Beyond VEGF-A:
Targeting VEGF-C/D for Wet AMD and DME

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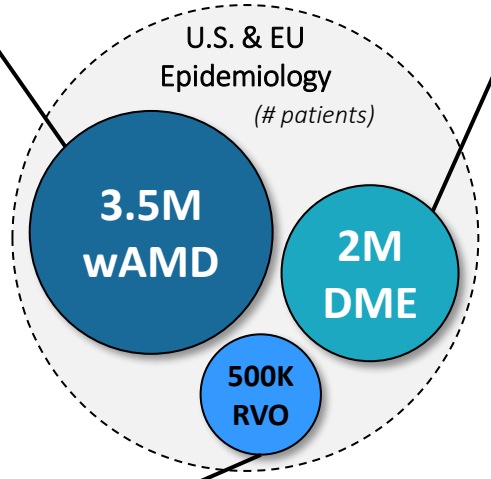
OPTHEA

Wet AMD & DME are the leading causes of vision loss in the elderly & diabetics

Increasing prevalence; large unmet medical need

Wet Age-Related Macular Degeneration

Edema caused by abnormal vasculature growth which ultimately results in the loss of visual function



Diabetic Macular Edema (DME)

A complication of diabetes that manifests as edema and hard exudates in the macula and leads to loss of VA

Additional market opportunity:

Macular Edema Secondary to Retinal Vein Occlusion (RVO)

Characterized by retinal vein blockage, which selectively leads to edema formation and loss of visual acuity

Additional market opportunities:

Diabetic Retinopathy

Characterized by vascular injury and permeability, which may be followed by active proliferation of new vessels

Myopic CNV

Characterized by ingrowth of new blood vessels beneath the retina in the myopic eye

Other non-AMD associated CNV

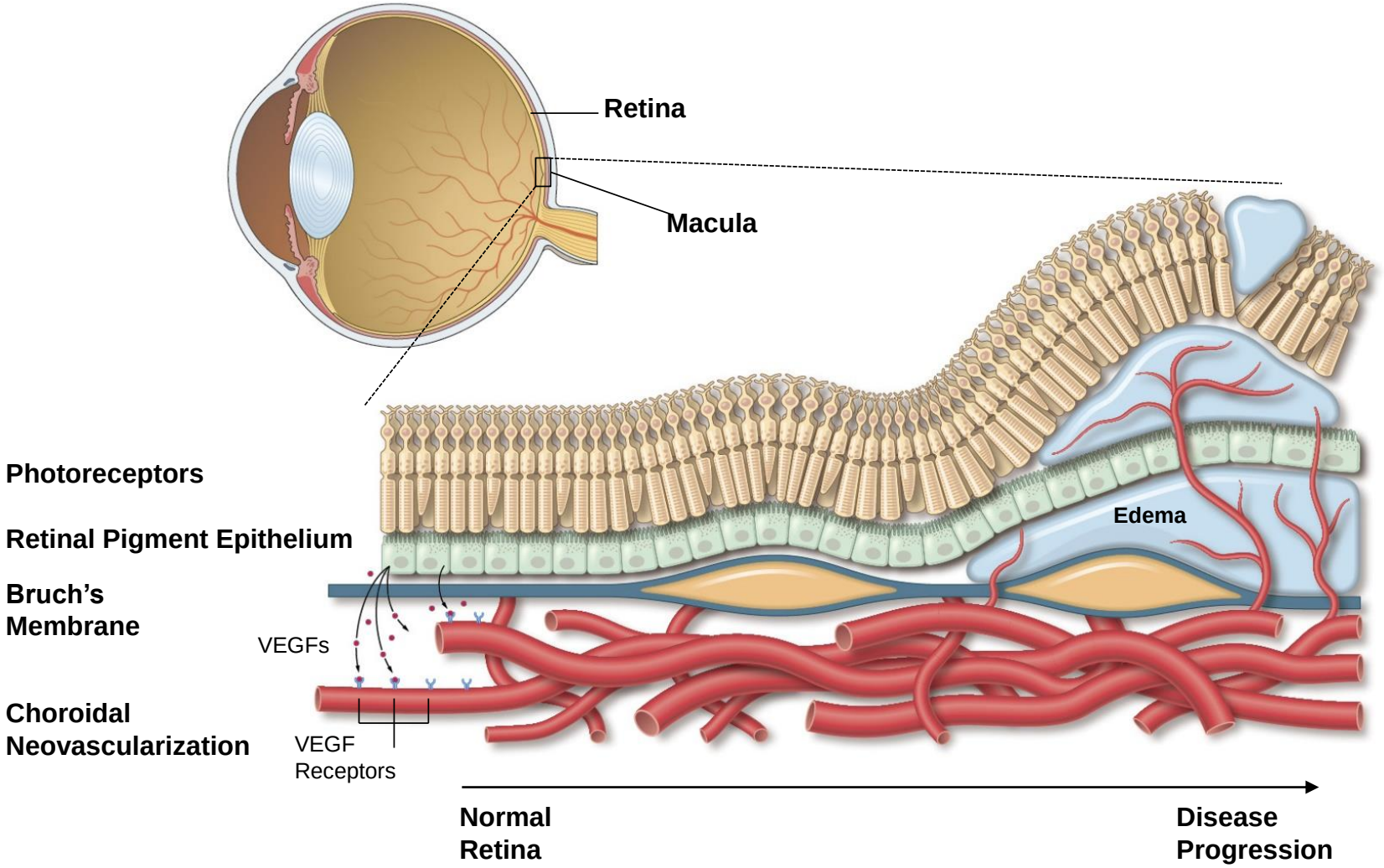
May occur secondary to other ophthalmic conditions

Source: GlobalData; EvaluatePharma; PubMed; Physician Interviews.

OPTHEA

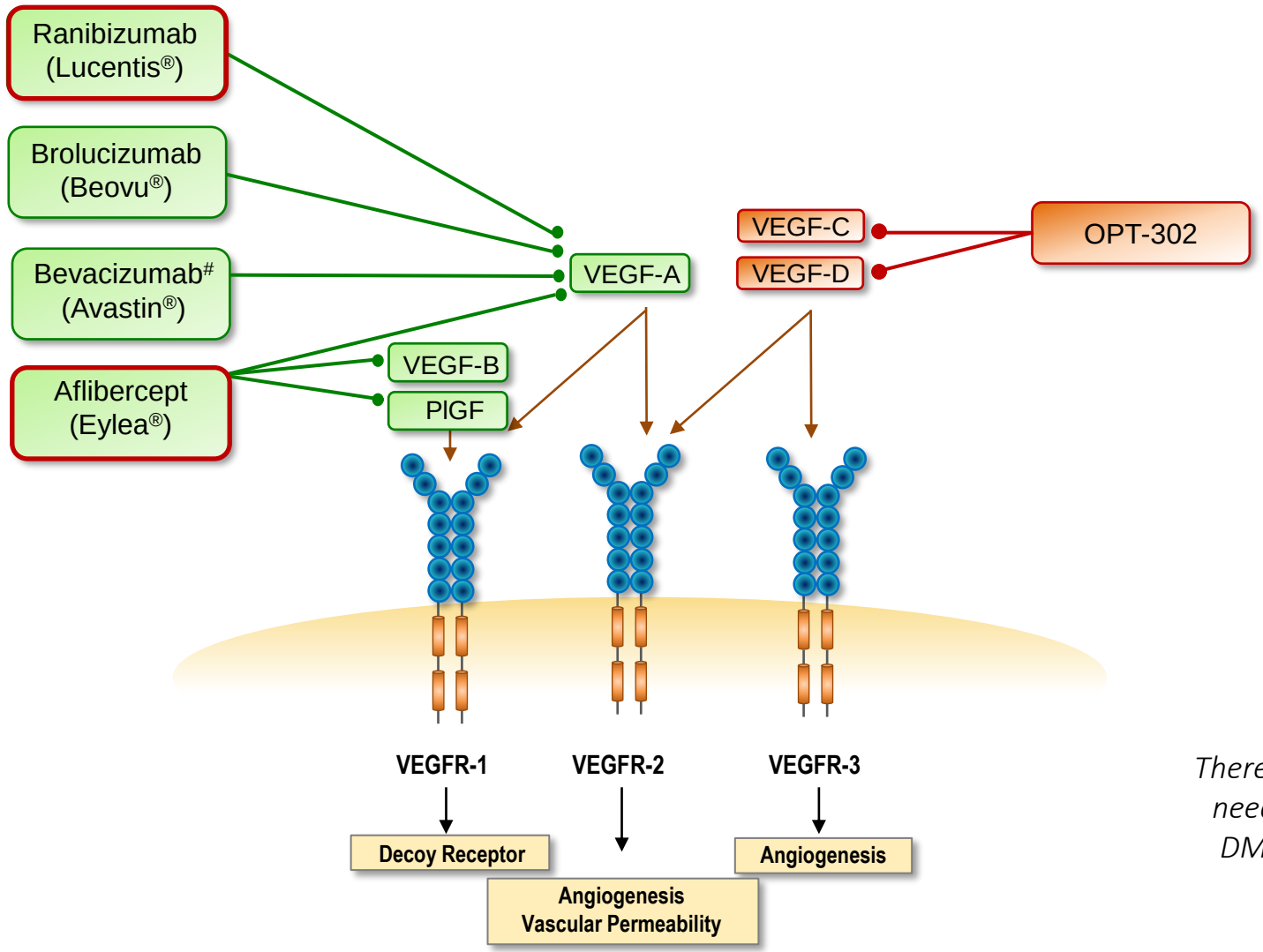
Retinal Eye Diseases – Angiogenesis and Vascular Permeability

