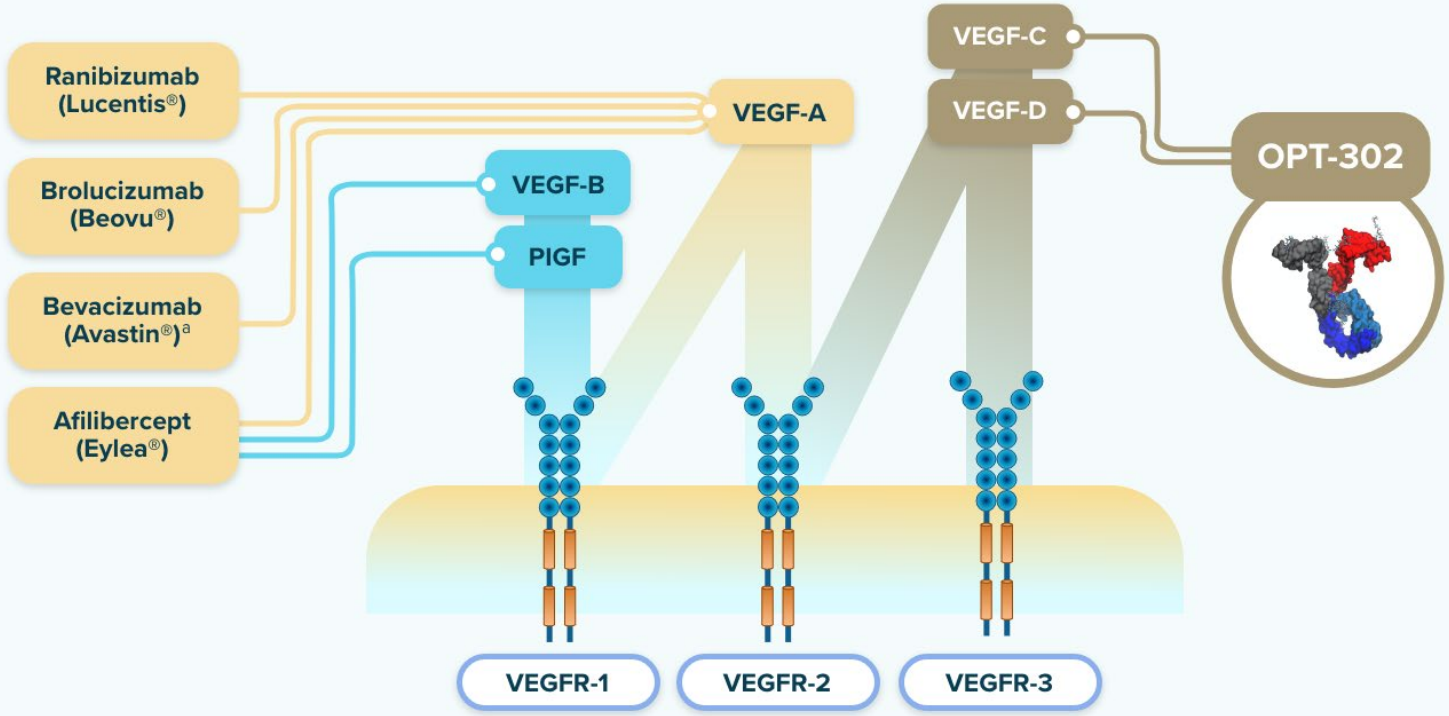
Key Take-Aways

- 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

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 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

