Phase 2b Clinical Results of OPT-302 (VEGF-C/D ‘Trap’) Combination Treatment in nAMD

Ophthalmology Innovation Summit @ American Academy Ophthalmology (OIS@AAO)

Megan Baldwin PhD, CEO & Managing Director

October 10 2019

Forward-Looking Statements

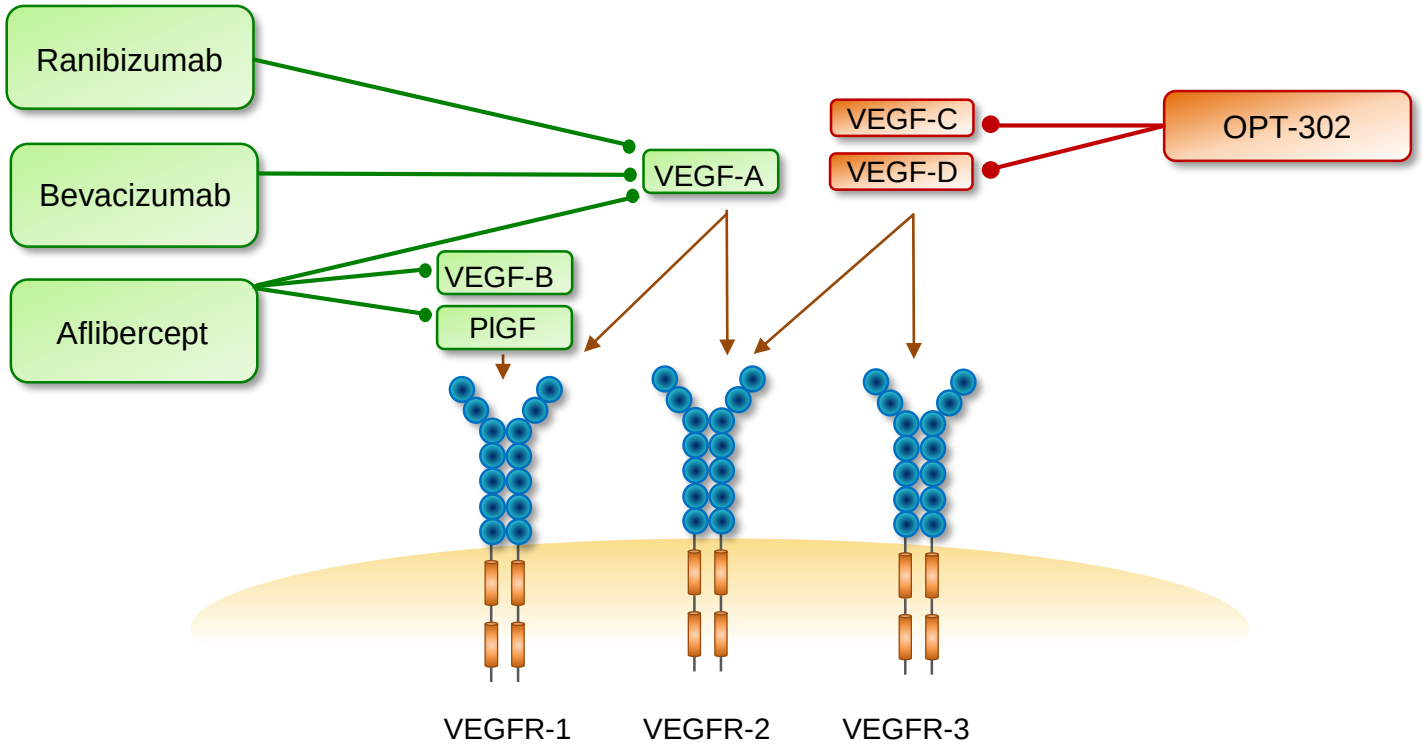
Investment in Opthea Limited ('Opthea') is subject to investment risk, including possible loss of income and capital invested. Neither Opthea nor any other member company of the Opthea Group guarantees any particular rate of return or performance, nor do they guarantee the repayment of capital.

This presentation is not an offer or invitation for subscription or purchase of or a recommendation of securities. It does not take into account the investment objectives, financial situation and particular needs of the investor. Before making any investment in Opthea, the investor or prospective investor should consider whether such an investment is appropriate to their particular investment needs, objectives and financial circumstances and consult an investment advisor if necessary.

This presentation may contain forward-looking statements regarding the potential of the Company's projects and interests and the development and therapeutic potential of the company's research and development. Any statement describing a goal, expectation, intention or belief of the company is a forward-looking statement and should be considered an at-risk statement. Such statements are subject to certain risks and uncertainties, particularly those inherent in the process of discovering, developing and commercialising drugs that are safe and effective for use as human therapeutics and the financing of such activities. There is no guarantee that the Company's research and development projects and interests (where applicable) will receive regulatory approvals or prove to be commercially successful in the future. Actual results of further research could differ from those projected or detailed in this presentation. As a result, you are cautioned not to rely on forward-looking statements. Consideration should be given to these and other risks concerning research and development programs referred to in this presentation.

OPTHEA

OPT-302 Inhibits VEGF-C and VEGF-D

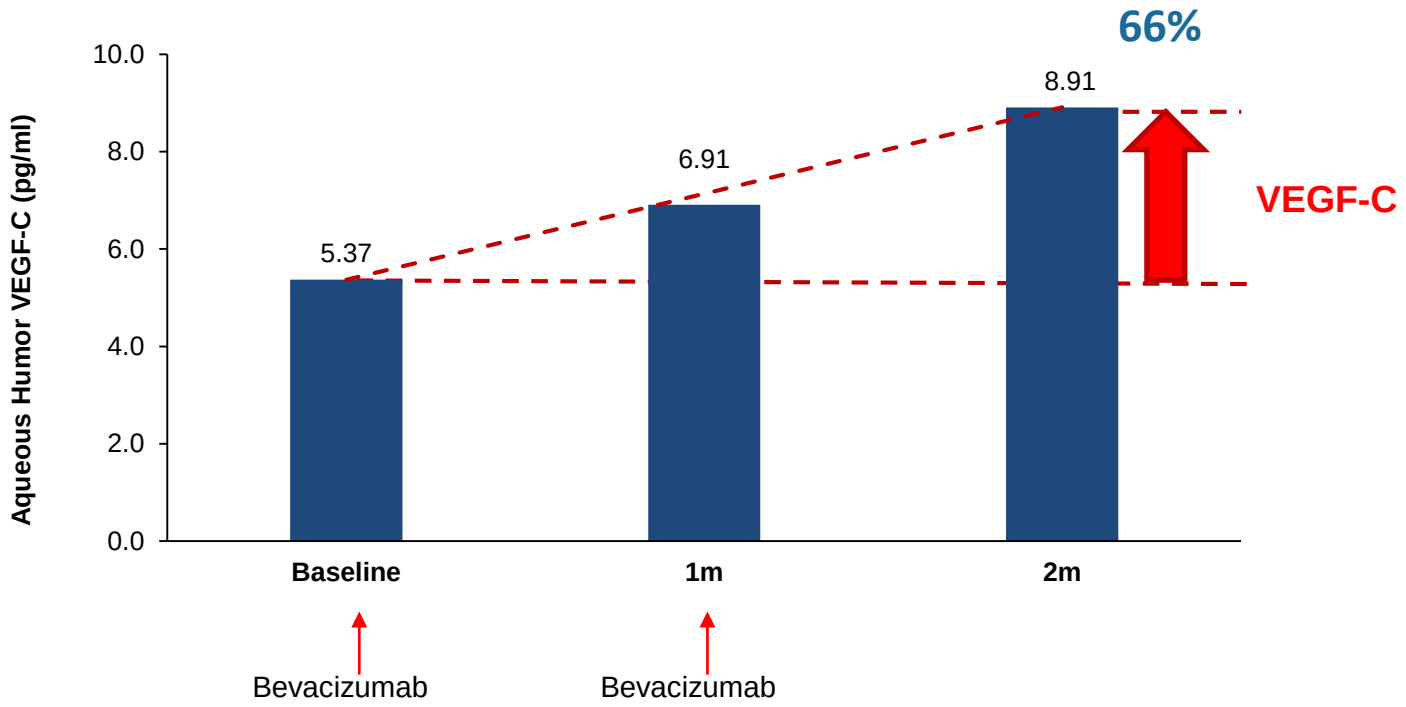


OPT-302 ‘trap’ blocks VEGF-C and VEGF-D binding to VEGFR-2 and VEGFR-3 receptors

OPTHEA

VEGF-A Inhibition Upregulates VEGF-C/D

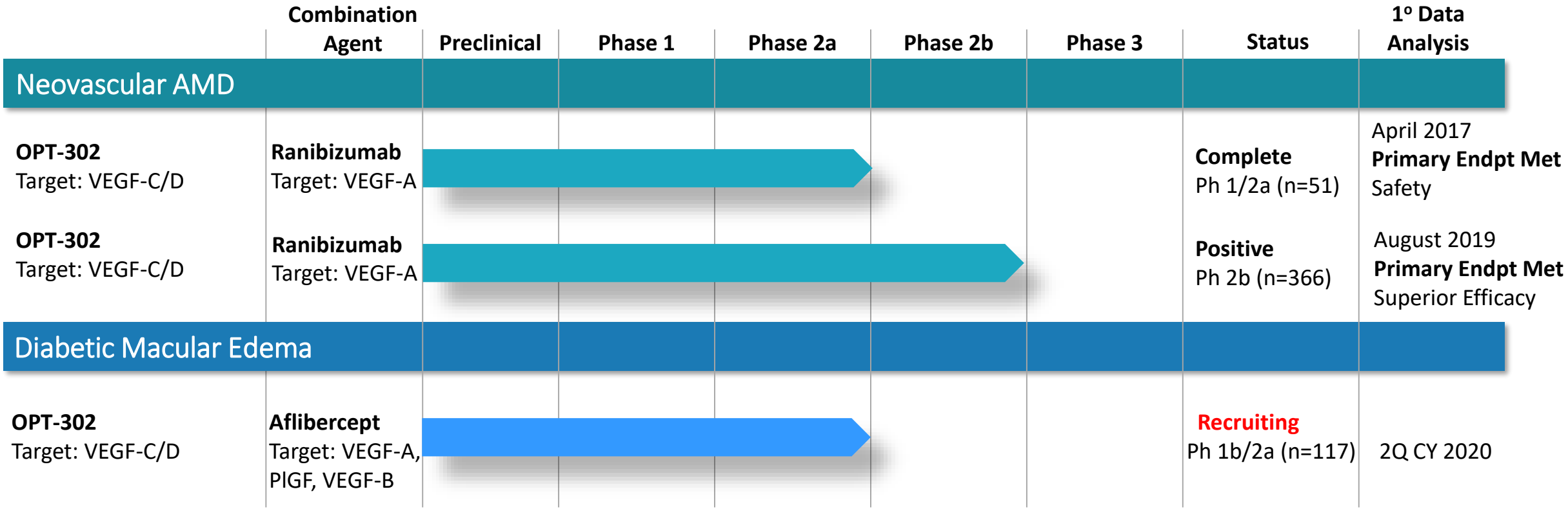
Upregulation in Neovascular AMD [1]



1 *"Bevacizumab injection in patients with neovascular age-related macular degeneration increases angiogenic biomarkers." Cabral T. et al., Ophthalmology Retina 2018;2(1): 31-37, 2018.*

OPTHEA

OPT-302 Clinical Program



OPTHEA

Phase 2b

A multicenter, randomized, double-masked, sham controlled study of intravitreal OPT-302 in combination with ranibizumab, in participants with neovascular (wet) AMD

Conducted at 113 sites across 10 countries: US, EU, Israel

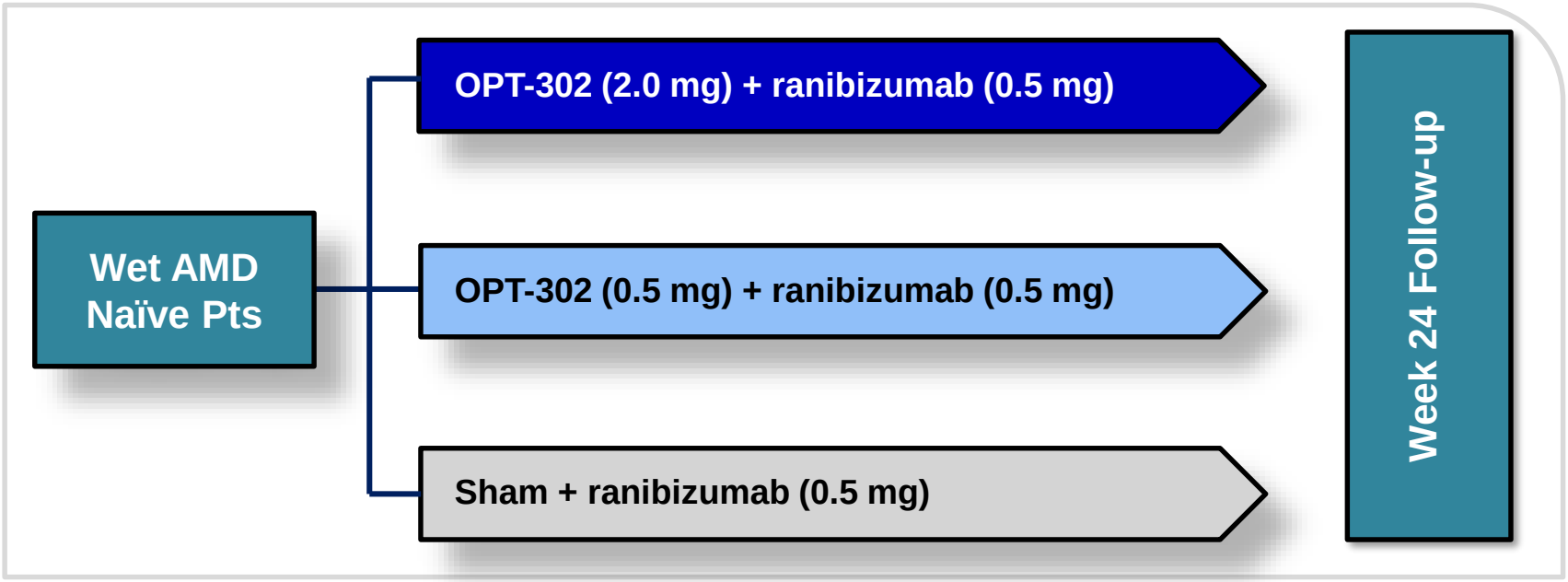
OPT-302-1002; NCT ClinicalTrials.gov Identifier: NCT03345082