Lead to lesion formation, edema & vision loss



The VEGF/VEGFR Pathway & Disease Progression

OPT-302 has potential to improve clinical EFFICACY by targeting VEGF-C/D



There remains a significant unmet medical need for the treatment of wet AMD and DME despite the availability of VEGF-A inhibitors

 # Bevacizumab is used 'off-label' for the treatment of nAMD

Large Market Opportunity for New Retinal Disease Therapies

Standard of Care VEGF-A Therapies

LUCENTIS® RANIBIZUMAB INJECTION	EYLEA® (aflibercept solution for injection)
USD 3.9 BN	USD 7.9 BN

2019 Sales Revenue[1] *(all indications)* **USD 11.9 BN**

61% wAMD
22% DME
17% RVO

~46% IVT injections administered globally are Avastin (bevacizumab), administered off-label[2]

1. *Evaluate Pharma*
2. *IRIS Registry (Intelligent Research in Sight) of the American Academy of Ophthalmology. From 2013 to 2016 across 6,259,470 injections, Avastin accounted for 46 percent of injections administered*

OPTHEA

Large Market Opportunity for OPT-302 in Retinal Diseases

The OPPORTUNITY for OPT-302

Objective: To develop OPT-302 for use in combination with any VEGF-A inhibitor

A commercial assessment of OPT-302, conducted by an Independent Research Firm, forecasts worldwide annual peak sales of OPT-302 for wet AMD and DME alone to be

US 5.3 BN[1]

1. *Commercial Assessment in 2020, ClearView Partners. Assumes market launch wet AMD late 2023, DME late 2025*

Majority of Agents in Development Seeking to Improve Durability of VEGF-A Inhibition

Therapeutic Landscape of Companies with Ophthalmic Pipeline Assets						
Company	**Market Cap US $M**	**Product**	**MOA**	**Stage**	**Disease Focus**	**Treatment Effect**
康弘药业 KANGHONG PHARMACEUTICAL	$5,970	Conbercept	Anti-VEGF-A	Phase III	wAMD, DME,	Durability
KODIAK	$2,100	KSI-301	Anti-VEGF-A	Phase I – III	wAMD, DME, RVO	Durability
ADVERUM BIOTECHNOLOGIES	$1,440	ADVM-022	Anti-VEGF-A VEGF-B, PIGF	Phase I/II	DME, DR, wAMD	Durability
REGENXBIO	$1,280	RGX-314	Anti-VEGF-A	Phase II	wAMD	Durability
GLAUKOS Transforming Glaucoma Therapy	$2,070	Bioerodible, drug delivery	Sustained Release	Early Stage	Glaucoma, wAMD, DME	Durability
Apellis	$2,100	APL-2	Complement C3	Phase III	Dry AMD	Efficacy
aerie	$552	ROCKi/PKCi implant	Rho kinase, Inflammation	Phase I/II	Glaucoma, wAMD, Dry Eye, Dry AMD	Durability
IVERIC bio	$380	Zimura	Complement C5	Phase III	GA Dry AMD	Efficacy
OXURION ADVANCING SCIENCE. ENHANCING VISION.	$124	THR-687 THR-149	Kallikrein, Pan-RGD integrin	Phase III	DME	Durability

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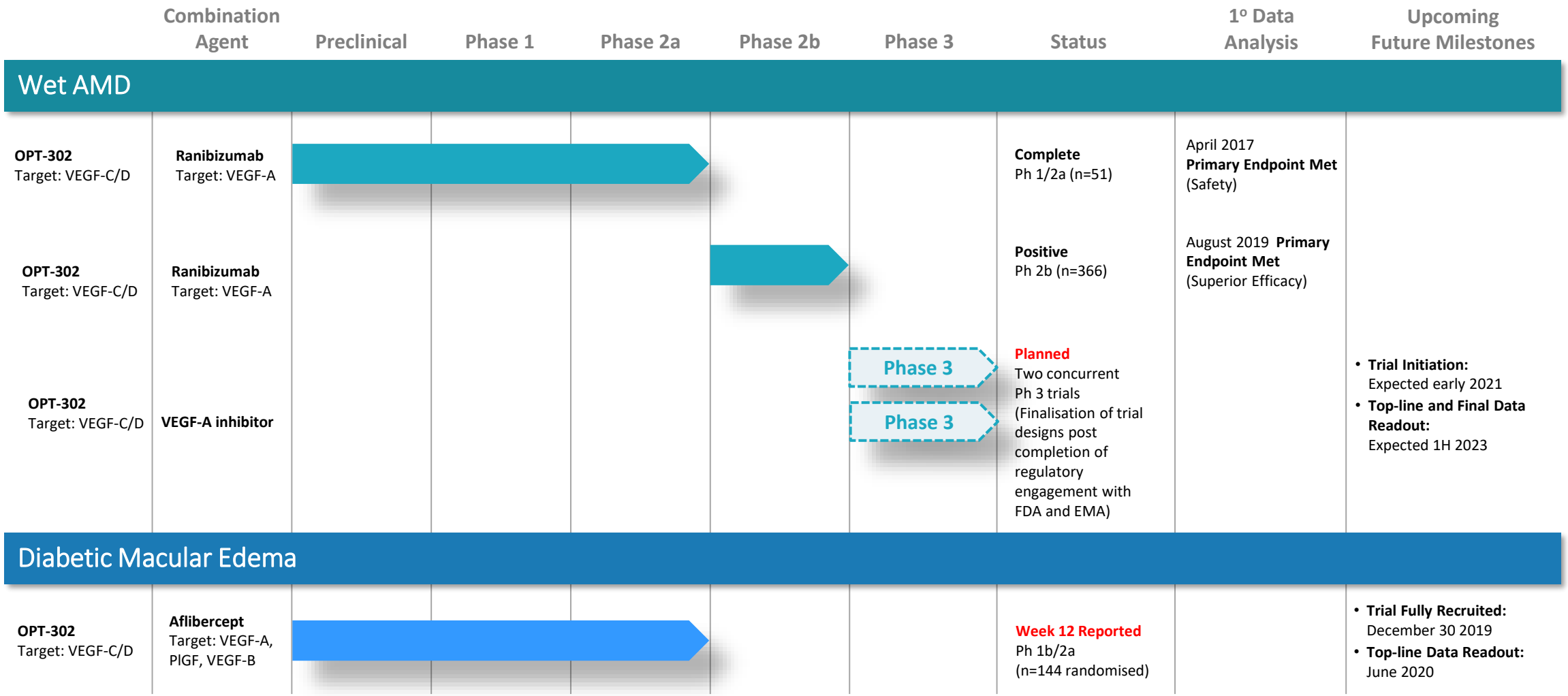
OPT-302 Clinical Program