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

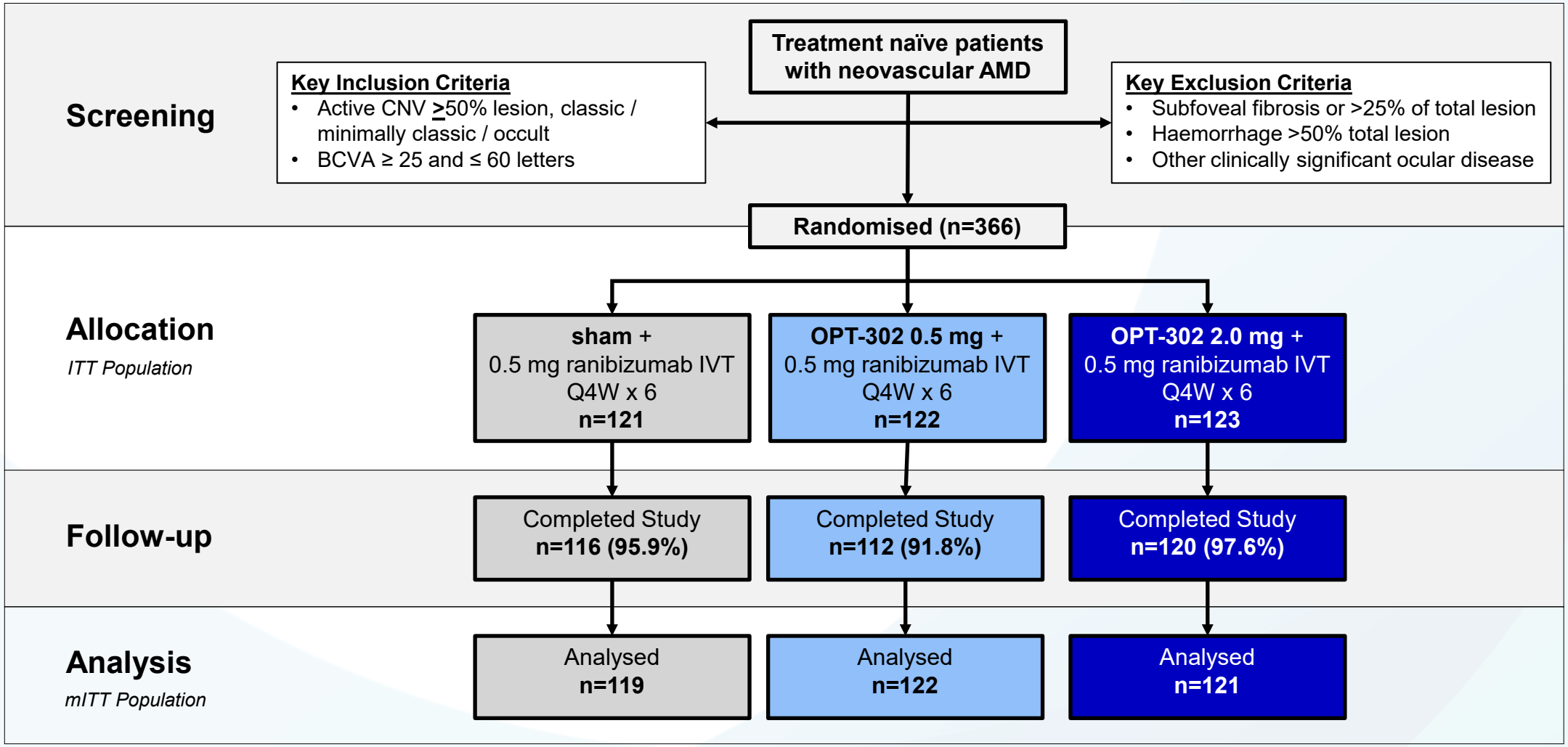
- **PCV is a common subtype of nAMD**
  - Distinct epidemiology, pathogenesis, natural history and treatment responses
- **PCV is more prevalent in the Asian population (up to 62%) than in the Caucasian population (8-13%)**
- **Role of VEGF-C/VEGF-D in wet AMD and PCV**
  - VEGF-C and VEGF-D are upregulated 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
PlGF	*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