OPTHEA

OPT-302 Phase 2b wAMD

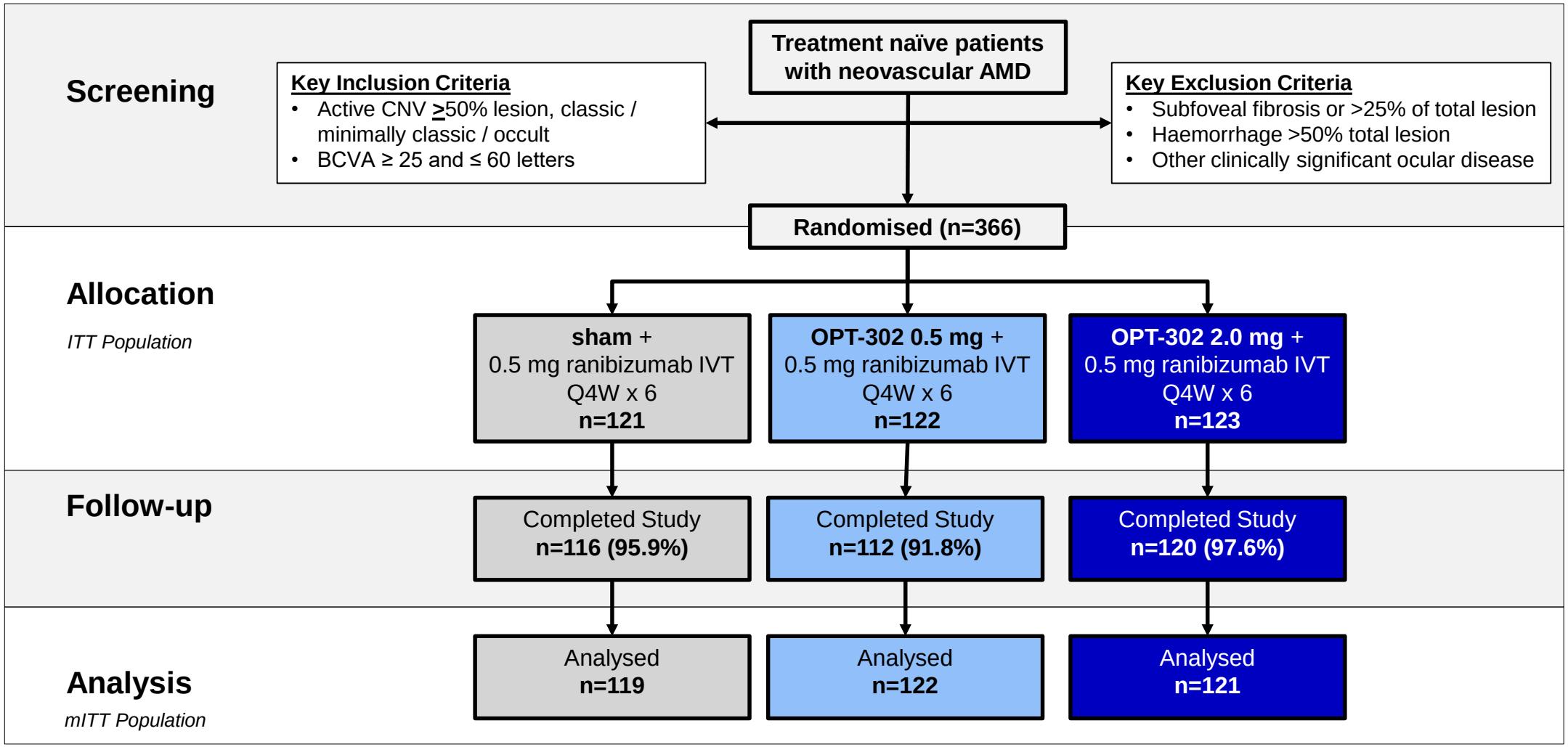
ClinicalTrials.gov Identifier: NCT03345082

Randomised 1:1:1 to treatment arms : intravitreal dosing every 4 weeks (x 6)



OPTHEA

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

Study Outcome Measures

Primary Outcome:

- Mean change from Baseline in ETDRS best corrected visual acuity at Week 24

Key Secondary Outcomes at Week 24:

- Patients gaining ≥15 or more ETDRS letters
- Patients losing ≥15 or more ETDRS letters
- Change in central subfield thickness (SD-OCT)
- Change in subretinal fluid and intraretinal fluid (SD-OCT)

Key Exploratory Outcomes at Week 24:

- Change in total lesion area and choroidal neovascularisation (CNV) area

Key Pre-Specified Subgroup Analyses:

- Polypoidal Choroidal Vasculopathy (PCV)
- Lesion type
- Retinal angiomatous proliferation (RAP)

Key Safety Outcome:

- Safety and tolerability

OPTHEA

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
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%

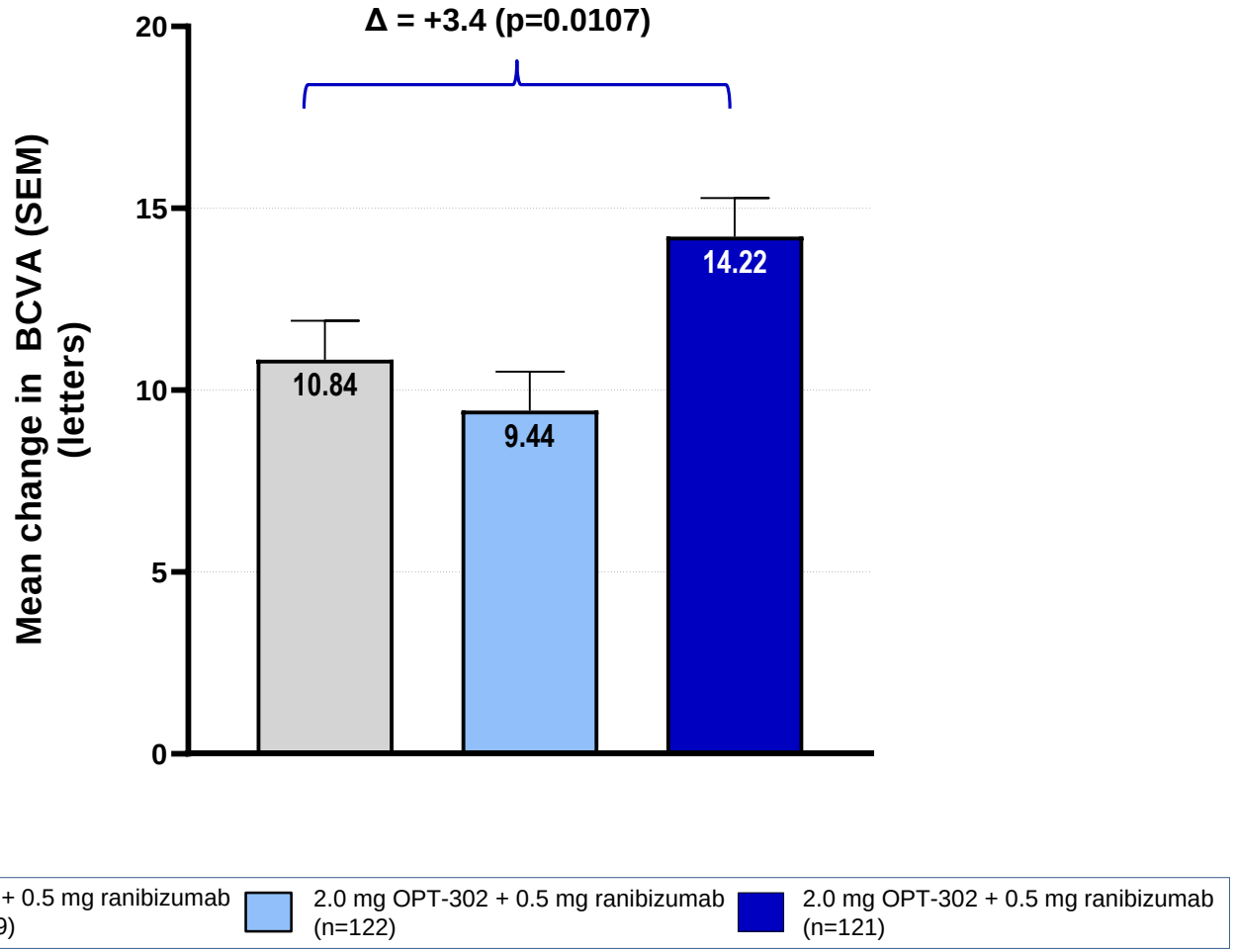
Intent-to-Treat (ITT) population; SD: standard deviation; BCVA: Best Corrected Visual Acuity
[1]PCV - polypoidal choroidal vasculopathy, detected by SD-OCT, FA and fundus photography
[2]RAP - retinal angiomatous proliferation, detected by SD-OCT, FA and fundus photography

OPTHEA

Primary Analysis – Mean Change in BCVA Baseline to Week 24

Primary endpoint achieved

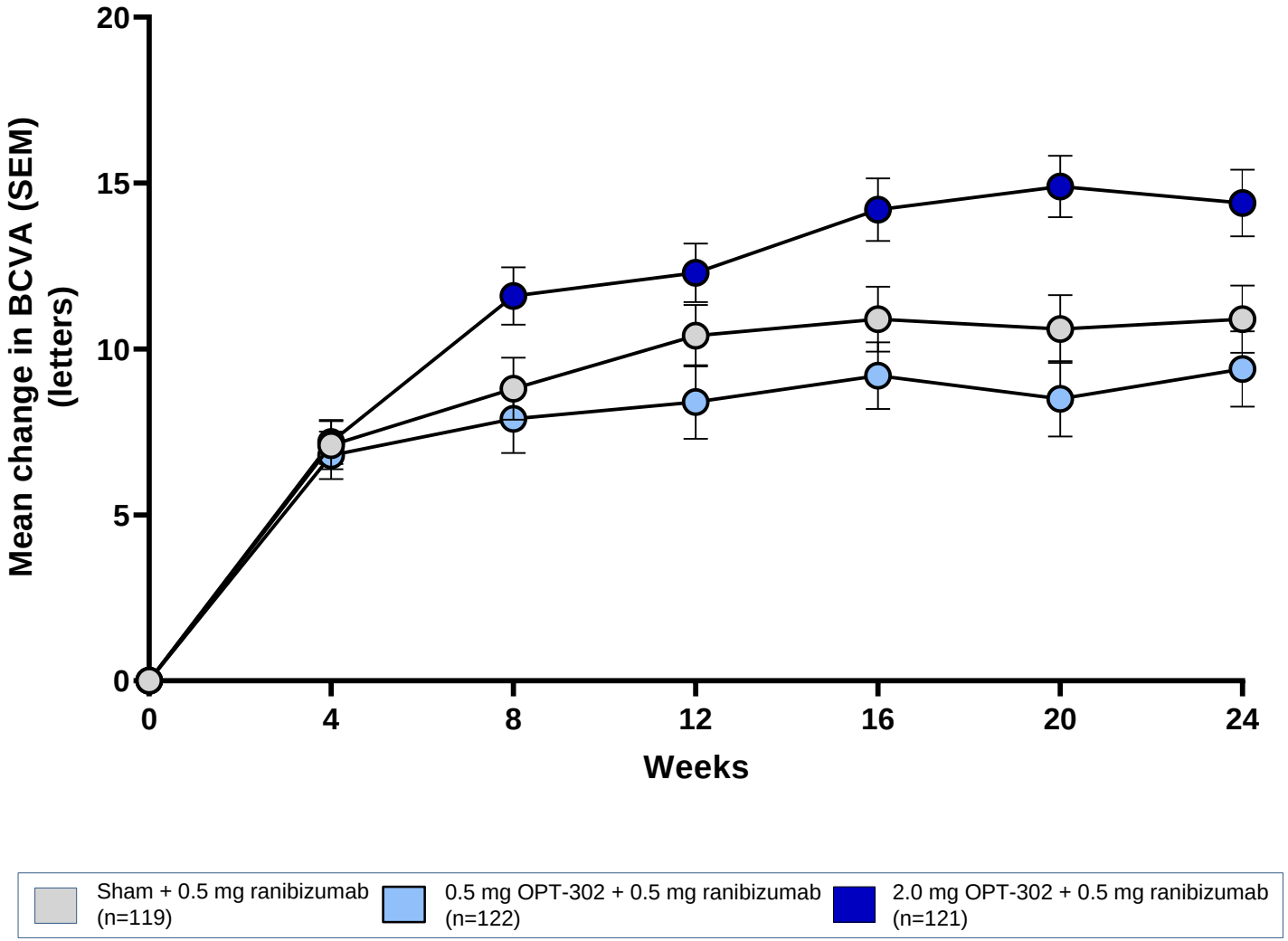
OPT-302 (2.0 mg) Combination Therapy Demonstrated Superiority in Visual Acuity over Ranibizumab



mITT; BCVA – best corrected visual acuity
Difference in Least Square Means, using Model for Repeated Measures (MRM) analysis

Mean Change in BCVA Over Time

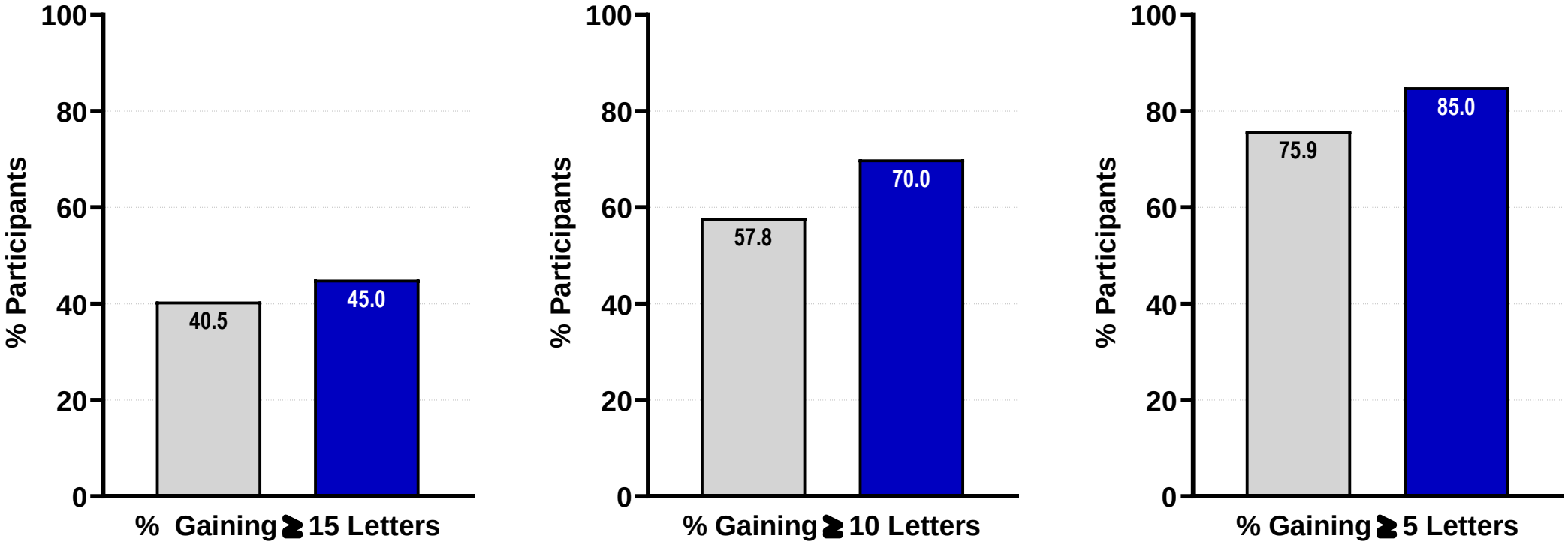
Additive visual acuity benefit of OPT-302 evident from 8-weeks