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Diabetic Macular Edema

Review & Opthea's Phase 1b/2a DME Trial

Arshad M. Khanani, MD, MA
Managing Partner, Director of Clinical Research, Sierra Eye Associates, Reno, NV

Practice Setting: Sierra Eye Associates, Reno, Nevada, USA

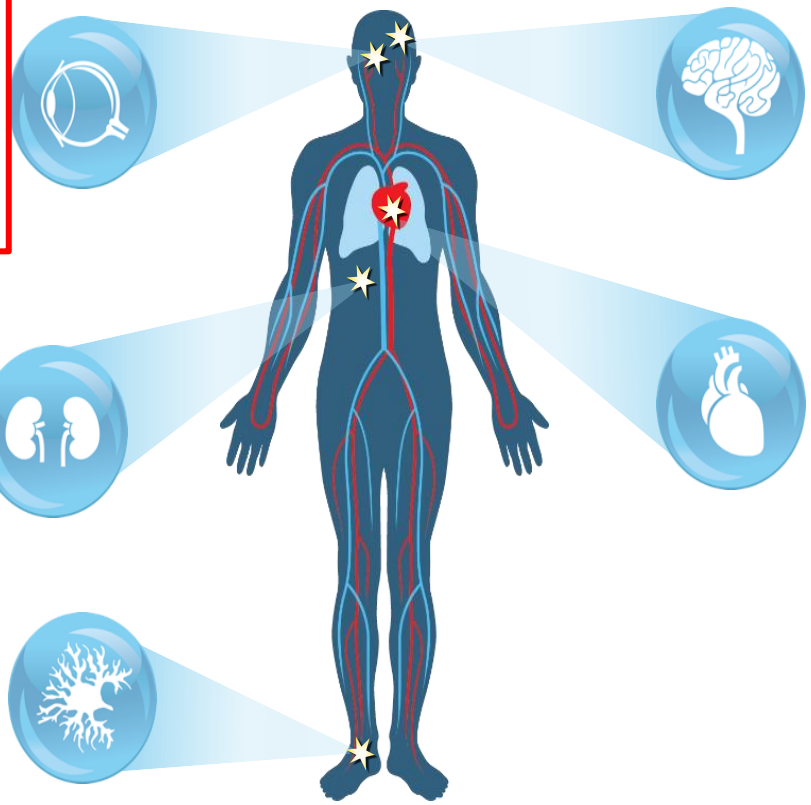
- Private office-based practice
- Multispecialty with 3 retinal physicians
- 75 employees total
- 8 technicians, 6 research coordinators
- 40+ active clinical trials
- 80 patients a day on average
- Approximately 600 anti-VEGF-A Intravitreal injections a month

Diabetes Associated With Serious Comorbidities: Retinopathy & DME

Diabetic retinopathy[1]

28.5% in patients aged ≥40

≈13.6% have diabetic macular edema (DME)[2]



Stroke[4]

11.5 per 1000 persons with diabetes

Diabetic nephropathy[3]

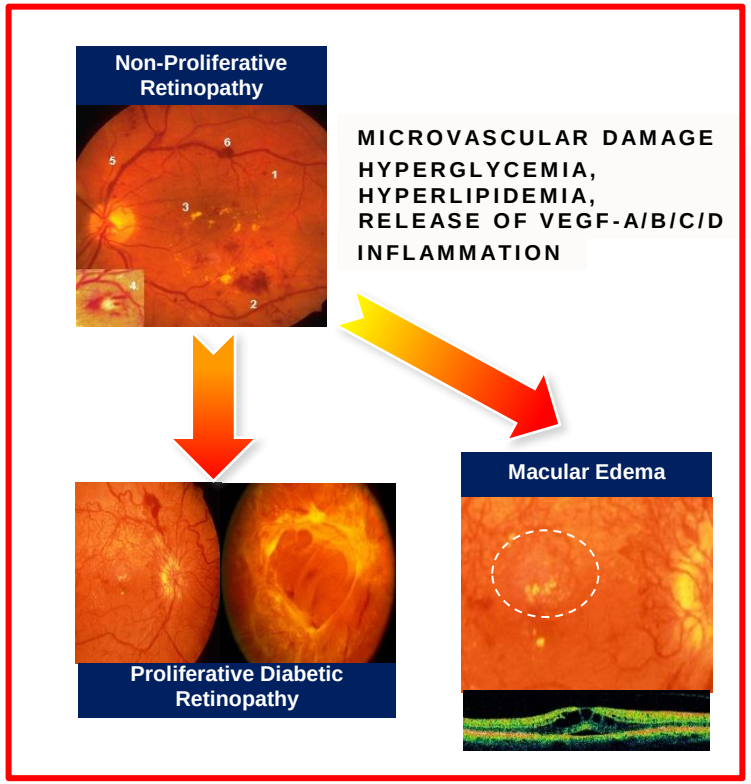
29.9% in diabetic patients

Ischemic Heart Disease[4]

18.3 per 1000 persons with diabetes

Diabetic neuropathy[1]

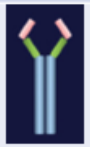
60%-70% in diabetic patients



1. Centers for Disease Control and Prevention. 2011. http://www.cdc.gov/diabetes/pubs/pdf/ndfs_2011.pdf. Accessed June 11, 2018. 2. Varma, et al. 2012 Joint Meeting of the American Academy of Ophthalmology and Asia-Pacific Academy of Ophthalmology; November 10-13, 2012; Chicago, IL. Poster PO252. 3. United States Renal Data System. 2012 atlas of CKD and ESRD. Bethesda, MD: National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases; 2012. http://www.usrds.org/atlas.aspx. Accessed February 7, 2013.
4. Centers for Disease Control and Prevention. 2017 National Diabetes Statistics Report. https://www.cdc.gov/diabetes/pdfs/data/statistics/national-diabetes-statistics-report.pdf. Accessed July 10, 2018.

Current First-line DME treatments primarily target VEGF-A
Second-line treatment includes corticosteroids

Current approved and off-label first-line standard of care therapy primarily targeting VEGF-A inhibition:

Aflibercept (Eylea)
VEGFR-1/2-Fc fusion protein

115 kDa
2.0 mg

Ranibizumab (Lucentis)
Monoclonal humanized antibody fragment

48 kDa
0.3 mg; 0.5 mg

Bevacizumab[a] (Avastin)
Full antibody (IgG1)

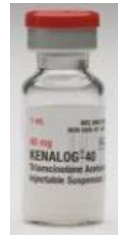
149 kDa
1.25 mg (unlicensed use)

Steroid treatments mostly used as second-line therapy:

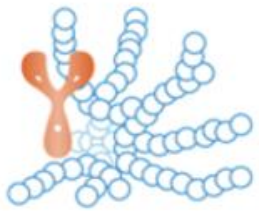
Fluocinolone acetonide

Dexamethasone

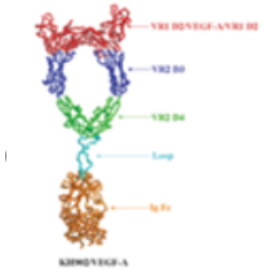
Triamcinolone



Investigational Treatments in DME Pipeline also Mostly Targeting VEGF-A and/or are Aimed at Durability