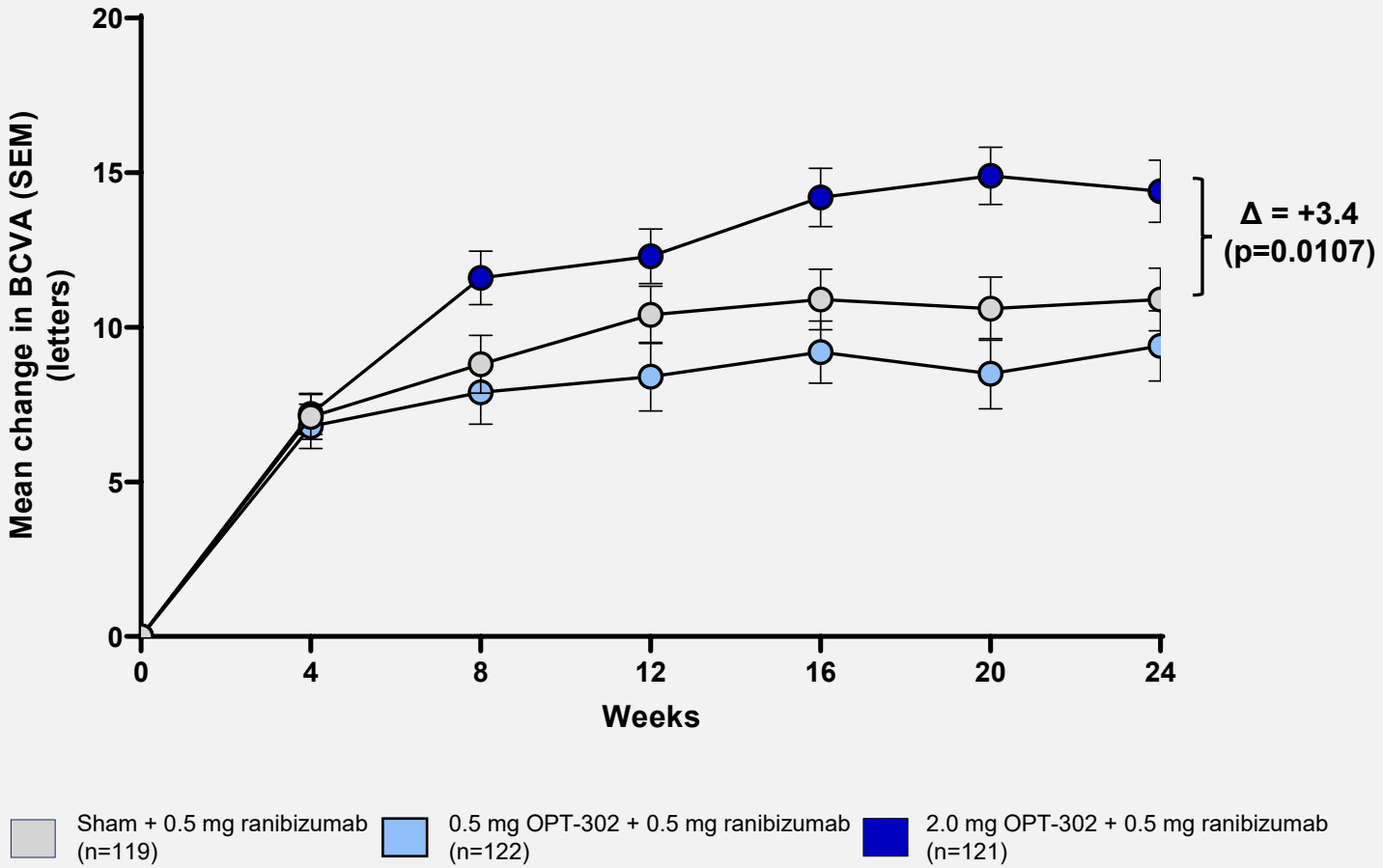
CNV – choroidal neovascularisation; IVT – intravitreal; Q4W – once very 4 weeks
ITT – Intent to Treat Population, all participants who were randomised into the study irrespective of whether study medication was administered or not
Safety Population - all participants in the ITT but excluding those who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