Modified Intent-to-Treat (mITT) population; BCVA – Best Corrected Visual Acuity; graph represents "as observed" data and SEM

Vision Gain - Baseline to Week 24

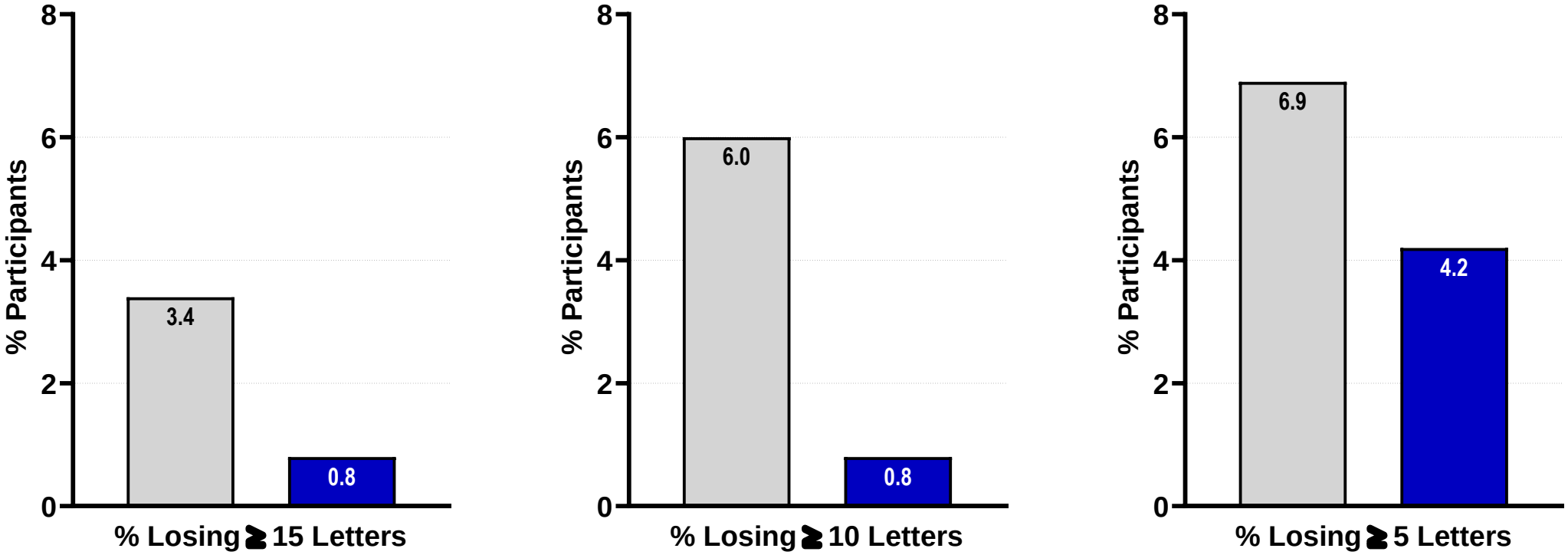
Higher proportion of patients gaining ≥15, ≥10 and ≥5 letters of vision in OPT-302 combination group



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

Vision Loss - Baseline to Week 24

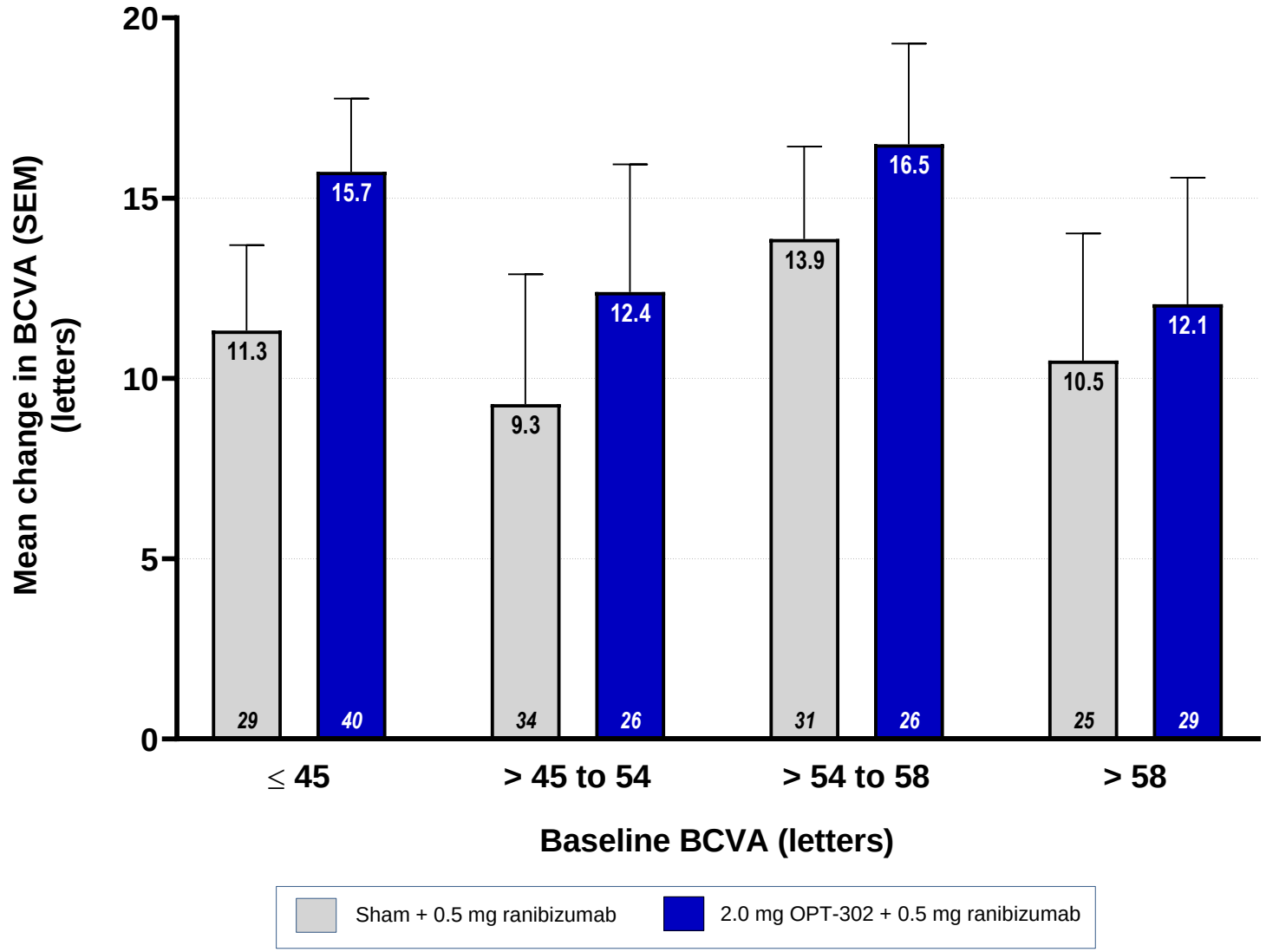
Fewer patients lose ≥15, ≥10 and ≥5 letters of vision in OPT-302 combination group



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

Mean Change in BCVA Baseline to Week 24

Vision gain in OPT-302 combination group compared to sham + ranibizumab is independent of baseline VA

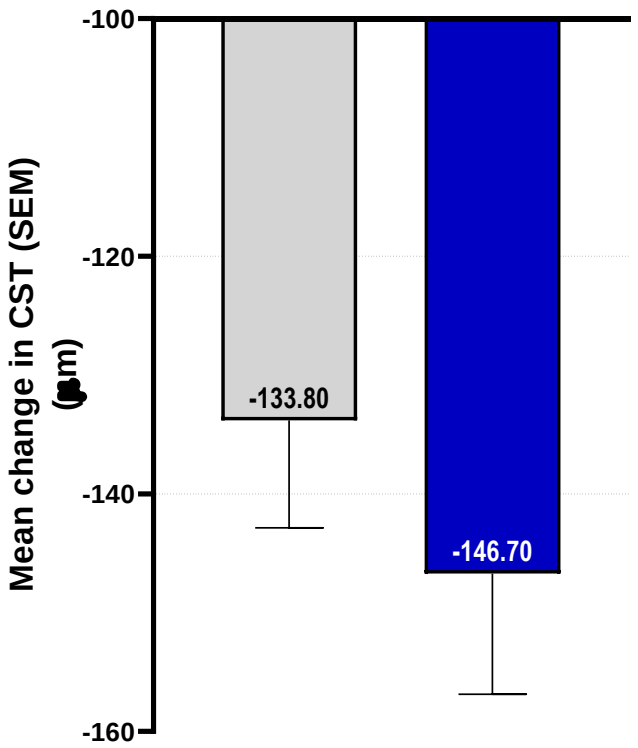


mITT; least square means (LSM) determined using Model for Repeated Measures (MRM) analysis (adjusted for baseline vision and lesion type as used in the randomisation as covariates).

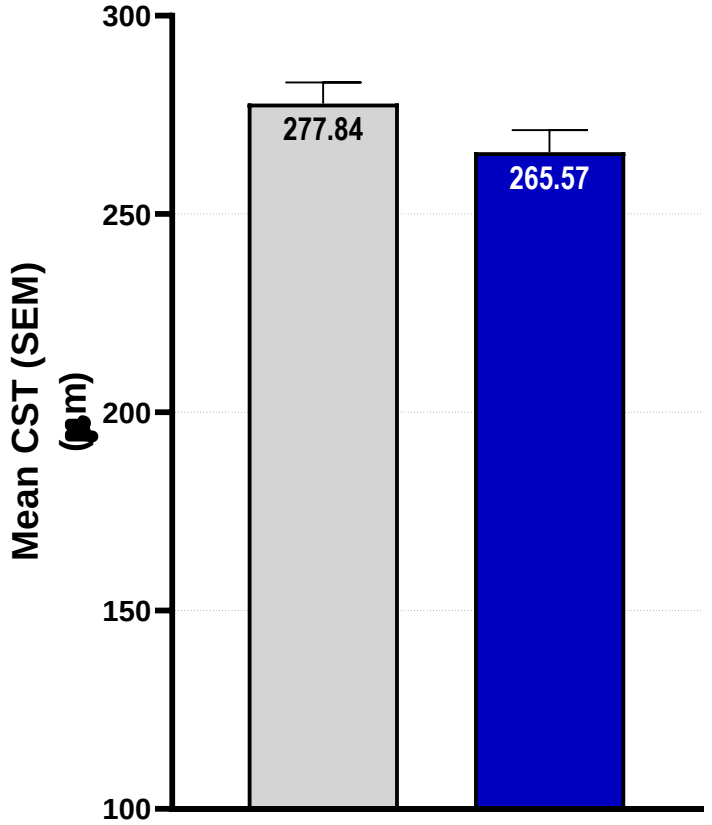
Central Subfield Thickness

Reduction in CST in OPT-302 combination group compared to sham + ranibizumab

Mean Change in CST – Baseline to Week 24



Mean CST at Week 24



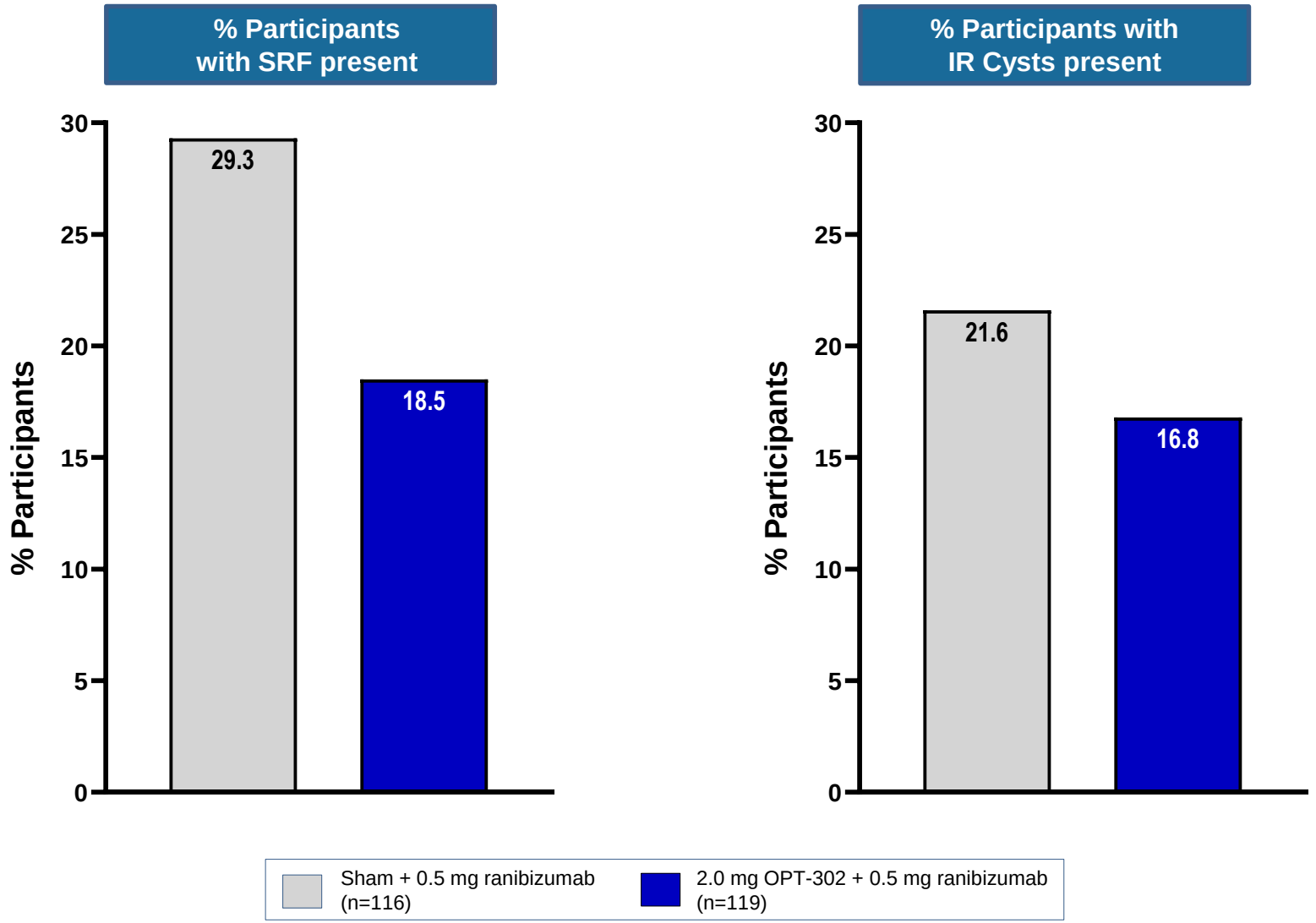
Sham + 0.5 mg ranibizumab (n=116)