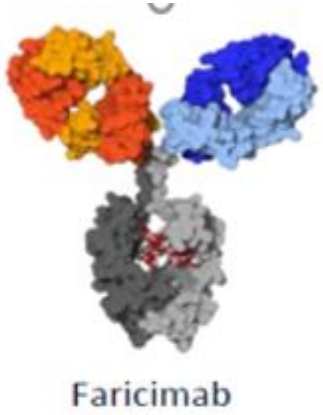


KSI-301



Conbercept

PDS



Faricimab

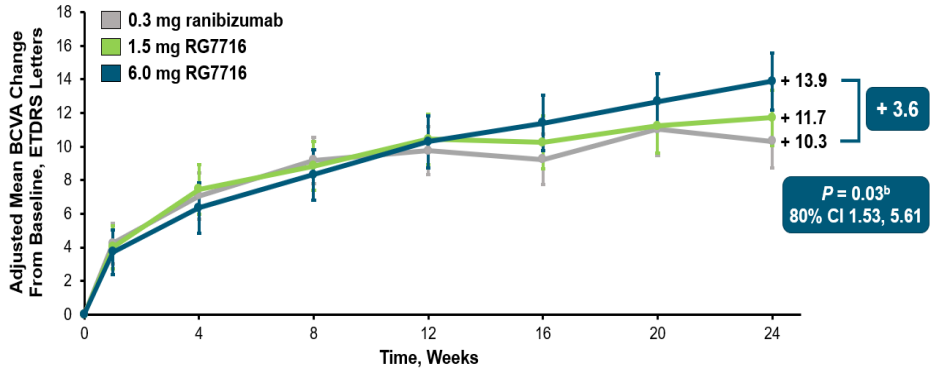
Anti-VEGF-A/Ang-2 Bispecific Antibody Faricimab in DME. Results of Phase 2 BOULEVARD trial

Treatment-Naïve

Mean BCVA Change From Baseline

RG7716 met its prespecified primary endpoint of efficacy

Linear model adjusted for baseline BCVA and randomization stratification factors[a]



Anti–VEGF treatment-naïve patients only. Error bars represent 80% CI.
[a] Linear model adjusted for baseline BCVA, previous macular laser treatment status at randomization, and BCVA category (≥ 64 letters vs ≤ 63 letters) at baseline. [b] $P = 0.03$ for 6.0 mg RG7716 vs 0.3 mg ranibizumab. Protocol prespecified significance level, $P < 0.2$. BOULEVARD clinical trial (NCT02699450). BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study.

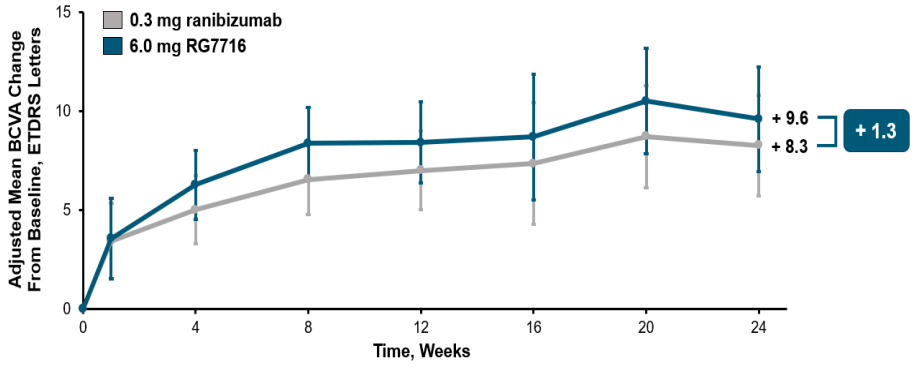
BOULEVARD
A Randomized Trial in DME

Previously-Treated

Mean BCVA Gains From Baseline

BCVA outcome directionally supports primary outcome

Linear model adjusted for baseline BCVA[a]



Previously anti–VEGF-treated patients only, intent-to-treat population. Error bars represent 80% CI.
[a] Least squares means from linear model analysis of study eye BCVA change from baseline, BOULEVARD clinical trial (NCT02699450). BCVA, best-corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study.

BOULEVARD
A Randomized Trial in DME

Patients With Persistent DME Are a Significant Unmet Need

There is a need for novel therapeutic approaches to improve clinical outcomes

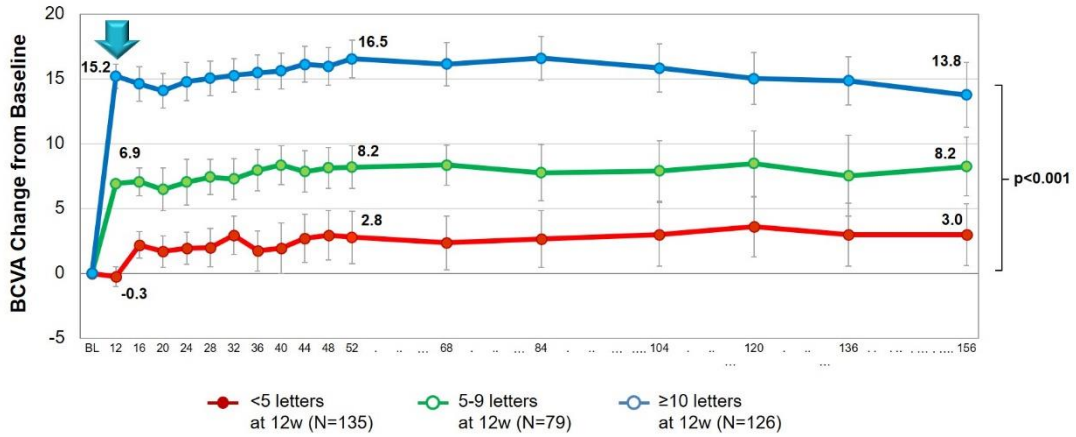
Many patients have limited BCVA gains despite regular anti-VEGF-A monotherapy

In Protocol I:

- 40% patients gained < 5 letters by week 12
- 23% patients gained 5-9 letters by week 12
  - Only ~25-30% patients show a further ≥ 5 letter gain from 12 weeks to 1 year
  - Mean BCVA from 12 weeks to 1 year only improved by ~1.3 to 3.1 letters

DRCR Protocol I

Sub-optimal responders identified as early as 12 weeks



- **Therapeutic options are limited for patients with persistent DME**
  - Switching of anti-VEGF-A therapy
  - IVT corticosteroids associated with cataracts & IOP increase

Combination therapy targeting alternative mediators of the disease such VEGF-C/-D may lead to improved outcomes

*Based on randomized, controlled clinical trial data; # Fail to achieve ≥ 2 lines gain in BCVA; ^ SD-OCT CST ≥ 300 μM or Time-Domain OCT CST ≥ 250 μM

Nguyen QD et al. Ophthalmology 2012; 119:789-801; Do DV, et al, JAMA Ophthalmol 2013; 131:139-45; Gonzalez VH et al, Am J Ophthalmol. 2016; Spooner K, et al, Clin Ophthalmol. 2017; 11: 161-177.; Regillo CD, et al, Ophthalmic Surg Lasers Imaging Retina 2017; 48:291-301. BCVA, best-corrected visual acuity; DME, diabetic macular edema; VEGF, vascular endothelial growth factor.

Role of VEGF-C and -D in the Pathophysiology of DR and DME

Rationale for inhibition of VEGF-C/D in DME

- VEGFR-2 expression is greater in diabetic retina than non-diabetics [1,2,3]
- Elevations of VEGF-C in diabetic retinopathy and VEGF-D in vitreous of diabetics[3,4]
- VEGF-C expression is elevated by glucose & pro-inflammatory cytokines [5,6]
- Advanced glycation end products accumulate faster in diabetics and stimulate VEGF-C expression and secretion from the RPE [7]
- Single nucleotide polymorphisms (SNPs) in diabetic patients indicate that genetic variation in the VEGF-C gene is associated with DR and DME [8]

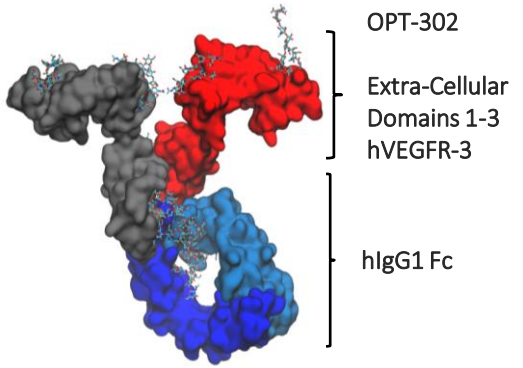
VEGF-C/D Signaling Pathway plays a functional role in the Pathogenesis of DME