Study Demographics and Baseline Characteristics

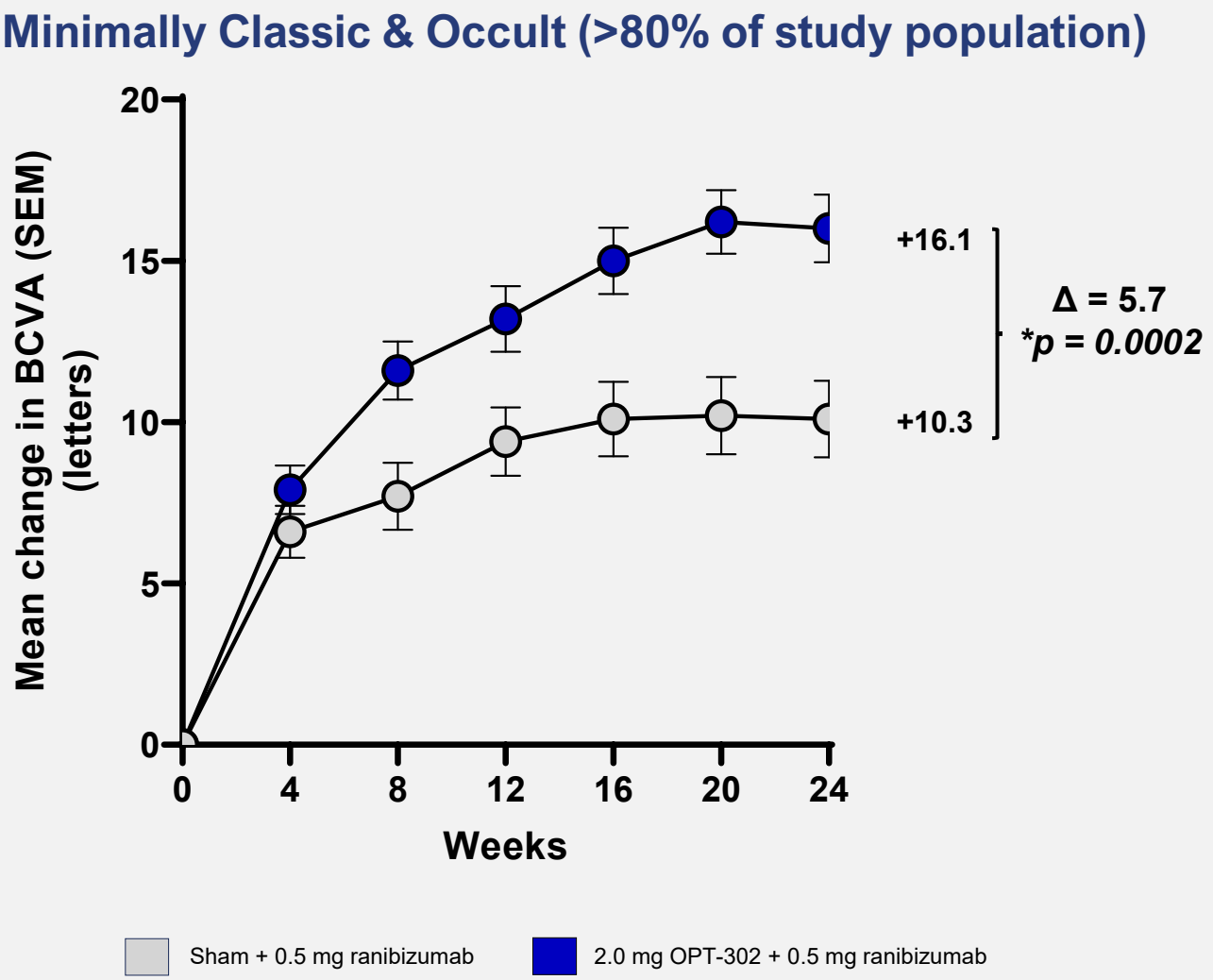
Demographic / Baseline Disease Characteristic		Sham + ranibizumab N=121	0.5 mg OPT-302 + ranibizumab N=122	2.0 mg OPT-302 + ranibizumab N=123
Mean Age – years ± SD		76.1 ± 9.48	78.8 ± 8.16	77.8 ± 8.82
Sex – n (%)	Male	48 (39.7%)	49 (40.2%)	45 (36.6%)
	Female	73 (60.3%)	73 (59.8%)	78 (63.4%)
Caucasian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