2.0 mg OPT-302 + 0.5 mg ranibizumab (n=119)

Modified Intent-to-Treat (mITT) population; as observed; CST – central subfield thickness

Sub-retinal Fluid and Intra-retinal Cysts at Week 24

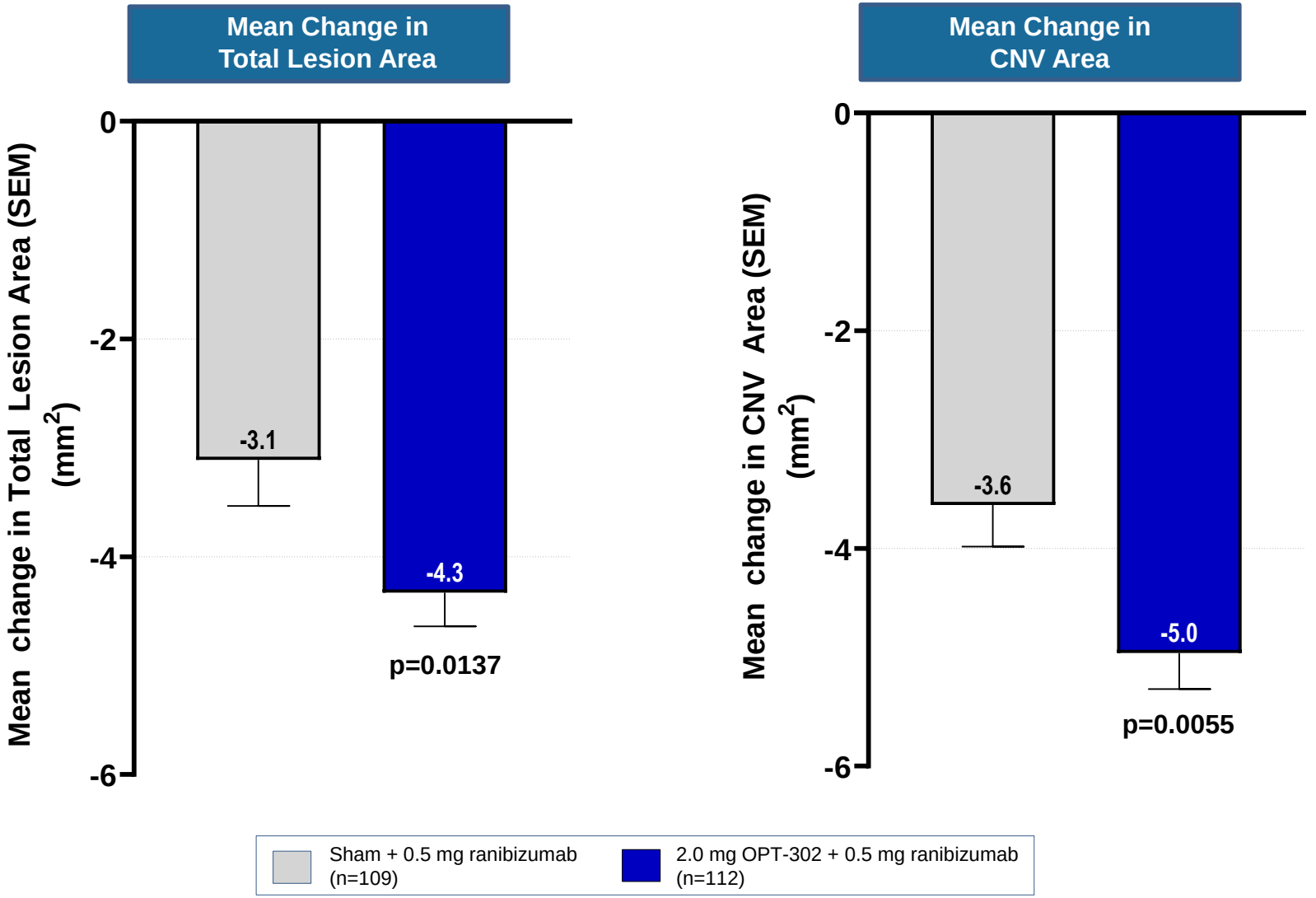
Fewer participants with retinal fluid present in OPT-302 combination group compared to sham + ranibizumab



Modified Intent-to-Treat (mITT) population; as observed; SRF – sub-retinal fluid; IR – intra-retinal

Total Lesion Area and CNV Area – Baseline to Week 24

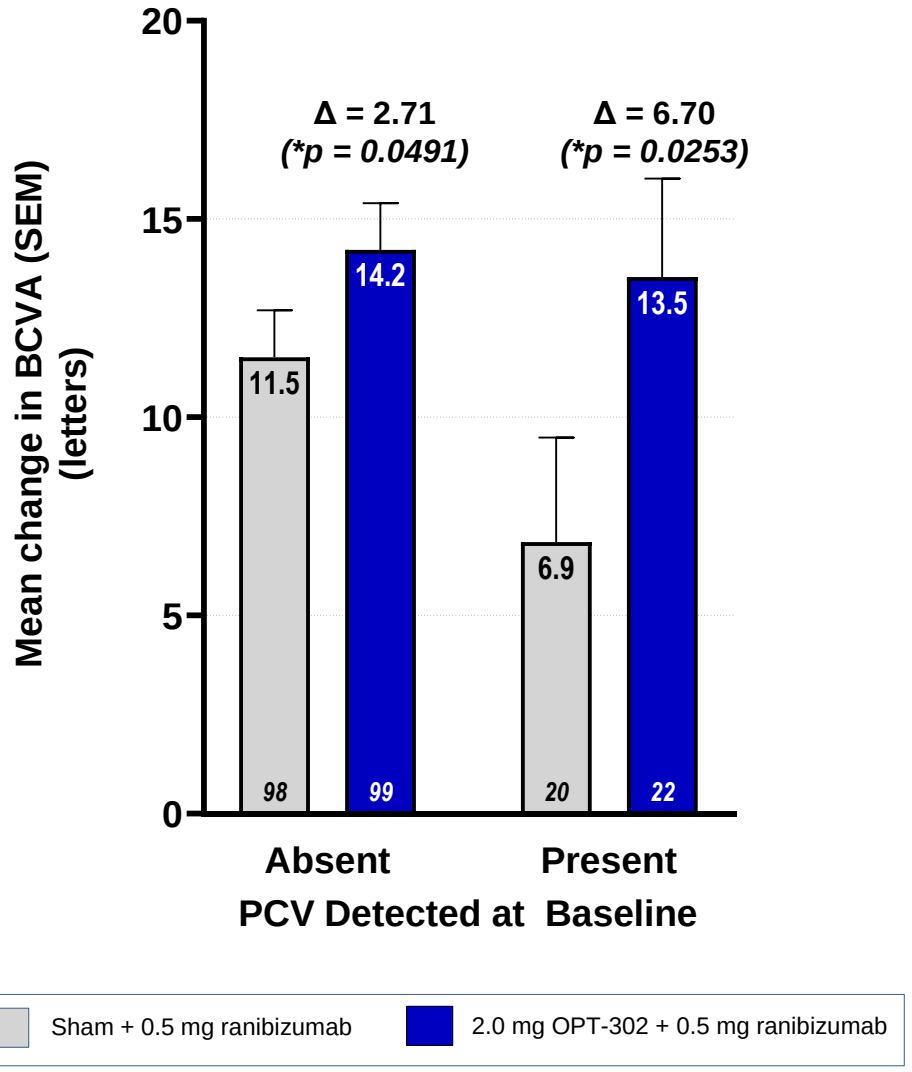
Greater reduction in Total Lesion and CNV Area in OPT-302 combination group compared to sham + ranibizumab



Modified Intent-to-Treat (mITT) population; as observed; CNV – choroidal neovascularisation; Difference in Least Square Means

Polypoidal Choroidal Vasculopathy

Mean change in BCVA to Week 24 in participants with and without PCV at baseline

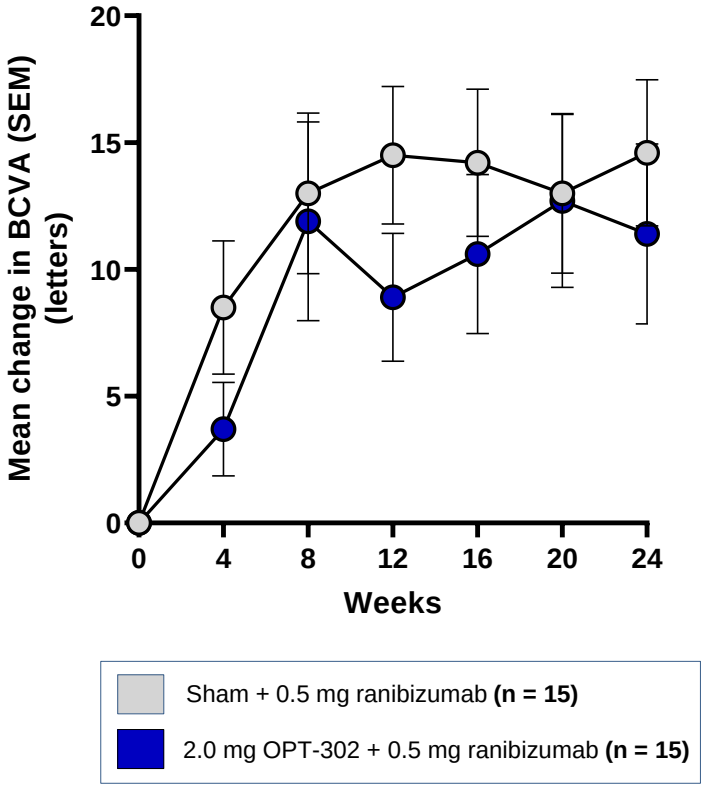


mITT; PCV – polypoidal choroidal vasculopathy;
Least square means determined using Model for Repeated Measures (MRM) analysis (adjusted for baseline vision and lesion type (randomisation) as covariates).
PCV determination by SD-OCT, FA and fundus photography

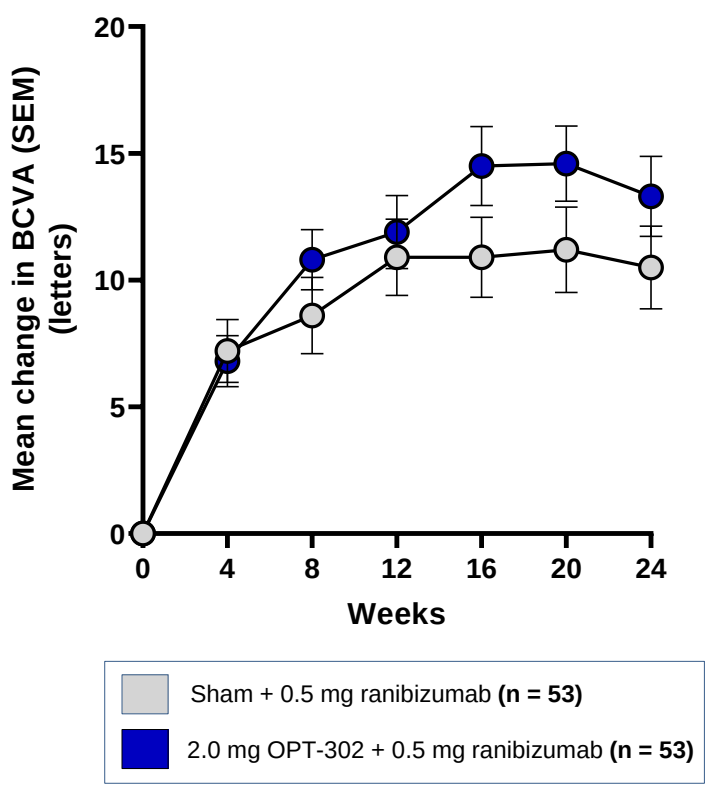
Mean Change in BCVA Over Time by Lesion Type