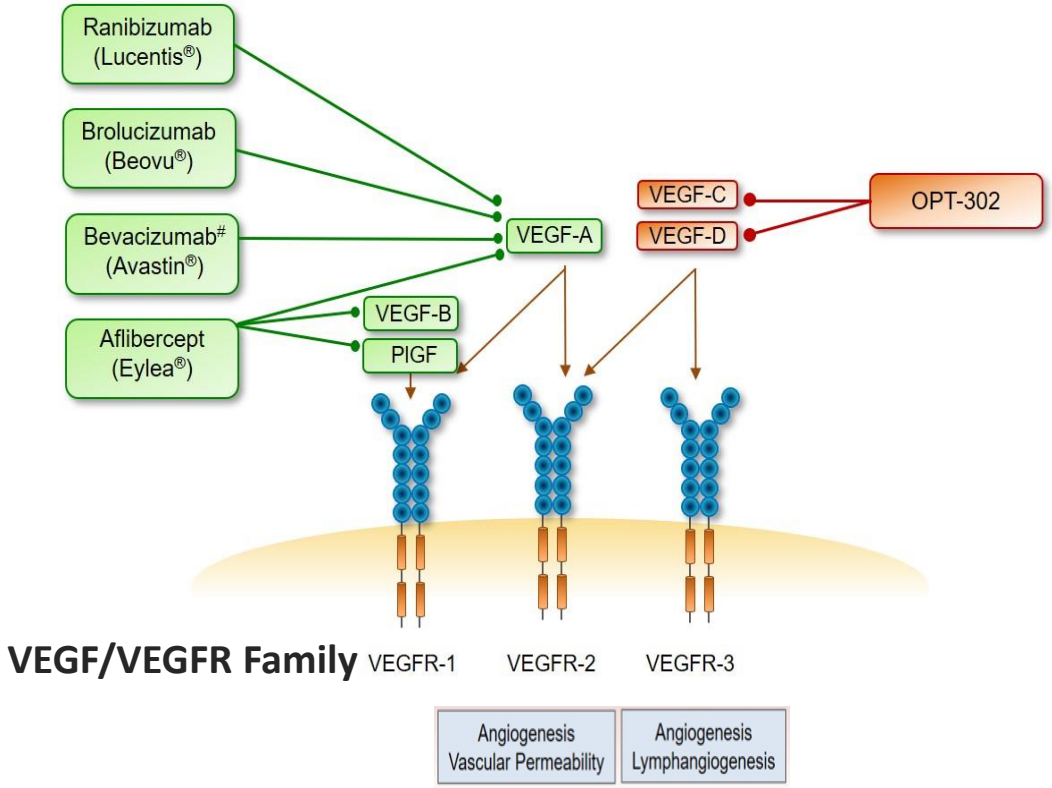
1. Sun et al., 2014; 2. Witmer et al., 2002; 3. Zhao et al., 2007; 4. Kovacs et al., 2015; 5. Puddu et al., 2012; 6. Nagineni et al., 2011; 7. Karaman et al., 2014; 8. Kaidonis et al., 2015
DME, diabetic macular edema; DR, diabetic retinopathy; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor

OPT-302: Inhibitor of VEGF-C and -D

Intravitreal OPT-302 combination therapy may improve outcomes in DME

- OPT-302 is a soluble VEGFR-3 'trap' fusion protein
  - Potent inhibitor of VEGF-C/-D interaction with VEGFR-2 & VEGFR-3
- Existing therapies target VEGF-A but not VEGF-C or VEGF-D





- VEGF-C is elevated in diabetic retinopathy and vitreous levels of VEGF-D are elevated in diabetes
- VEGF-C/-D are upregulated in response to VEGF-A suppression
- OPT-302 combination therapy targets this escape mechanism with broad inhibition of the VEGF/VEGFR pathway
- OPT-302 combination therapy demonstrated superiority in BCVA gains from baseline to week 24 over anti-VEGF-A monotherapy in treatment naïve patients with nAMD*

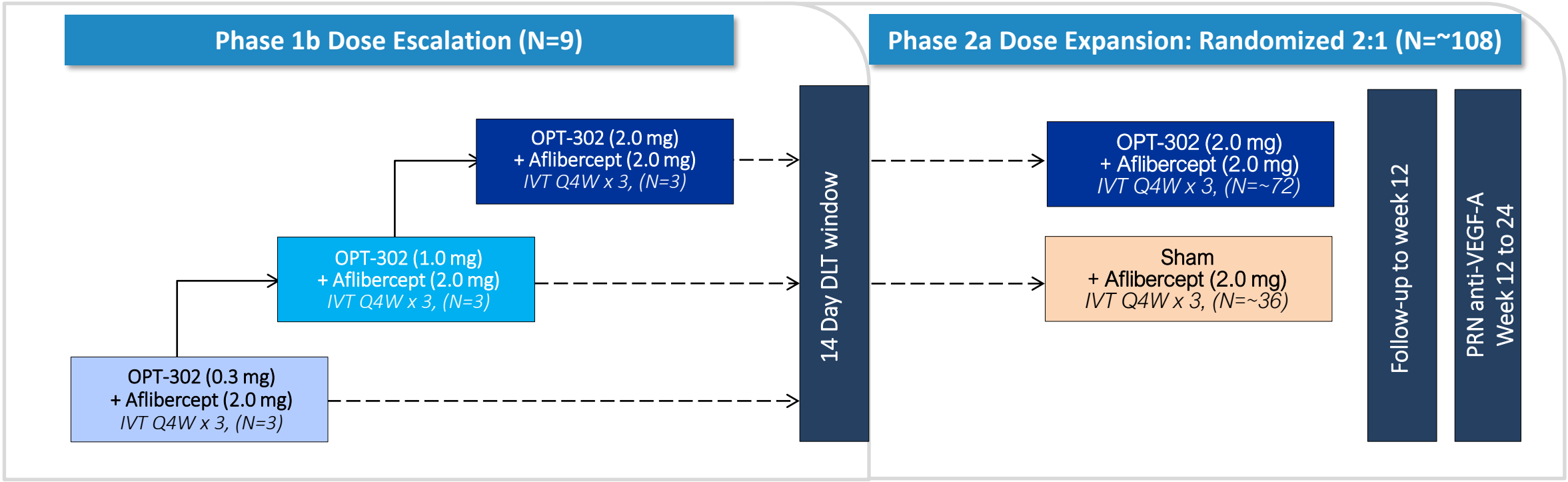
Dugel PU et al, 2020; Zhao B, et al. 2007; Kovacs K, et al. 2015; Lieu C, et al. 2013; Li D, et al. 2014; Rose S and Aghi M. 2010; Fan F, et al. 2011; Cabral T, et al. 2018

*Based on Phase 2b randomized, controlled clinical trial data in 366 patients ; Jackson, T, Euretina 2019.

BCVA, best-corrected visual acuity; DME, diabetic macular edema; VEGF, vascular endothelial growth factor; VEGFR, vascular endothelial growth factor receptor.