Best Responders:

Minimally Classic & Occult lesions

Represents primary analysis population in OPT-302 phase 3 program



** Unadjusted p-value; RAP absent patients*

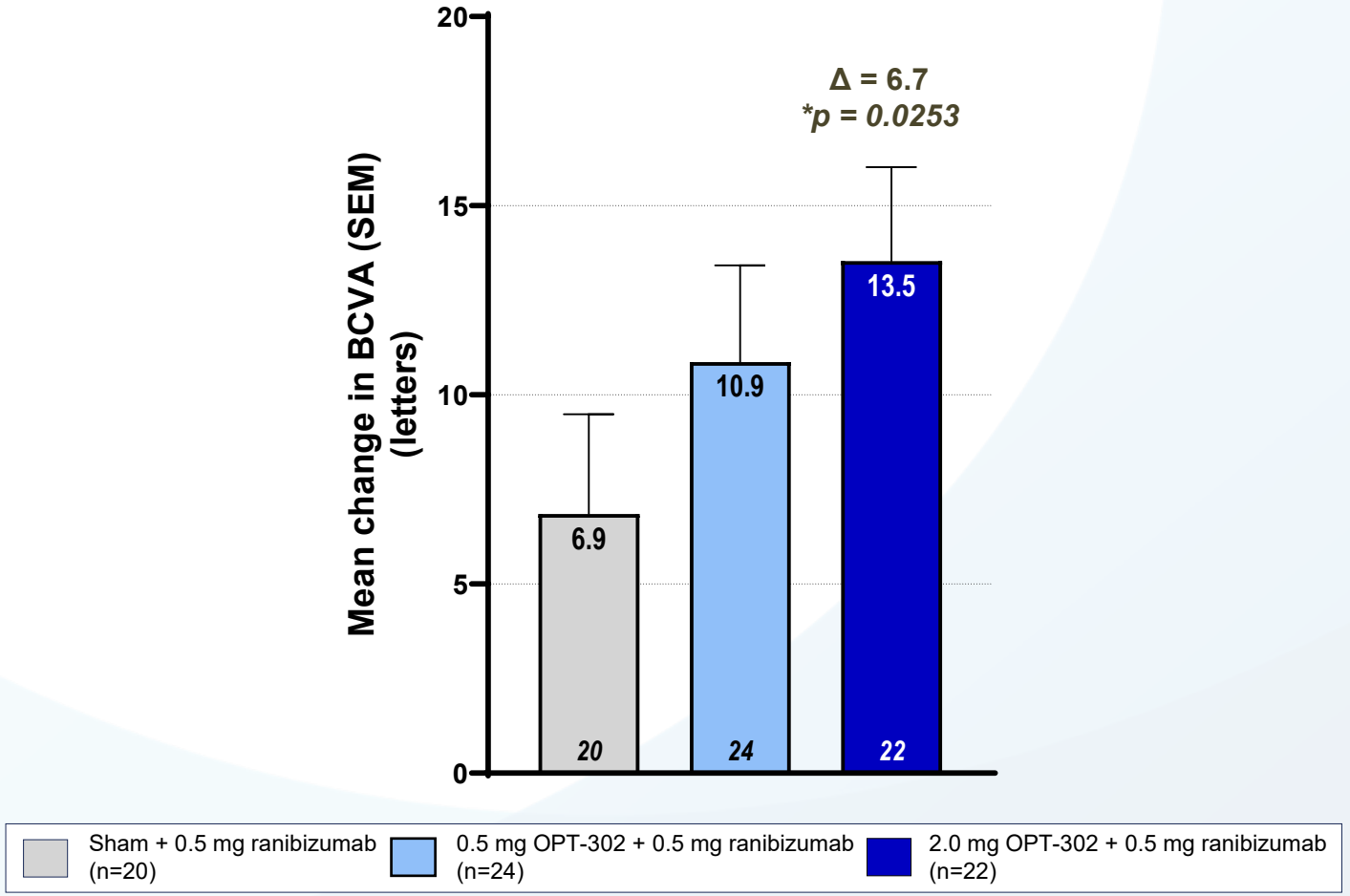
Pre-specified subgroup analysis of Phase 2b PCV Sub-Group