Small number of predominantly classic patients

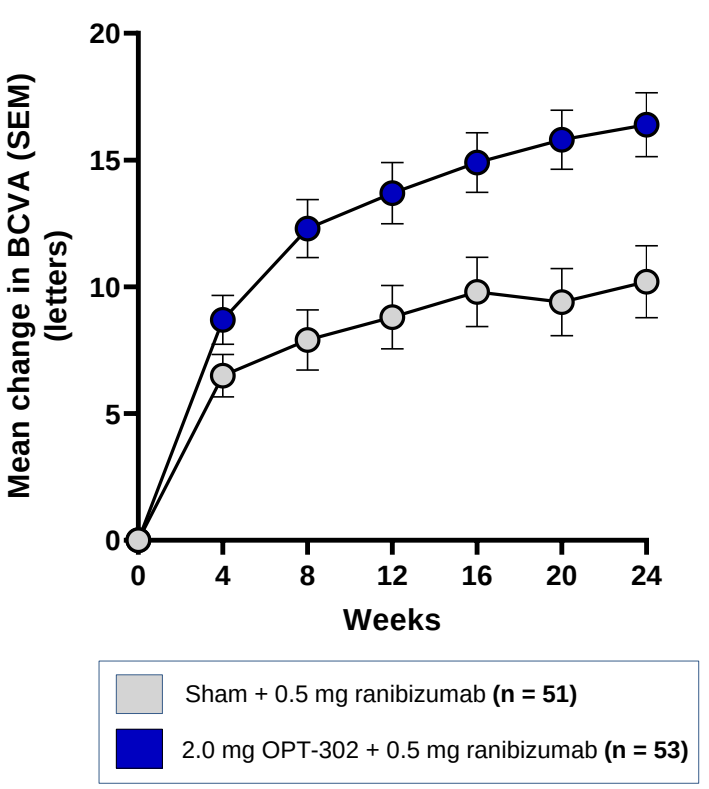
Predominantly Classic



Minimally Classic



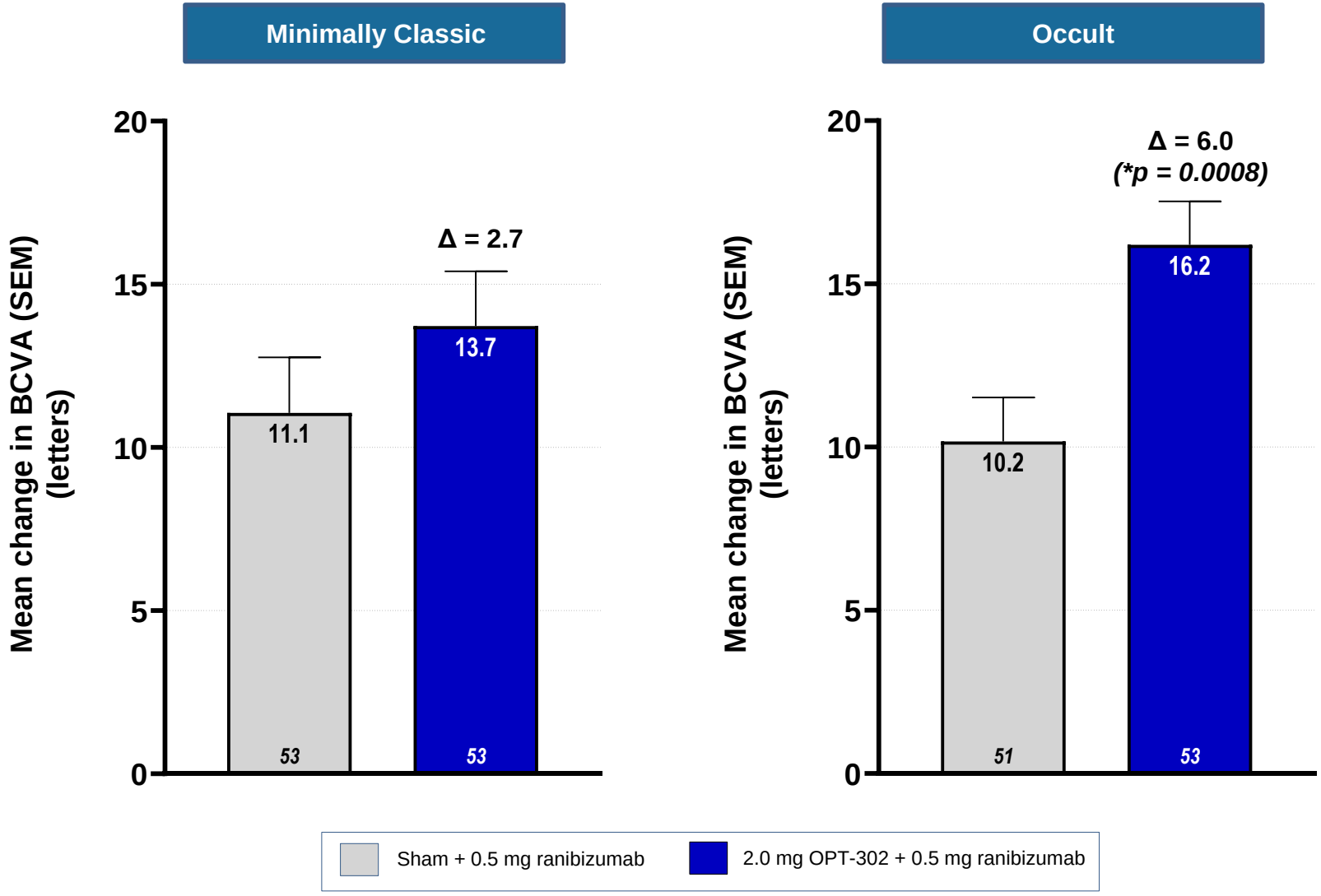
Occult



mITT; as observed

Mean Change in BCVA at week 24 by Lesion Type

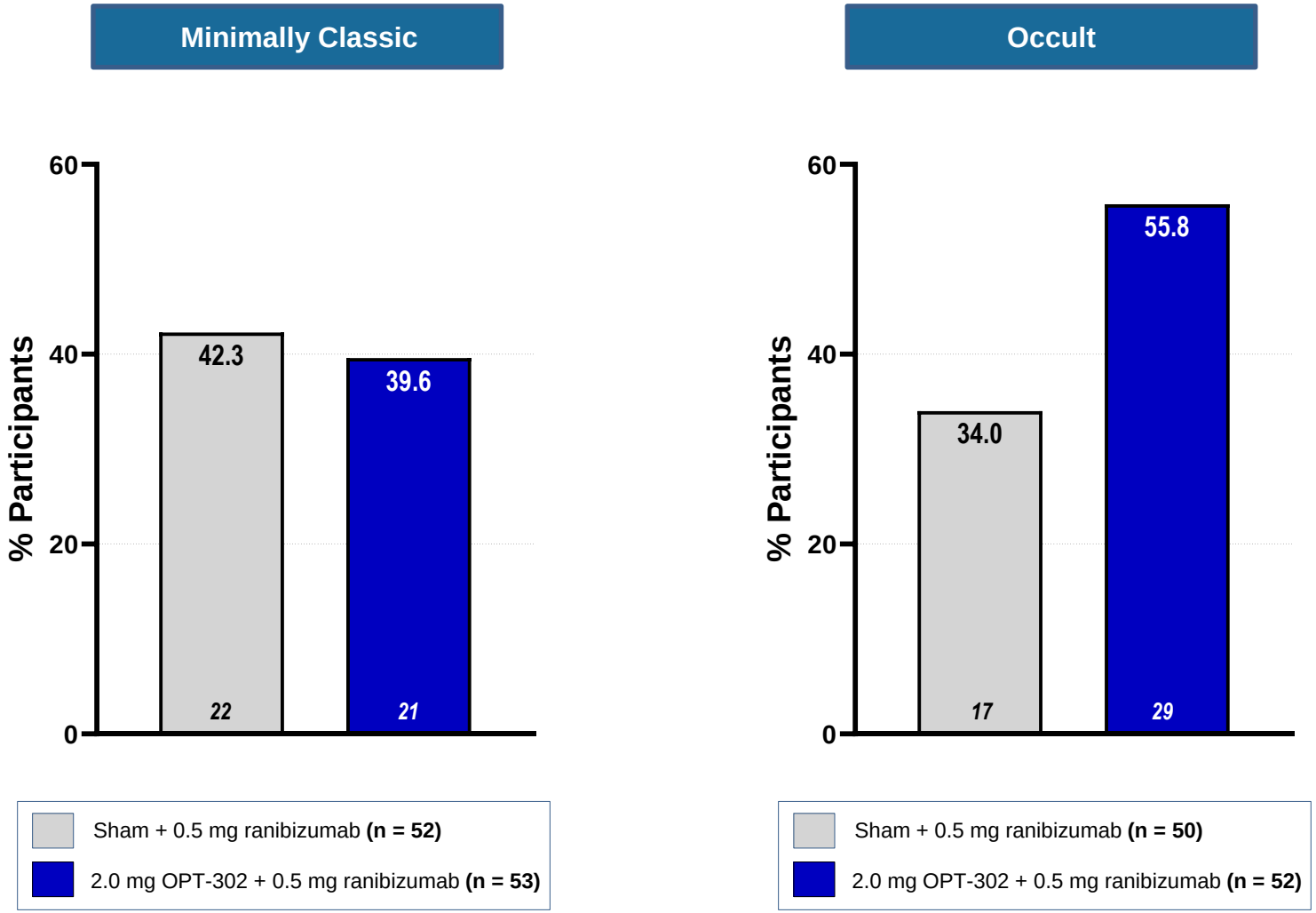
Greater vision gains at Week 24 in OPT-302 2.0 mg group in minimally classic and occult lesions



mITT; Least square means determined using Model for Repeated Measures (MRM) analysis (adjusted for baseline vision and lesion type (randomisation) as covariates).

3-Line Vision Gain at Week 24 by Lesion Type

>20% increase in 3-line gainers in participants with occult lesions treated with OPT-302 combination therapy

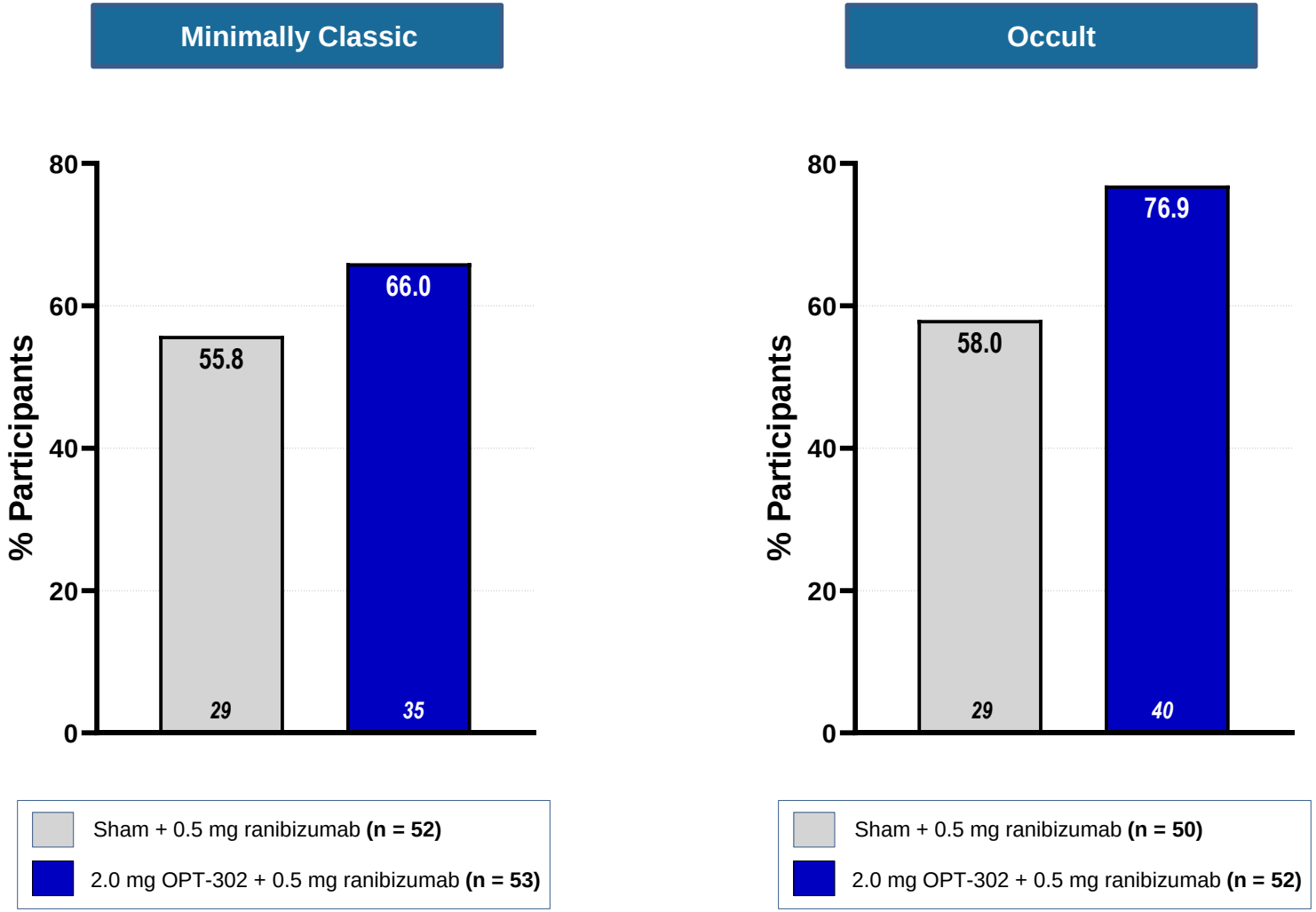


mITT; as observed

OPTHEA

2-Line Vision Gain at Week 24 by Lesion Type

Greater proportion of 2-line gainers in participants with minimally classic and occult lesions following OPT-302 combination therapy

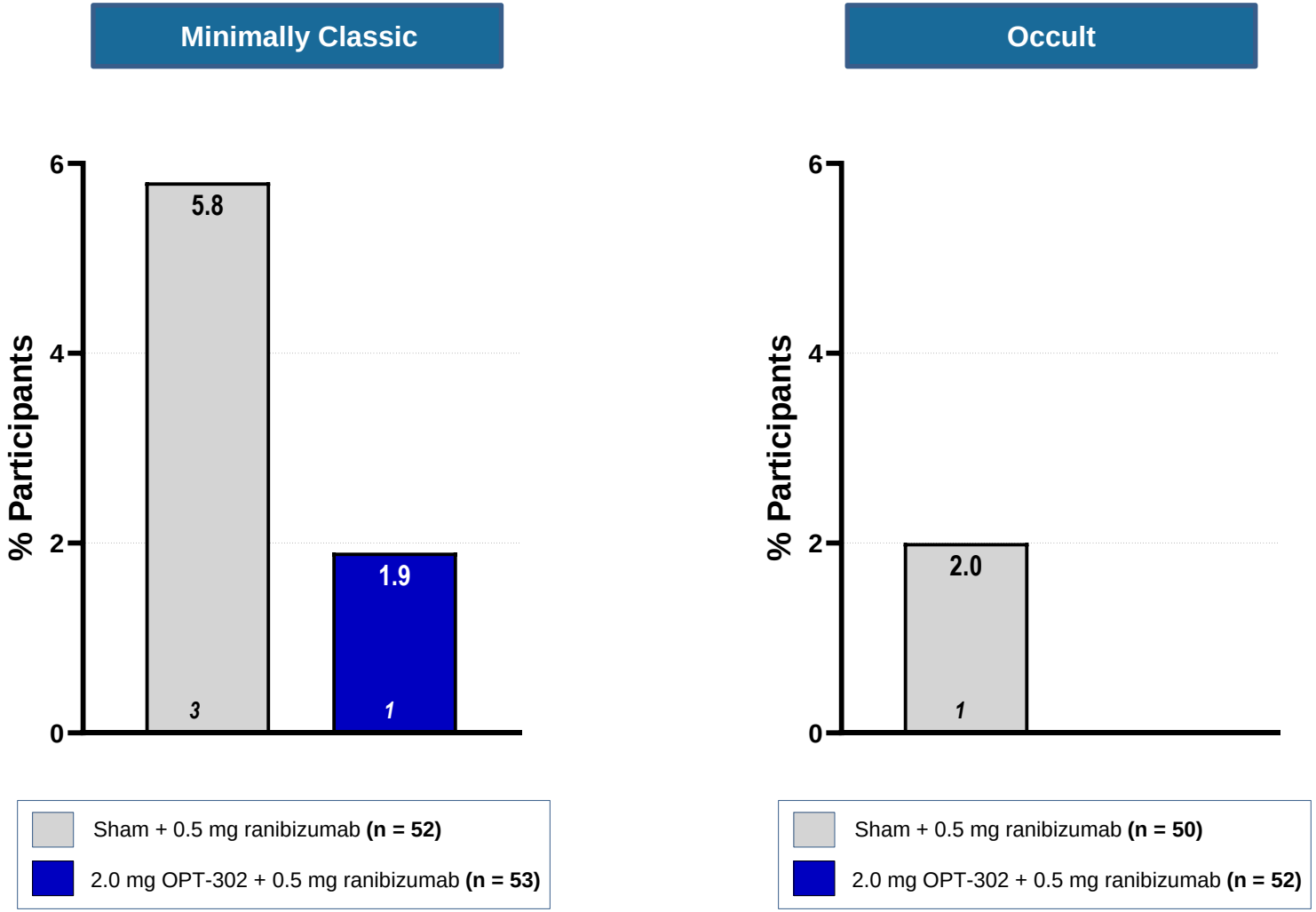


mITT; as observed

OPTHEA

3-Line Vision Loss Baseline to Week 24

Fewer patients with minimally classic and occult lesions lose ≥15 letters following OPT-302 combination therapy