OPT-302 DME Trial Design

Previously anti-VEGF-A-treated patients with persistent DME, a difficult-to-treat population



Key Inclusion Criteria

- Age ≥ 18 years; centre-involving DME
- CST ≥ 320 µm*
- BCVA 73 – 24 ETDRS letters (20/40 – 20/320 Snellen)
- Prior exposure to anti-VEGF-A therapy
  - ≥ 3 intravitreal injections in last 5 months prior to study day 1
  - Last injection ≤ 42 days prior to study day 1
  - Prior off-label bevacizumab only allowed if switched to ≥ 1 injection of aflibercept or ranibizumab prior to study

Key Exclusion Criteria

- HbA1c ≥ 12%
- Uncontrolled hypertension ≥ 180 mmHg systolic or ≥ 110 mmHg diastolic
- Eyes needing PRP within 3 months of screening
- Concurrent / prior use of intravitreal injections of steroids within 4 months of study start
- Concurrent / prior dexamethasone or fluocinolone implant in study eye

OPT-302-1003 Phase 1b/2a clinical trial (NCT03397264)
*CST as measured by Spectralis (Heidelberg) at screening, ≥ 305 µm for Cirrus.
DLT, Dose Limiting Toxicity; Q4W, once every 4 weeks; VEGF, vascular endothelial growth factor;

Phase 2a Clinical Analyses of OPT-302 Combination Therapy

All patients enrolled had persistent center-involved DME despite prior anti-VEGF-A treatment

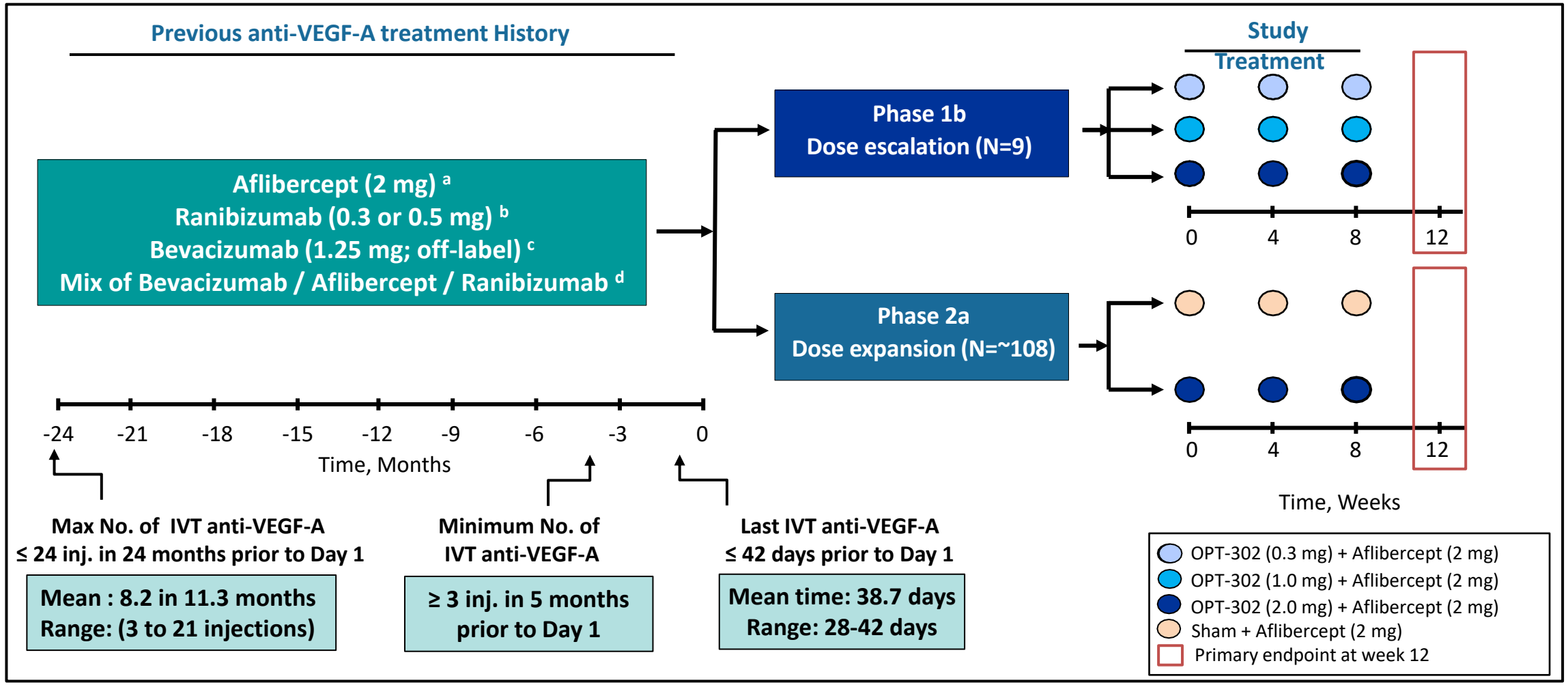
Clinical Analyses:

- All patients in the Per Protocol Population
  - Heterogeneous all comer's population for prior anti-VEGF-A history
    - (aflibercept / ranibizumab / bevacizumab)
  - Variable prior-treatment history
    - number and frequency of previous intravitreal anti-VEGF-A injections
- Patients who had received prior aflibercept therapy (exploratory subgroup)
  - More homogenous population for prior anti-VEGF-A history
  - Less variable prior treatment history & greater VEGF-A suppression at baseline
  - Most stringent and least variable patient population to test the ability of OPT-302 to provide additional benefit over VEGF-A inhibition

OPT-302 Phase 1b/2a

Phase 1b dose escalation and Phase 2a randomised, controlled, double masked, proof-of-concept study

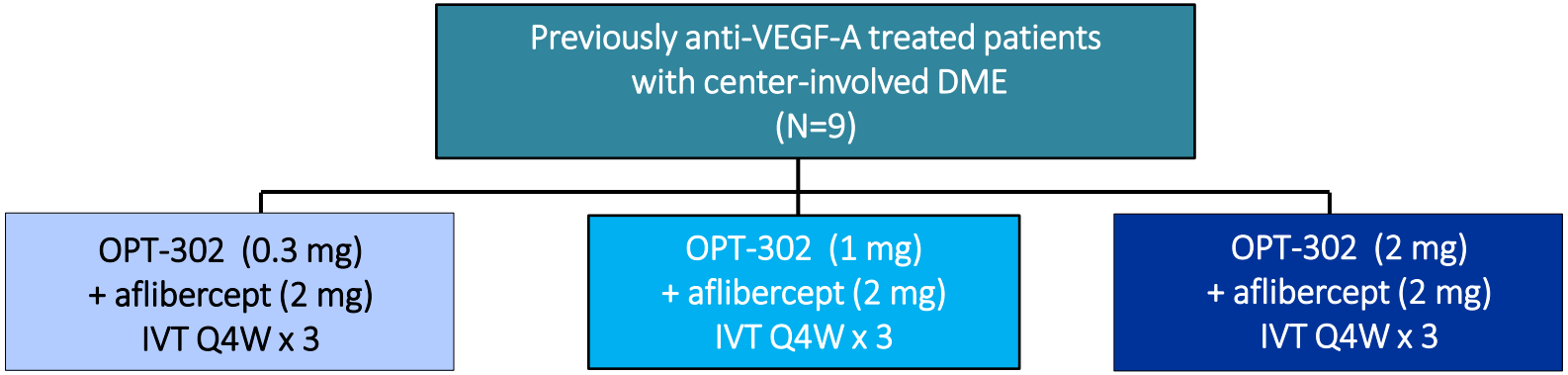
- **Heterogeneous all comer's population for prior anti-VEGF-A history (aflibercept / ranibizumab / bevacizumab) in patients with persistent DME**
  - Variable treatment history including number and frequency of prior intravitreal injections of anti-VEGF-A monotherapy



a Includes patients receiving only all Aflibercept or last 3 injections of Aflibercept prior to study entry
b Includes patients receiving only all Ranibizumab or last 3 injections of Ranibizumab prior to study entry
c Includes patients receiving only all off-label Bevacizumab. For last injection prior to study entry patients must be switched to 1 injection of either Aflibercept or Ranibizumab
d Includes patients receiving multiple switching of anti-VEGF-A therapy. For last injection prior to study entry patients must be switched to 1 injection of either Aflibercept or Ranibizumab