- 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

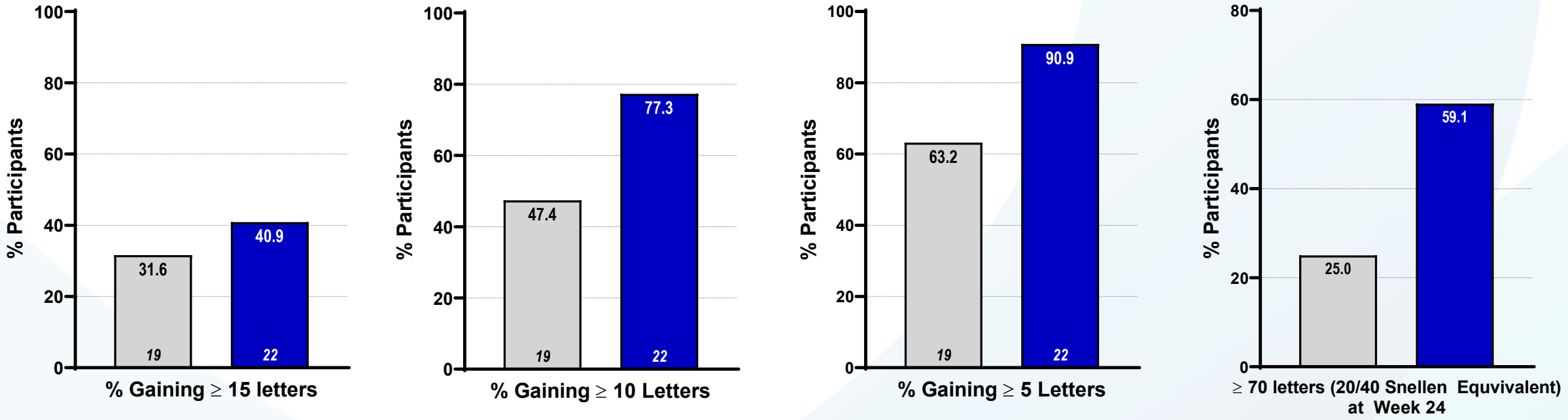
Characteristic	0.5 mg ranibizumab + Sham N=20	0.5 mg ranibizumab + 0.5 mg OPT-302 N=24	0.5 mg ranibizumab + 2.0 mg OPT-302 N=22
Vision			
Mean visual acuity (VA) – letters (±SD)	52.5 (±9.51)	54.8 (±5.45)	54.7 (±6.02)
Anatomic			
Mean lesion area - mm^2 (±SD)	6.71 (±3.66)	6.19 (±2.46)	5.92 (±2.89)
Mean CNV Area - mm^2 (±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