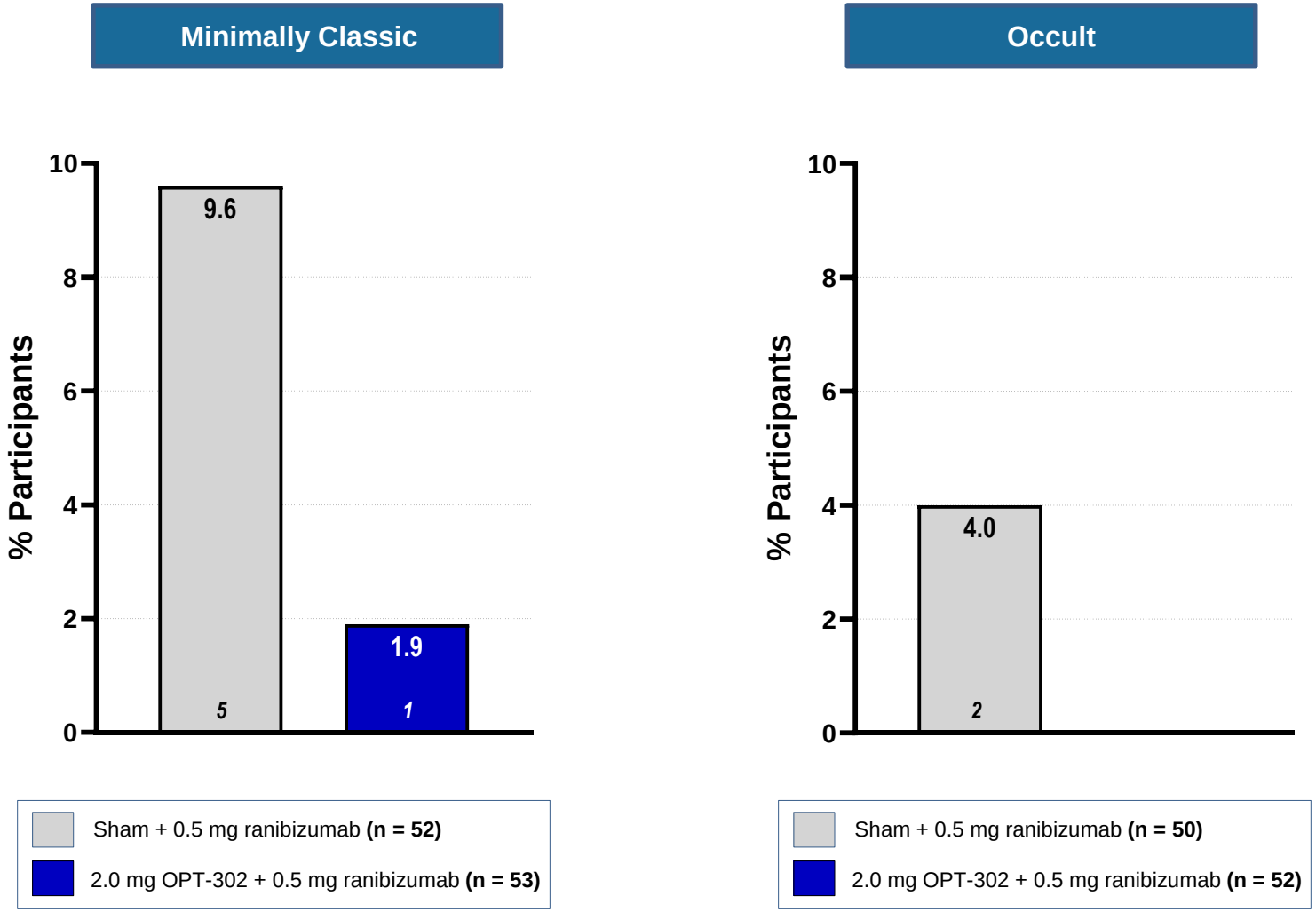


mITT; as observed

OPTHEA

2-Line Vision Loss Baseline to Week 24

Fewer patients with minimally classic and occult lesions lose ≥10 letters following OPT-302 combination therapy

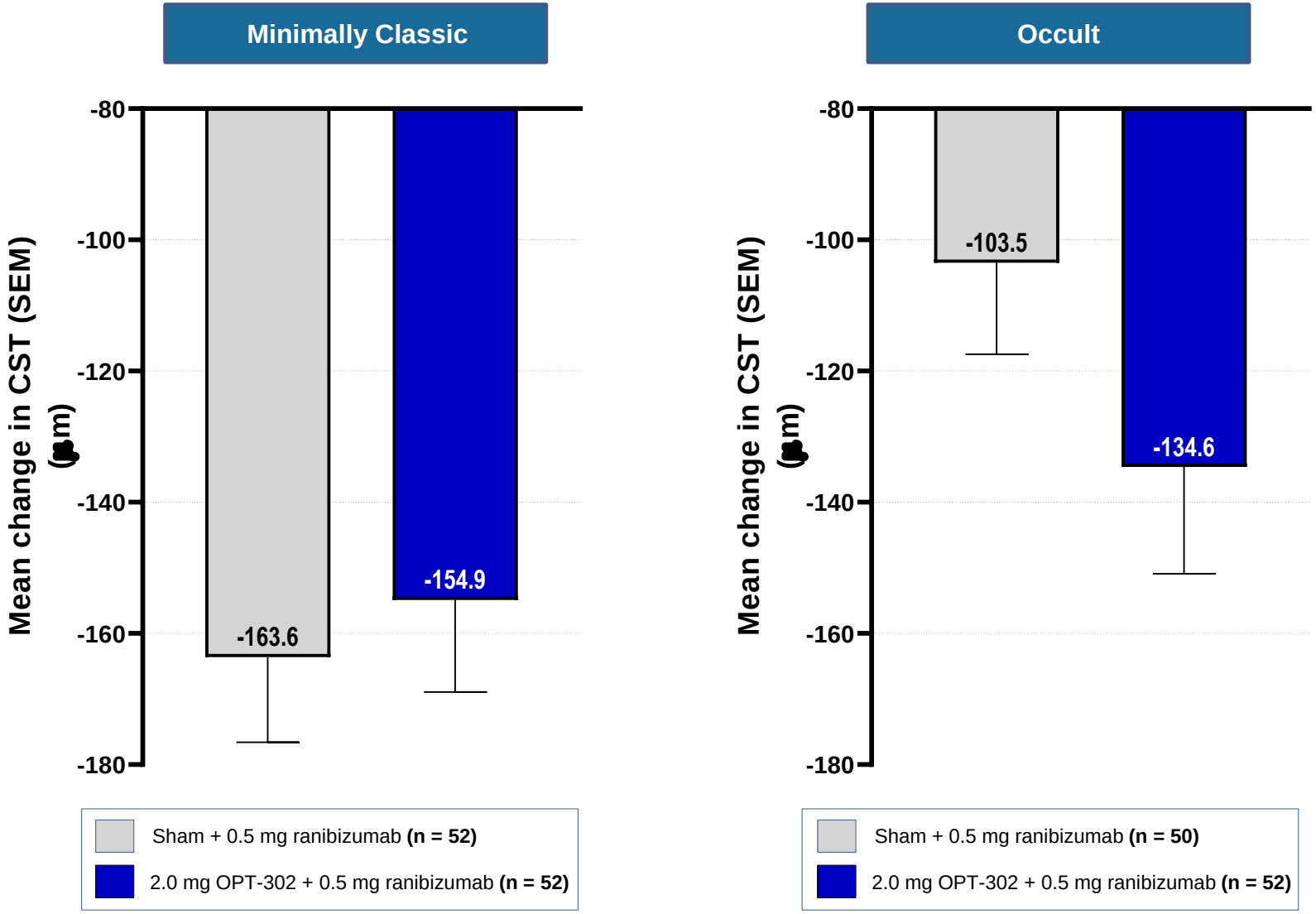


mITT; as observed

OPTHEA

Central Subfield Thickness by Lesion Type

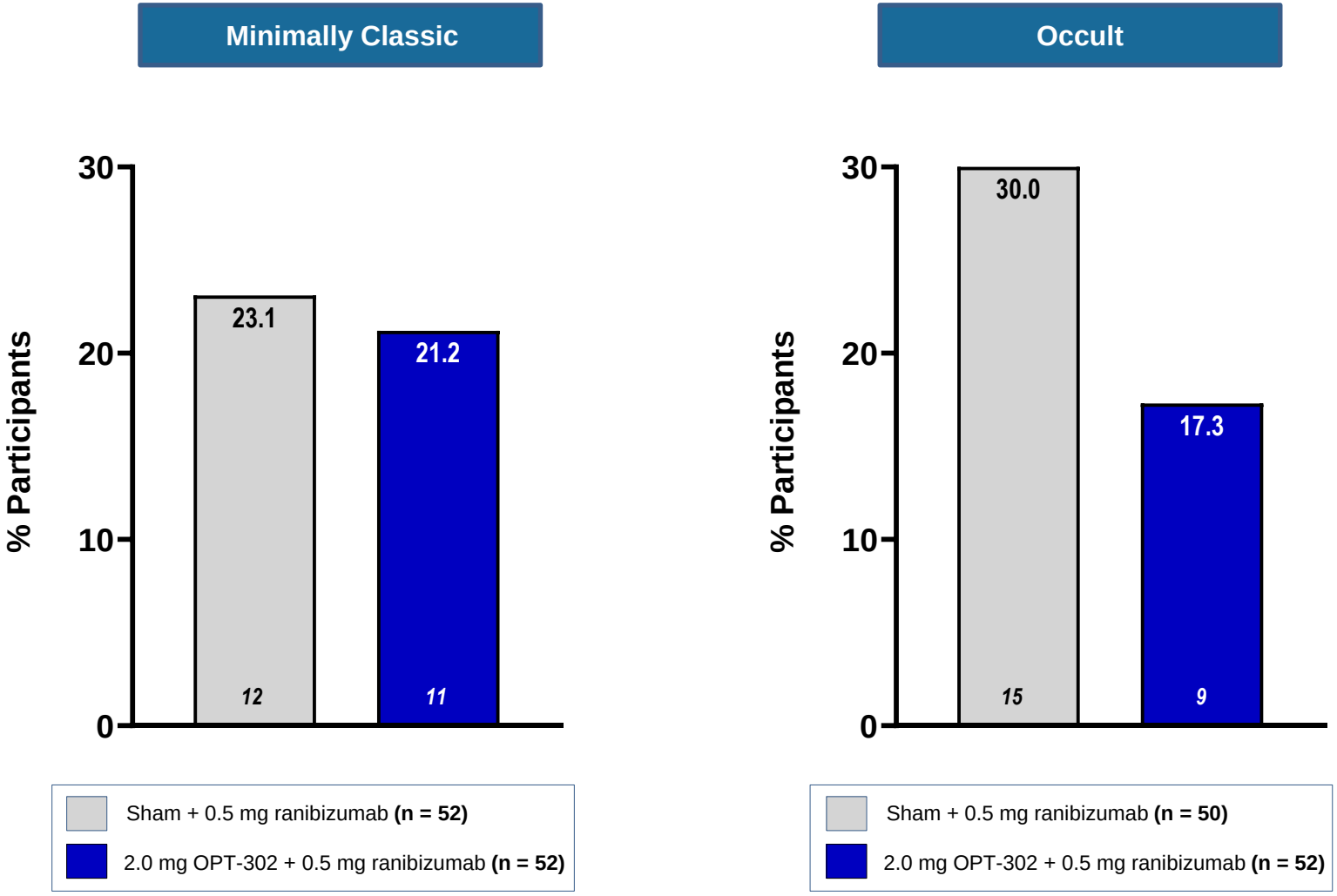
Reduction in CST in participants with occult lesions treated with OPT-302 combination compared to sham + ranibizumab



Modified Intent-to-Treat (mITT) population; as observed; CST – central subfield thickness

Sub-Retinal Fluid at Week 24 by Lesion Type

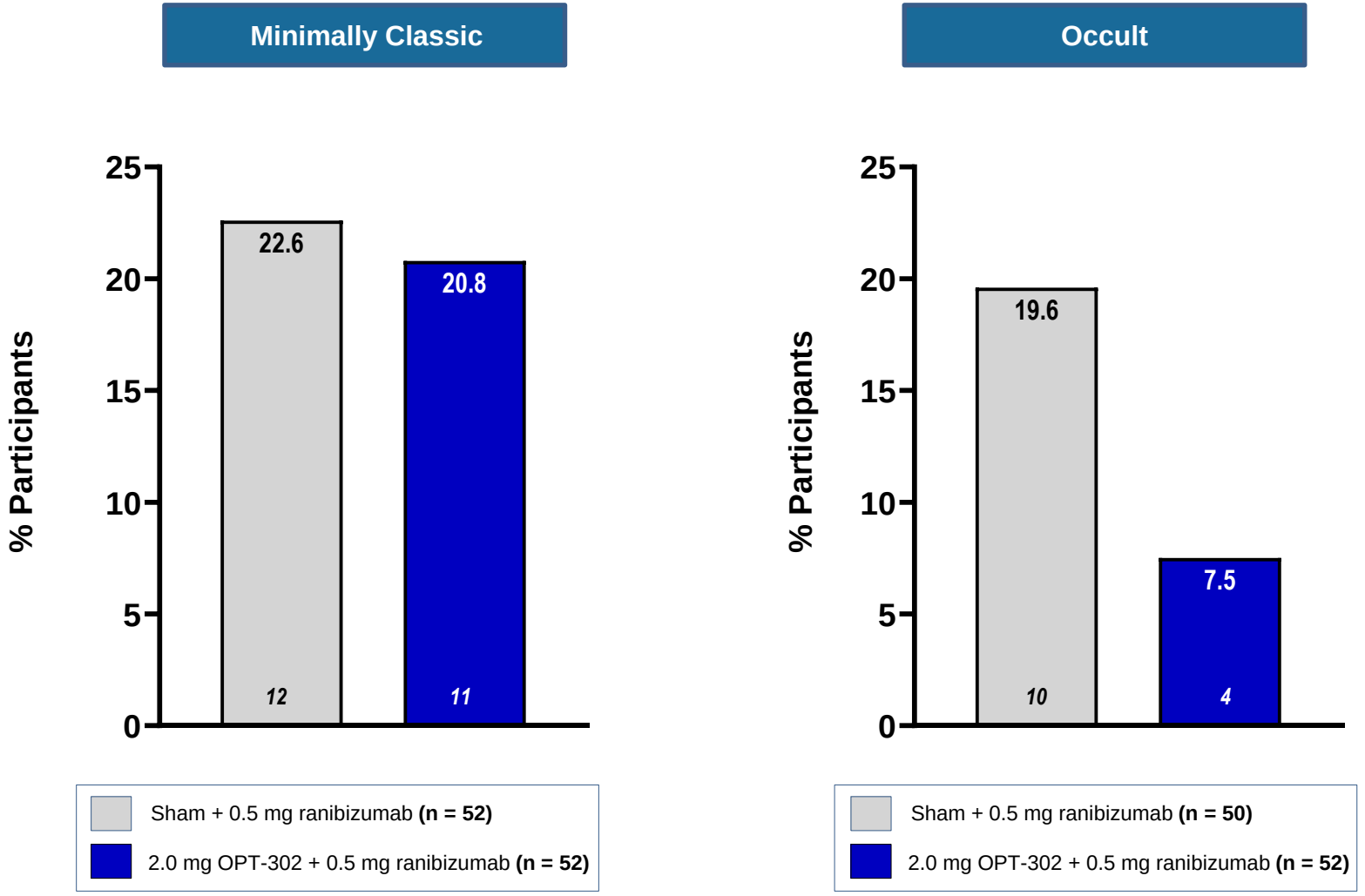
Fewer participants with minimally classic & occult lesions have SRF at week 24 following OPT-302 combination therapy