Phase 1b Dose Escalation of OPT-302 Combination Therapy

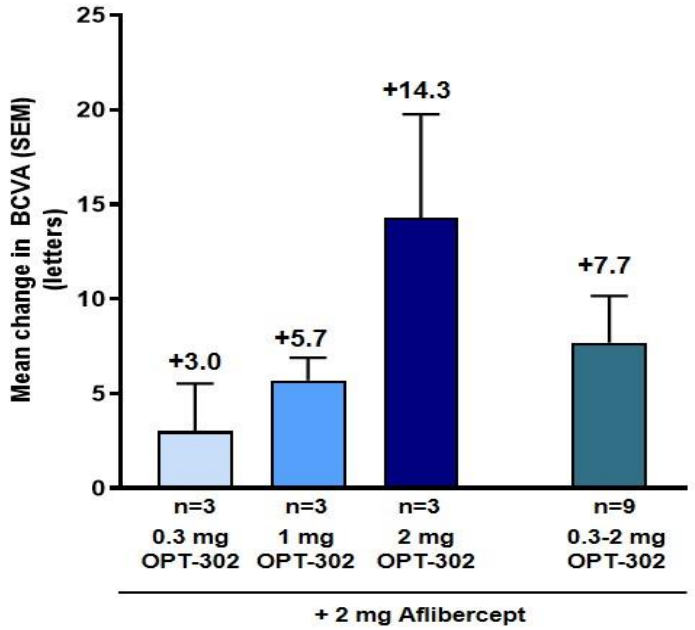
Summary of results

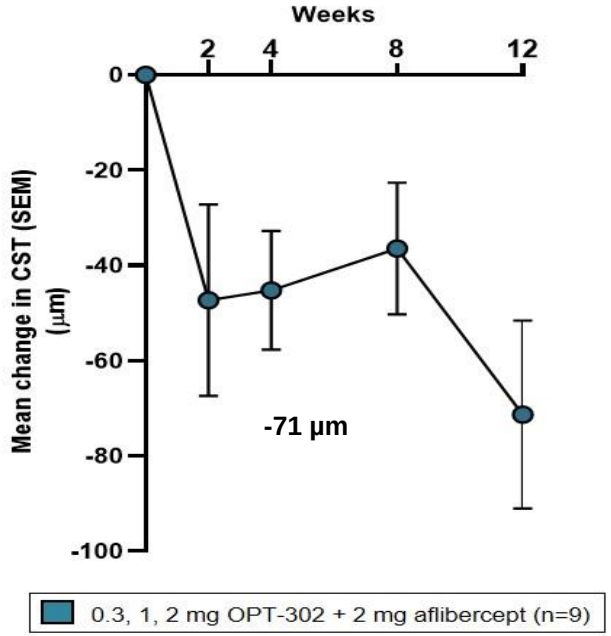


- OPT-302 + Aflibercept showed a dose-response for BCVA gains to Week 12 with a corresponding decrease in CST

Safety / Tolerability:

- IVT OPT-302 up to 2 mg in combination with aflibercept (2 mg) was well tolerated
- No dose limiting toxicities
- Maximum Tolerated Dose not reached
- No study drug related adverse events





IVT – intravitreal; Q4W – once very 4 weeks

Baseline Demographics

Well balanced across treatment groups in Phase 2a

Characteristic	Aflibercept (2mg) + Sham (N = 48)	Aflibercept (2mg) + OPT-302 (2 mg) (N = 96)
Mean age, years (SD)	61.2 (9.40)	61.8 (10.07)
Male, n (%)	30 (62.5%)	60 (62.5%)
Race, n (%) American Indian or Alaska native Asian Black or African American White Other	 0 (0%) 1 (2.1%) 8 (16.7%) 37 (77.1%) 2 (4.2%)	 0 (0%) 1 (1.0%) 8 (8.3%) 87 (90.6%) 0 (0%)
Mean duration of diabetes, years (SD)	15 (9.23)	14.5 (8.97)
Diabetes Type n (%)		
Type I	3 (6.3%)	5 (5.2%)
Type II	45 (93.8%)	87 (90.6%)
Type not reported	0 (0%)	4 (4.2%)
Mean HbA1c, % (SD)	8.1 (1.27)	7.5 (1.37)

Intent to Treat population (n=144)

Baseline Demographics

Well balanced across treatment groups in Phase 2a

Characteristic	2.0 mg aflibercept + Sham (N=48)	2.0 mg aflibercept + 2.0 mg OPT-302 (N=96)
Vision		
Mean best corrected visual acuity (BCVA) – letters (±SD)	63.9 (9.44)	63.3 (8.31)
>55 letters vision - n (%)	41 (85.4%)	81 (84.4%)
≤55 letters vision - n (%)	7 (14.6%)	15 (15.6%)
Anatomic		
Mean central subfield thickness (CST) - µm (±SD)	427.3 (99.7)	433.8 (104.5)
CST >450 µm - n (%)	17 (35.4)%	30 (31.3)%
CST ≤450 µm - n (%)	31 (64.6)%	66 (68.8)%
Diabetic Retinopathy Severity Score		
Absent or mild NPDR (level 10-20)	4 (8.4%)	4 (4.4%)
Mild-moderate NPDR (level 35)	4 (8.3%)	13 (14.2%)
Moderate NPDR (level 43)	11 (22.9%)	15 (16.5%)
Moderately Severe NPDR (level 47)	20 (41.7%)	46 (50.5%)
Severe NPDR (level 53)	7 (14.6%)	13 (14.3%)
Mild PDR (level 61)	2 (4.2%)	0 (0.0%)

Intent to Treat population (n=144)

Prior Treatment History Study Eye

Characteristic	2.0 mg aflibercept + Sham (N=40)	2.0 mg aflibercept + 2.0 mg OPT-302 (N=75)
Mean Duration of Diabetic Macular Edema – years (±SD)	1.6 (1.70)	1.3 (1.30)
Mean Number of Prior IVT Anti-VEGF-A Injections for CI-DME (±SD)	8.4 (4.56)	8.0 (4.35)
Mean Duration of Prior IVT Anti-VEGF-A injections – months (±SD)	12.4 (6.43)	10.7 (5.95)
Mean time from Prior Treatment to Day 1 – days (±SD)	38.4 (3.59)	38.8 (3.87)
Prior Anti-VEGF-A Therapies n (%)		
3 injections	4 (10.0%)	6 (8.0%)
4-6 injections	13 (32.5%)	33 (44.0%)
7-12 injections	15 (37.5%)	24 (32.0%)
13-24 injections	8 (20.0%)	12 (16.0%)
Prior Anti-VEGF-A Treatment n (%)		
Aflibercept [a]	13 (32.5%)	22 (29.3%)
Ranibizumab [b]	4 (10.0%)	9 (12.0%)
Bevacizumab [c]	19 (47.5%)	35 (46.7%)
Multiple switching of anti-VEGF-A therapy (aflibercept, ranibizumab, bevacizumab) [d]	4 (10.0%)	9 (12%)

Per Protocol population (n=115), must have received all 3 intravitreal study treatments and evaluable at Baseline through Week 12 and sufficiently compliant with the protocol.
a Includes patients receiving only all Aflibercept or last 3 injections of Aflibercept prior to study entry
b Includes patients receiving only all Ranibizumab or last 3 injections of Ranibizumab prior to study entry
c Includes patients receiving only all Bevacizumab. For last injection prior to study entry patients must be switched to 1 injection of either Aflibercept or Ranibizumab
d Includes patients receiving multiple switching of anti-VEGF-A therapy. For last injection prior to study entry patients must be switched to 1 injection of either Aflibercept or Ranibizumab

Safety

Well tolerated & consistent with previous OPT-302 Phase 1 and Phase 2b clinical trials in wet AMD