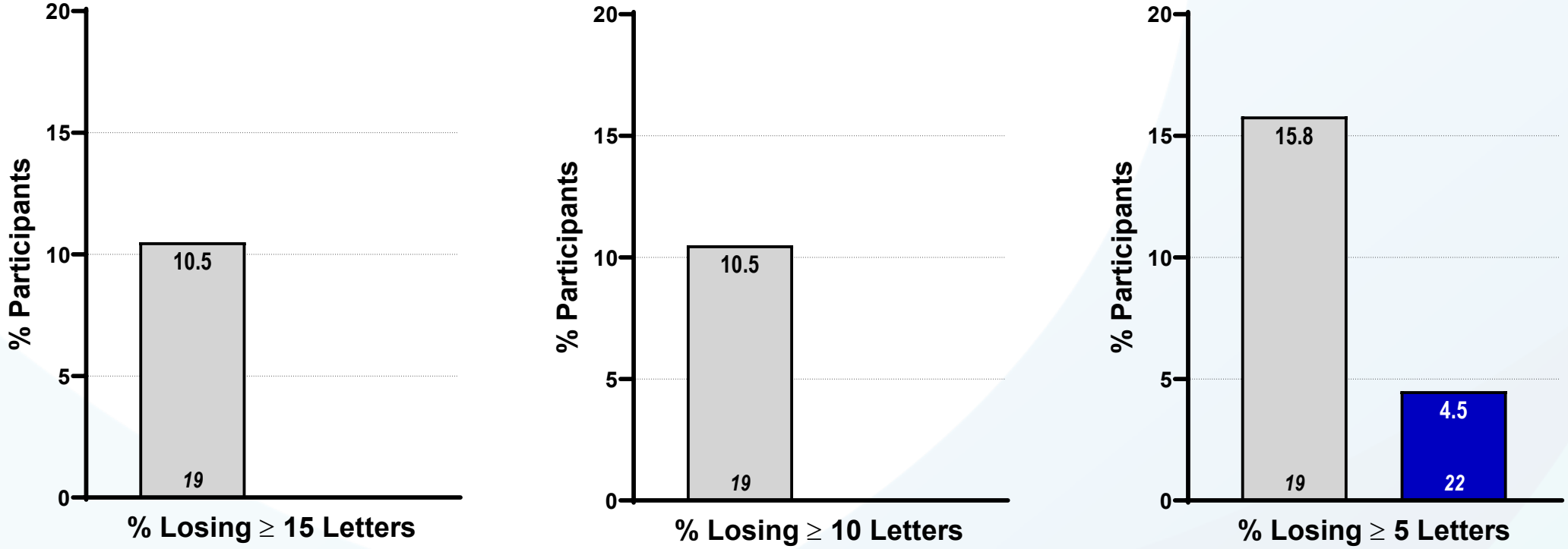
mITT; as observed

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



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

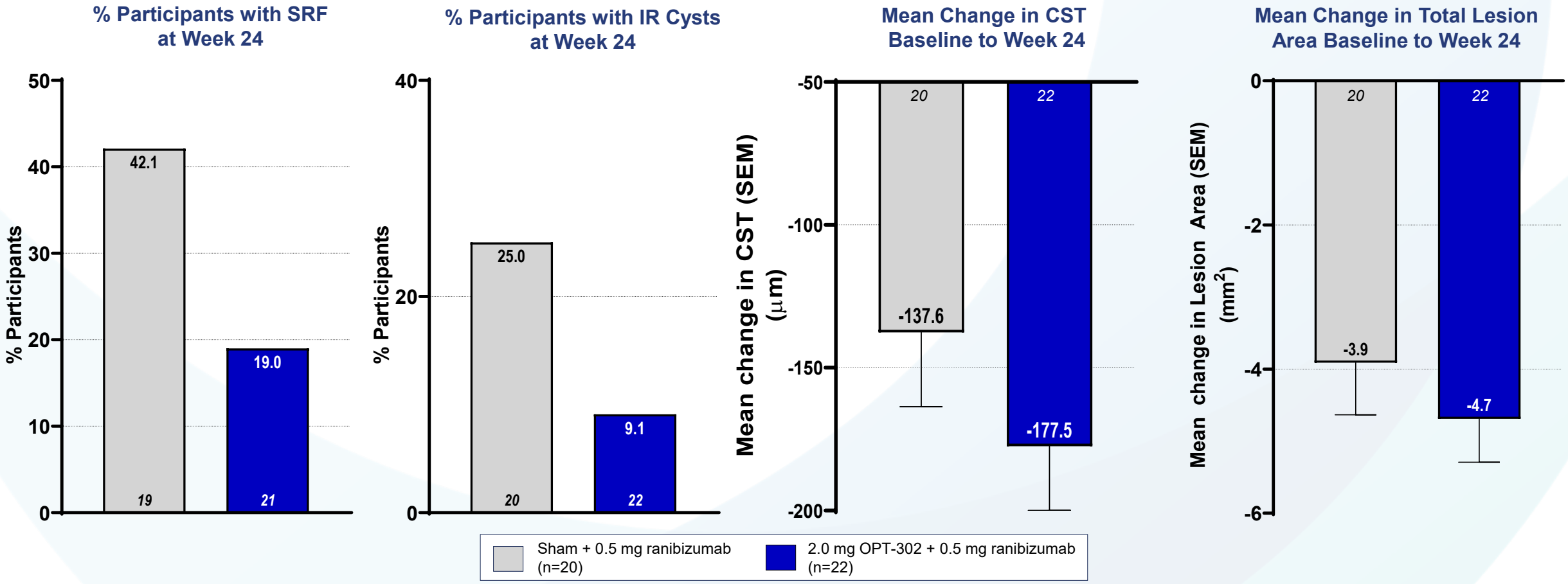
Fewer PCV patients receiving OPT-302 combination therapy lost vision