mITT; as observed

Intra-Retinal Cysts at Week 24 by Lesion Type

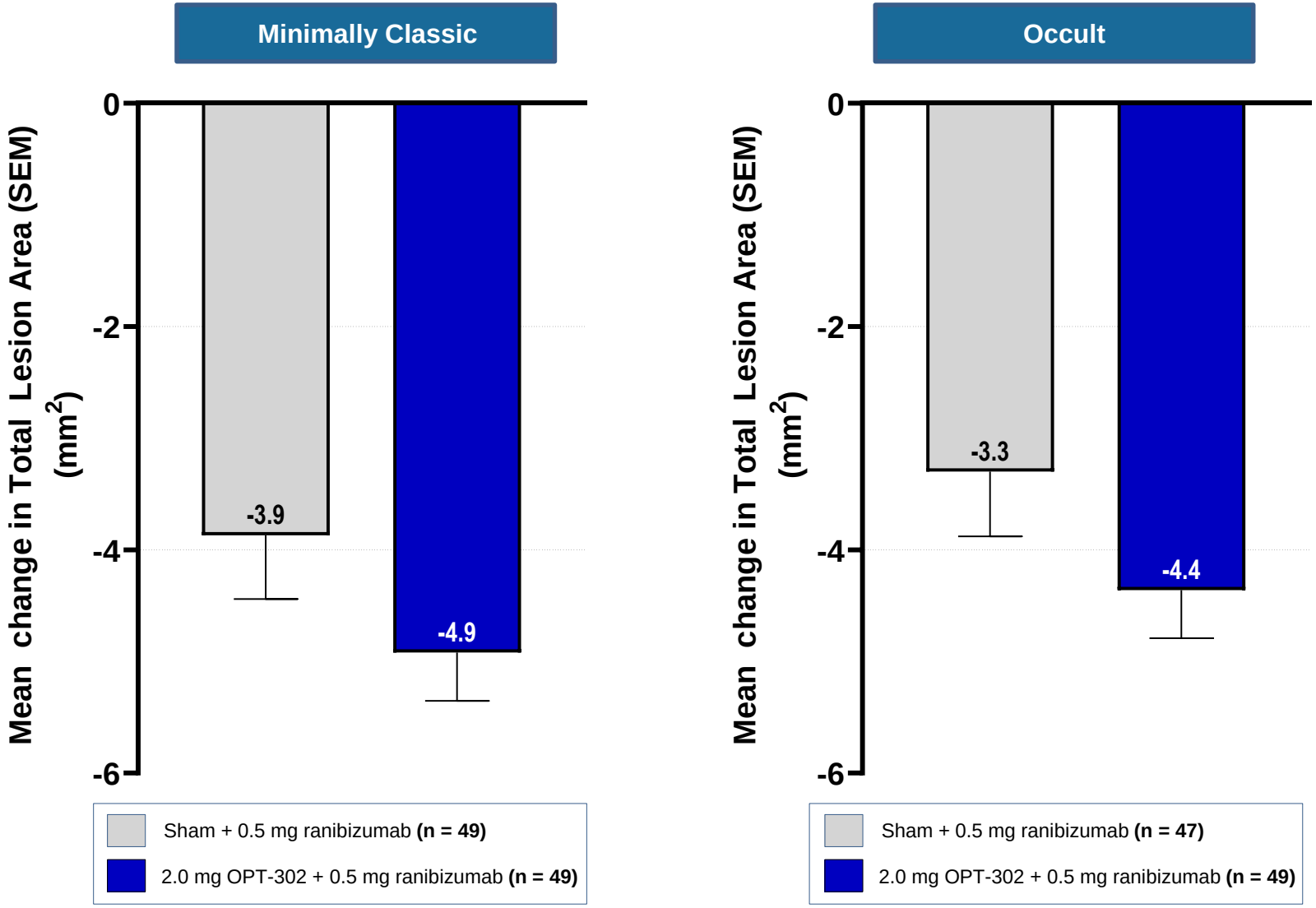
Fewer participants with minimally classic & occult lesions have intra-retinal cysts following OPT-302 combination therapy



mITT; as observed

Total Lesion Area at Week 24 in Minimally Classic and Occult Lesions

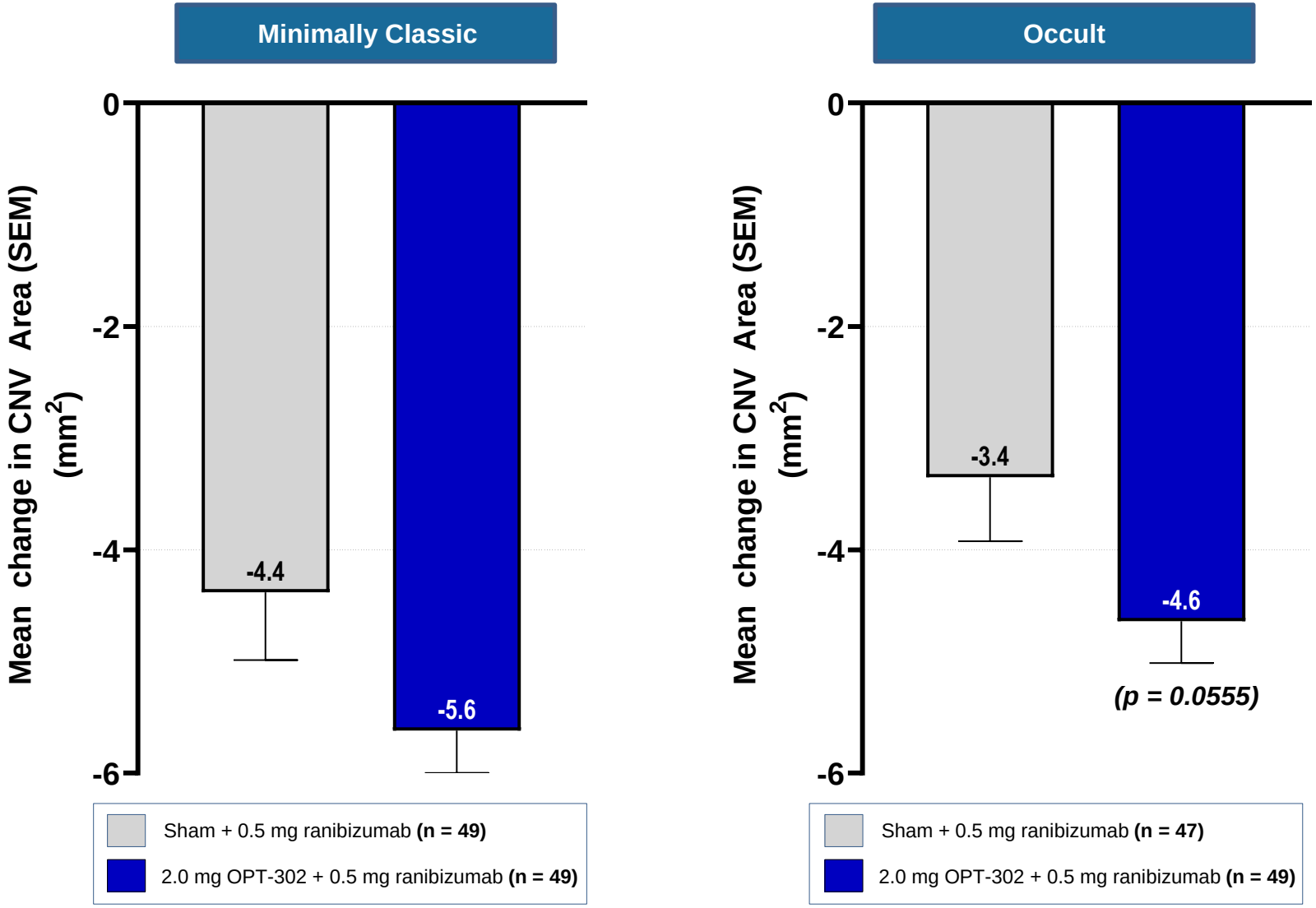
Greater reductions in Total Lesion Area following OPT-302 combination therapy



mITT; as observed

CNV Area at Week 24 in Minimally Classic and Occult Lesions

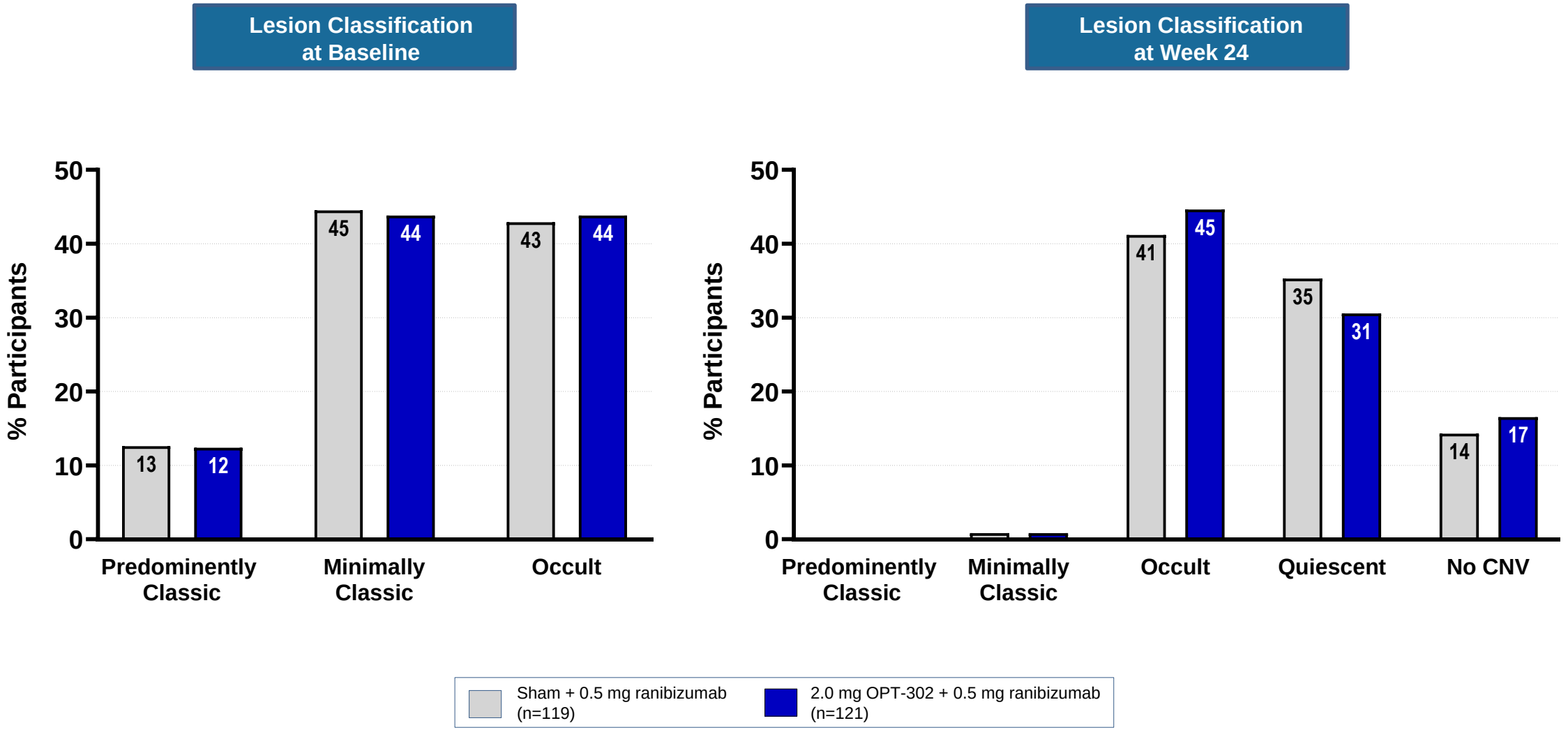
Greater reductions in CNV Area following OPT-302 combination therapy



mITT; as observed; p based on difference in least square means determined using Model for Repeated Measures (MRM) analysis (adjusted for baseline vision and lesion type (randomisation) as covariates).

Lesion classification at Baseline and at Week 24

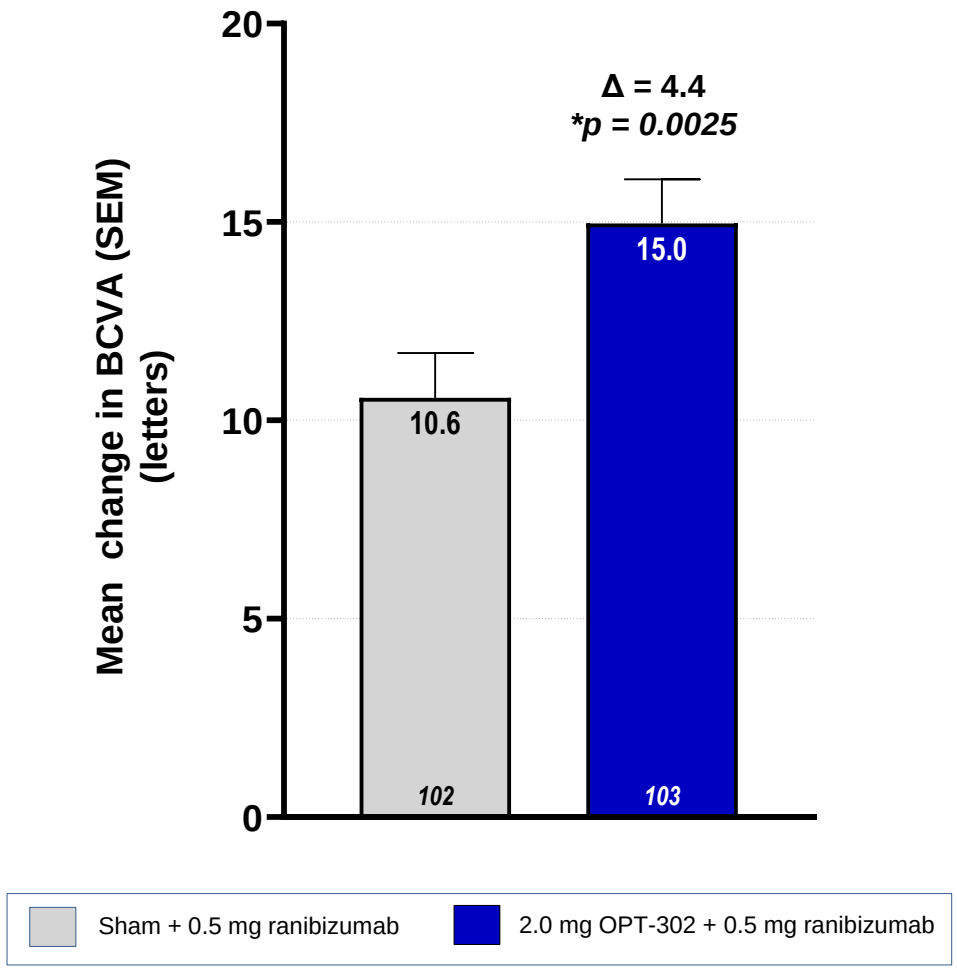
Lesions shift to an occult, quiescent biology or no CNV following treatment