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



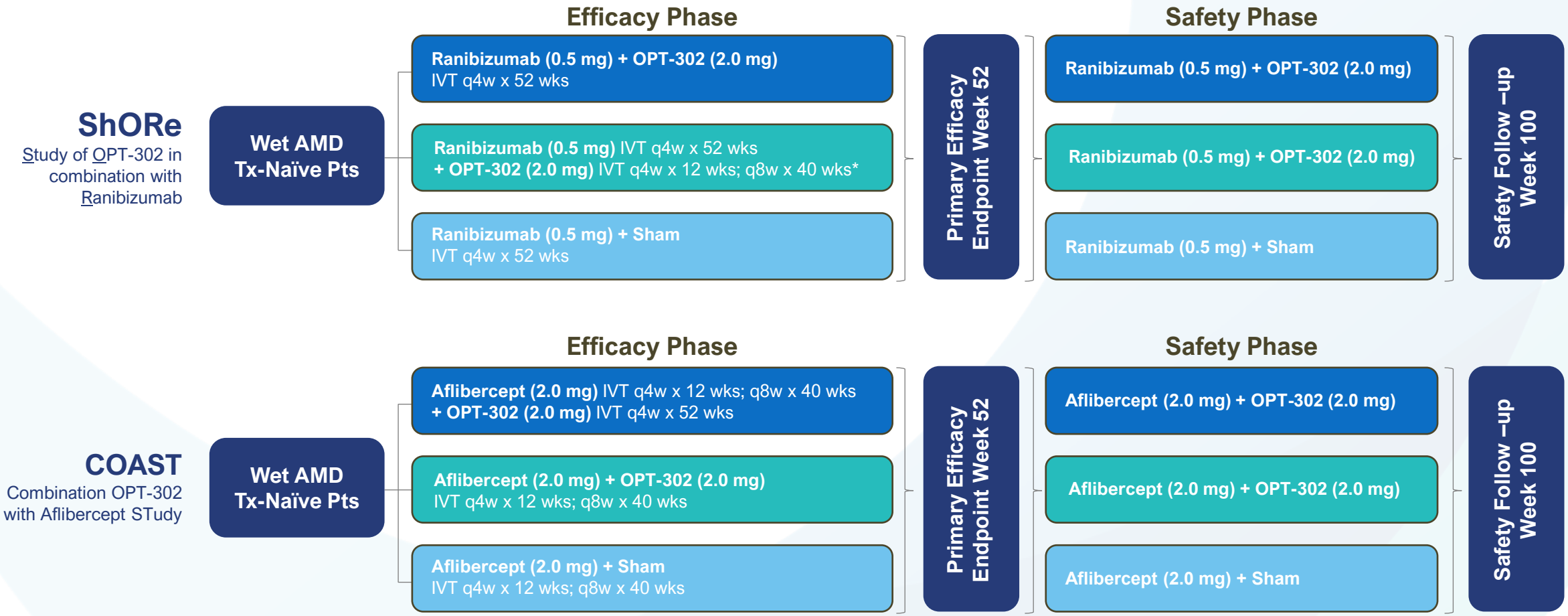
mITT; as observed; SRF: Sub-retinal Fluid; IR: Intra-retinal; CST: Central Subfield Thickness

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 ≥ 15, ≥ 10 or ≥ 5 letters
  - More patients achieved 20/40 or better vision
  - Fewer patients lost ≥ 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



- **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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