mITT; as observed

Retinal Angiomatous Proliferation (RAP) Lesions

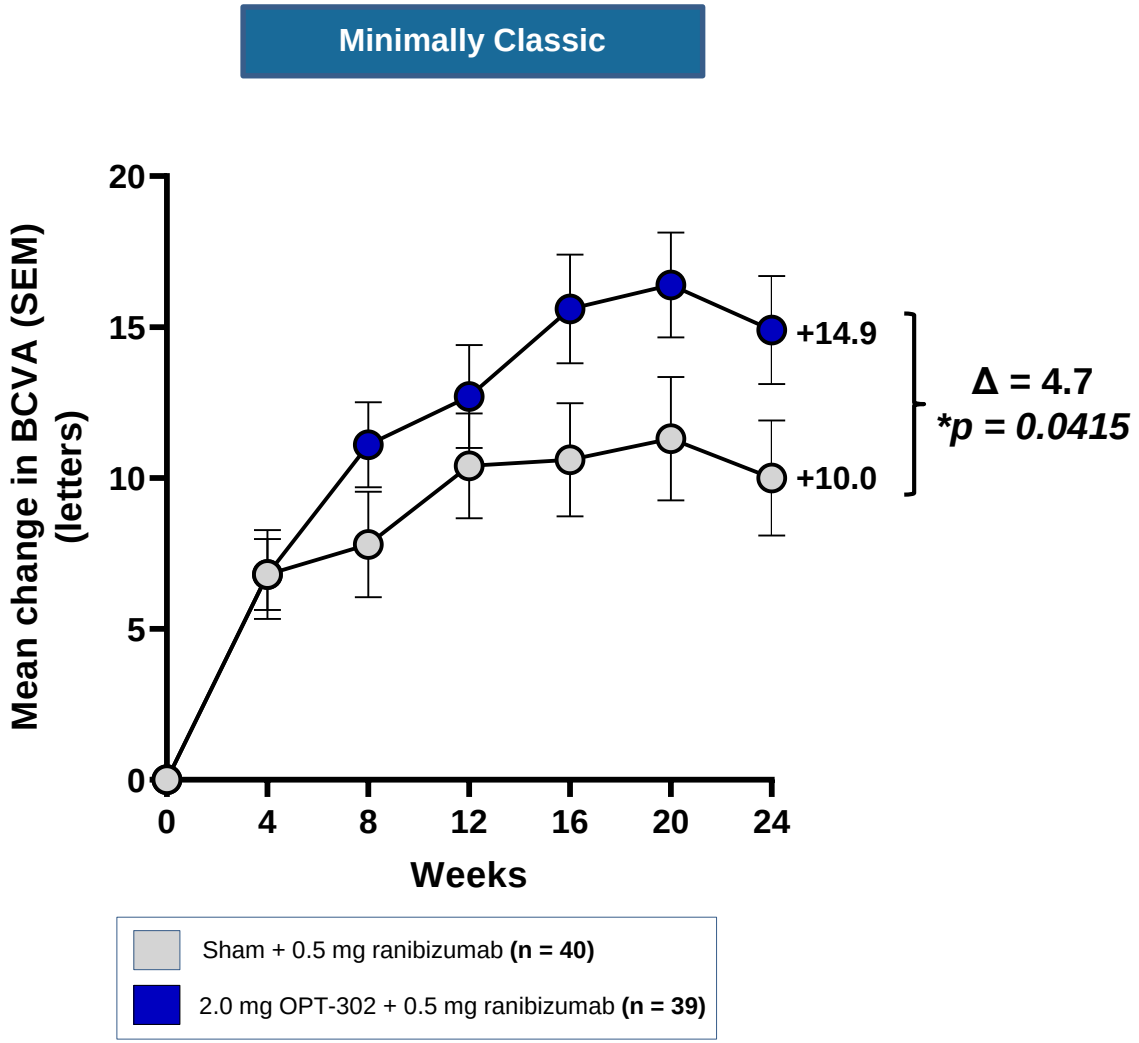
Mean change in BCVA to Week 24 in participants without RAP at baseline

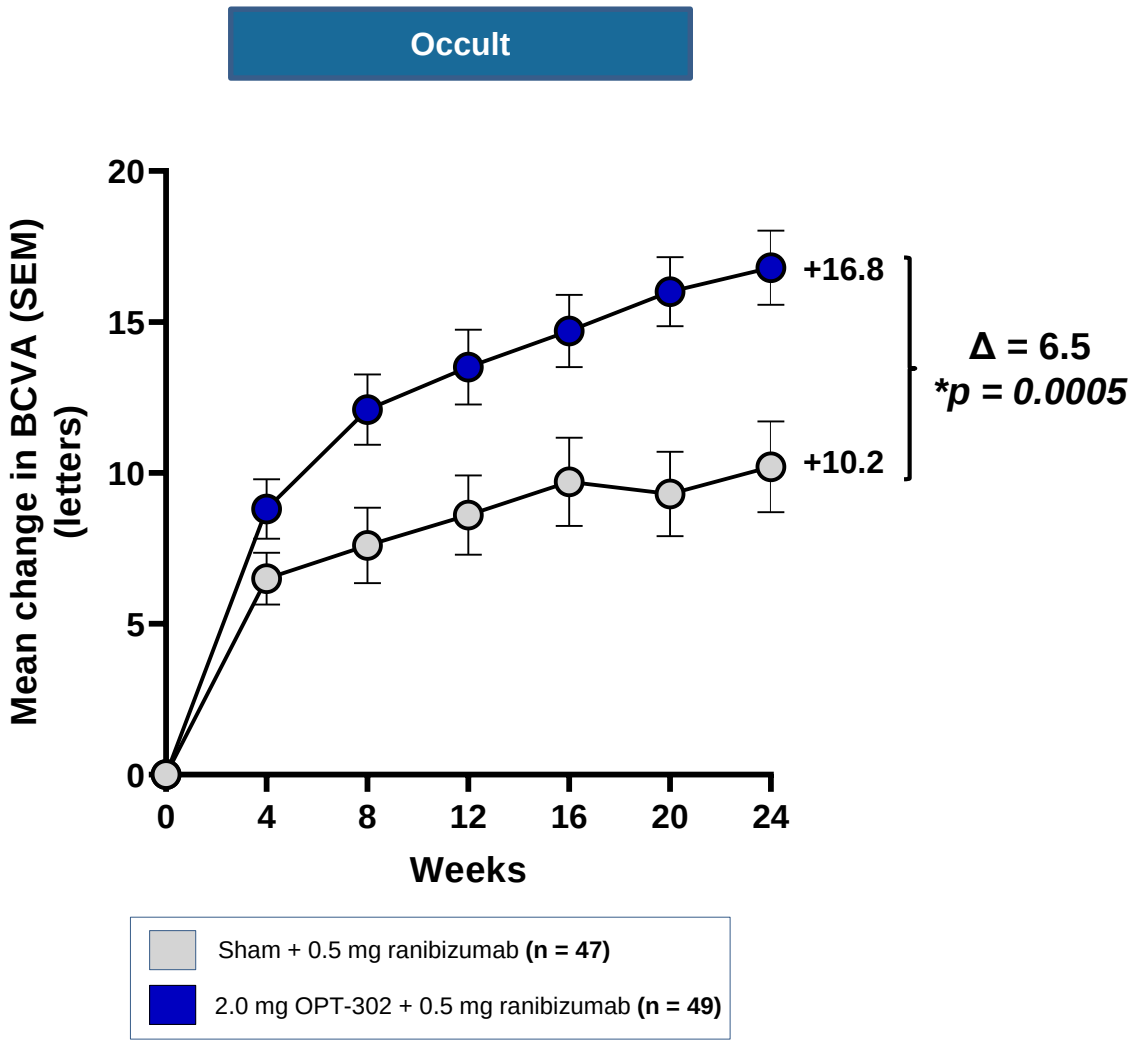


mITT; RAP – retinal angiomatous proliferation;
Least square means (LSM) determined using Model for Repeated Measures (MRM) analysis (adjusted for baseline vision and lesion type as used in the randomisation as covariates).

Mean Change in BCVA Over Time by Lesion Type, RAP Absent

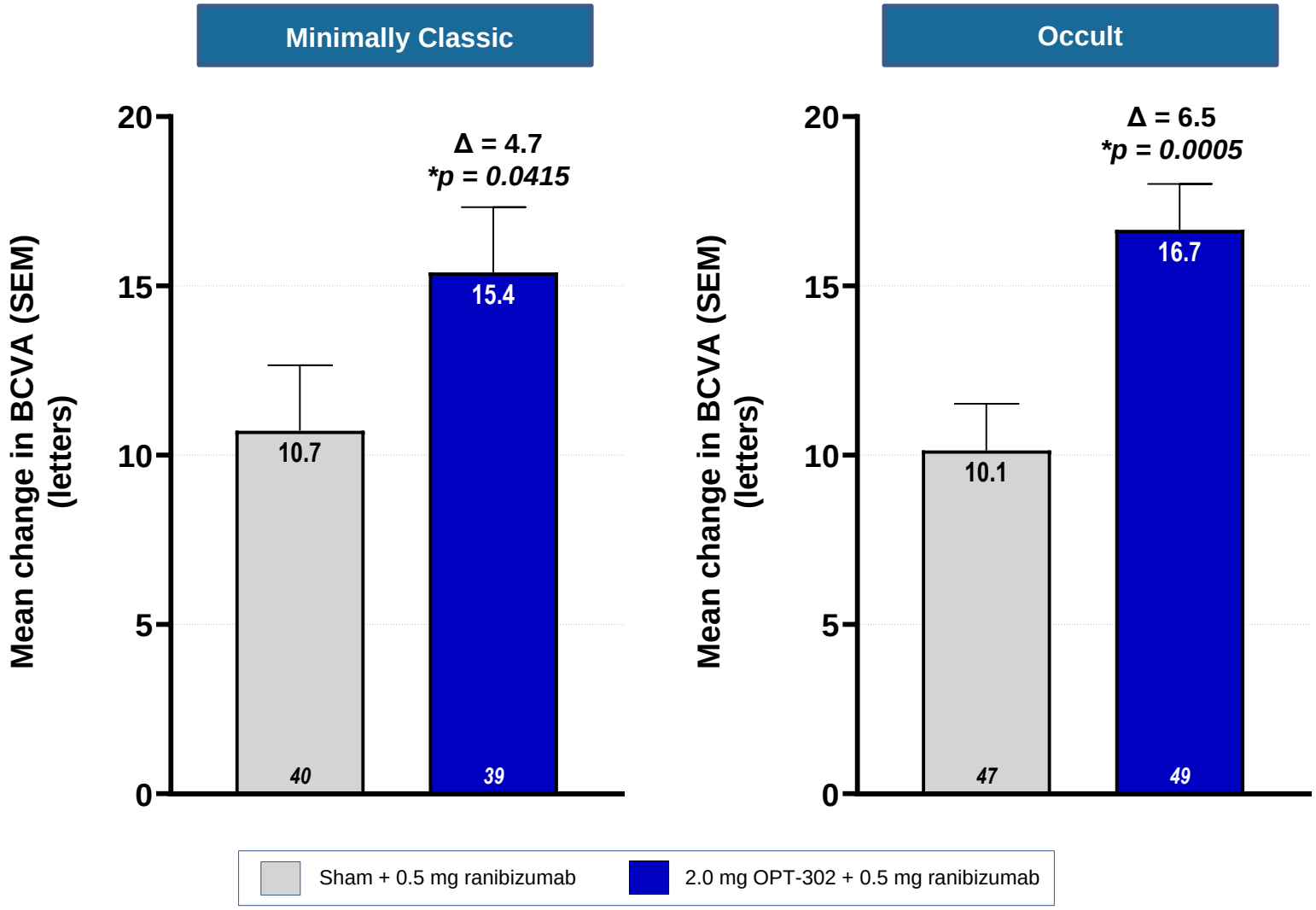
In RAP absent participants, +4.7 letter gain in minimally classic and +6.5 letter gain in occult participants treated with OPT-302 combination therapy compared to sham + ranibizumab





mITT, as observed, Δ based on least square means determined using Model for Repeated Measures (MRM) analysis (adjusted for baseline vision and lesion type (randomisation) as covariates).

Mean Change in BCVA at Week 24 by Lesion Type, RAP Absent



mITT; Least square means (LSM) determined using Model for Repeated Measures (MRM) analysis (adjusted for baseline vision and lesion type as used in the randomisation as covariates).

Safety – Adverse Events (AEs)

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	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	0 (0.0%)	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[6] (0.8%)	0 (0.0%)	0 (0.0%)
Any APTC event	0 (0.0%)	1[7] (0.8%)	0 (0.0%)
Deaths	2[8] (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] Anterior chamber cell (trace 1-4 cells)

[6] Squamous cell carcinoma of the lung diagnosed shortly after Baseline visit

[7] Non-fatal myocardial infarction

[8] Pneumonia (n=1), infective endocarditis (n=1)

OPTHEA

Conclusions – OPT-302 Phase 2b nAMD Trial

- **Phase 2b trial met primary endpoint**
  - OPT-302 (2.0 mg) combination therapy demonstrated superiority in visual acuity over ranibizumab + sham
  - Vision gain of 3.4 letters
  - Statistically significant (p=0.0107)
  - High ranibizumab control arm
- **Secondary outcomes were supportive of the primary endpoint:**
  - **Vision**
    - More patients gained ≥ 15 letters of vision
    - Fewer patients lost ≥ 15 letters of vision
  - **Retinal anatomical improvements**
    - Reductions in CST, subretinal and intraretinal fluid
    - Greater decreases in Total Lesion Area and CNV Area
- **Exploratory & pre-specified subgroup analyses**
  - Suggest greater activity of OPT-302 in lesion-types considered more difficult to treat with anti-VEGF-A therapy & highest unmet need
  - Promising evidence of activity in polypoidal AMD (PCV) and minimally classic/occult lesions that are less responsive to VEGF-A inhibitors
- **Favourable safety profile similar to ranibizumab alone**

OPTHEA

Megan Baldwin
CEO & Managing Director

T +61 (3) 9826 0399
E megan.baldwin@opthea.com

Suite 0403, Level 4,
650 Chapel Street,
South Yarra 3141 Victoria Australia
www.opthea.com