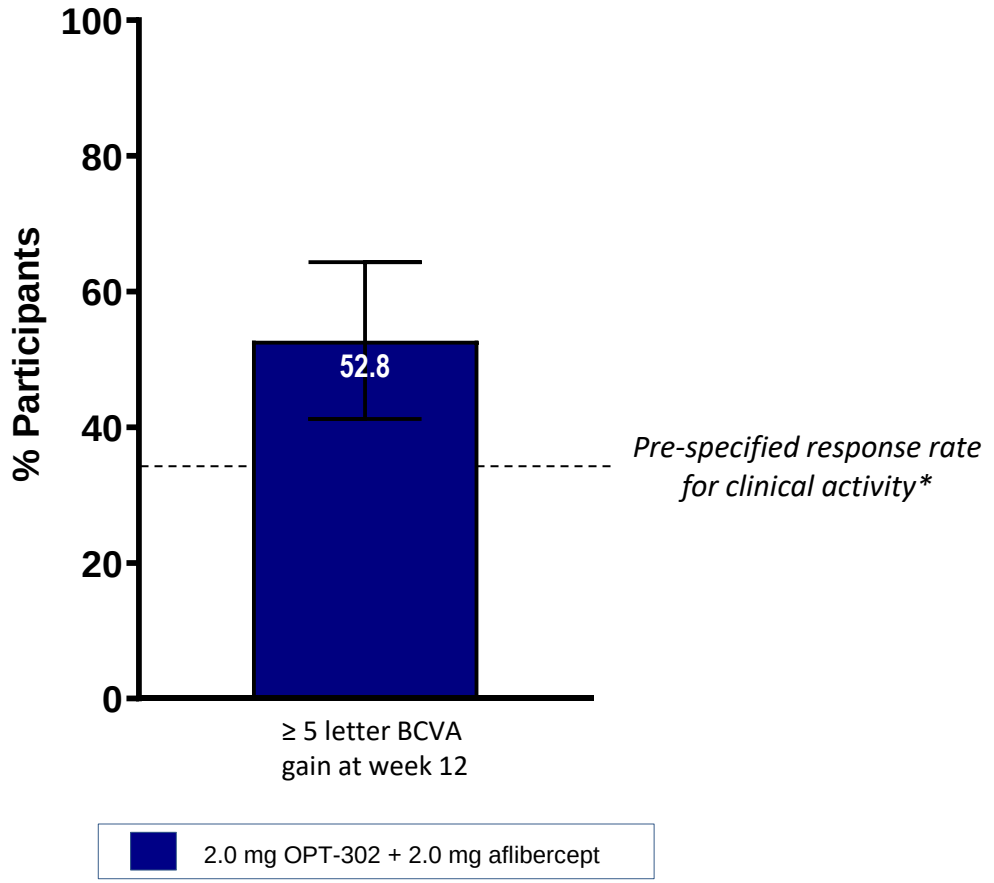
Selected Adverse Events Study Eye or Systemic, n (%)	Aflibercept (2mg) + Sham (N = 49)	Aflibercept (2mg) + OPT-302 (2 mg) (N =95)
Intraocular inflammation	1 (2.0%)	1 (1.1%)
Endophthalmitis	0 (0%)	0 (0%)
Retinal detachment	0 (0%)	0 (0%)
Cataract	1 (2.0%)	3 (3.2%)
Intraocular Pressure Increased^	3 (6.1%)	14 (14.7%)
Non-fatal myocardial infarction	0 (0%)	0 (0%)
Non-fatal stroke*	0 (0%)	1 (1.1%)
Vascular death	0 (0%)	0 (0%)
Any other death	0 (0%)	0 (0%)

- A total of 299 intravitreal injections of OPT-302 (any dose) were co-administered with aflibercept (2 mg) in the Phase 1b/2a DME trial

Safety population (n=144); TEAEs reported through Week 12.
^Changes in IOP were transient and there were no sustained changes to post-treatment mean IOP values compared to baseline.
*Grade 3 cerebrovascular accident, 21 days following the second dosing of study products, participant was hospitalized. No evidence of occlusion of the great vessels.
It was concluded that a CVA could not be ruled out however its location is unclear. The event was assessed as possibly related as it was confounded by the underlying diabetes mellitus, which is a risk factor for the event, as well as underlying Bladder cancer as having potential to induce thrombotic events. Participant withdrew consent and was discontinued due to the event

Primary Efficacy Endpoint: Response Rate of ≥ 5 letter gain to Week 12

Previously anti-VEGF-A treated DME patients after switching to OPT-302 + aflibercept combination therapy

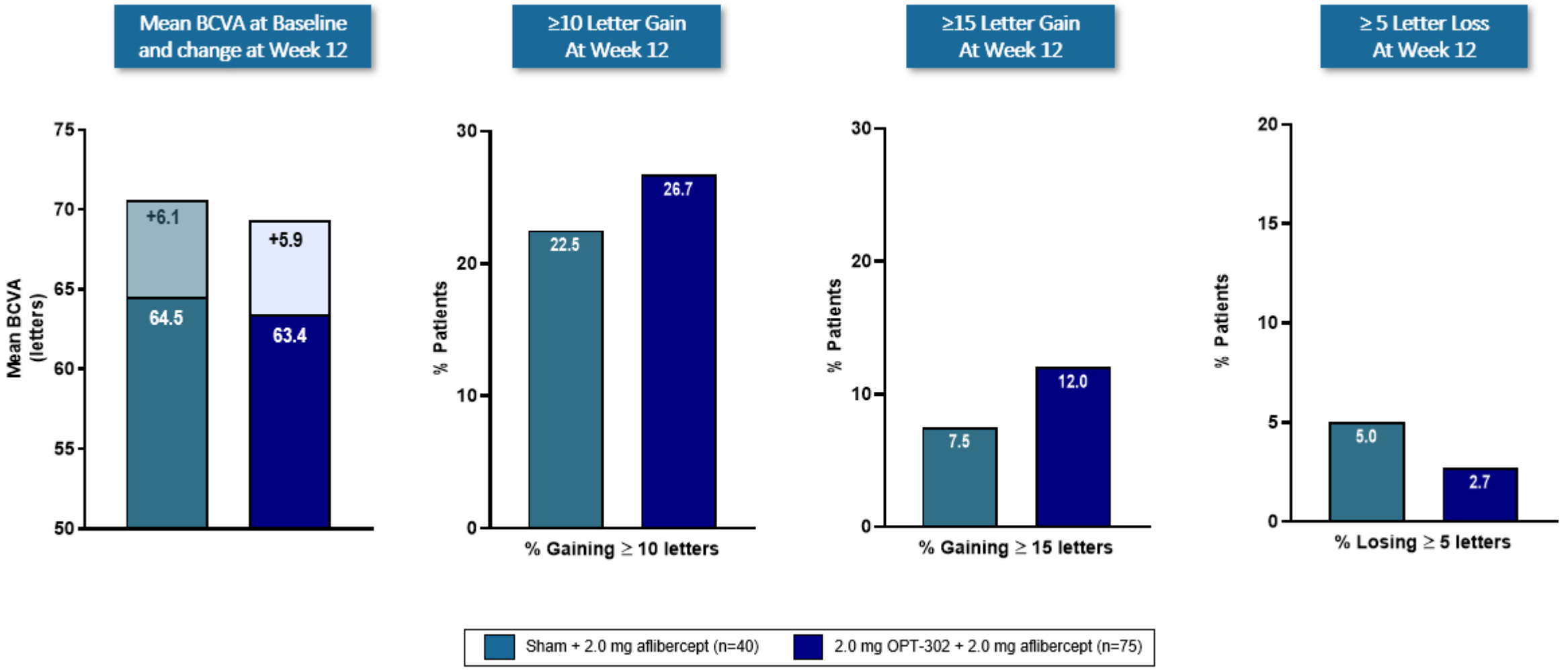


* A one stage design was used (Sargent, Control Clin Trials 2001;22:117–125) based on the pre-specified response rate primary outcome of a total of 72 evaluable patients receiving aflibercept + OPT-302, in Per Protocol population, must have received all 3 intravitreal study treatments and evaluable at Baseline through Week 12,and sufficiently compliant with the protocol.

- Clinical activity if ≥ 27 of 72 patients have a ≥ 5 letter gain in BCVA from baseline to week 12; Type I and II error rates set to 5% and with probability of at least 90%
- Bars represent 95% Confidence Intervals
- Based on previous studies that show limited scope to achieve a further 5 letter or more improvement gain in visual acuity following an initial loading dose period and ongoing anti-VEGF-A monotherapy, and historical anti-VEGF-A response rate (Gonzalez VH, et al. Am J Ophthalmol 2016; 172:72-79.; Chatziralli I, et al. Eye. 2017; 31: 1594-1599; Maturi RK, et al. JAMA Ophthalmology. 2018; 136: 29-38; Based on (Gonzalez VH et al, Am J Ophthalmol. 2016).

Mean Change in BCVA and % Vision Gains & Loss - Baseline to Week 12

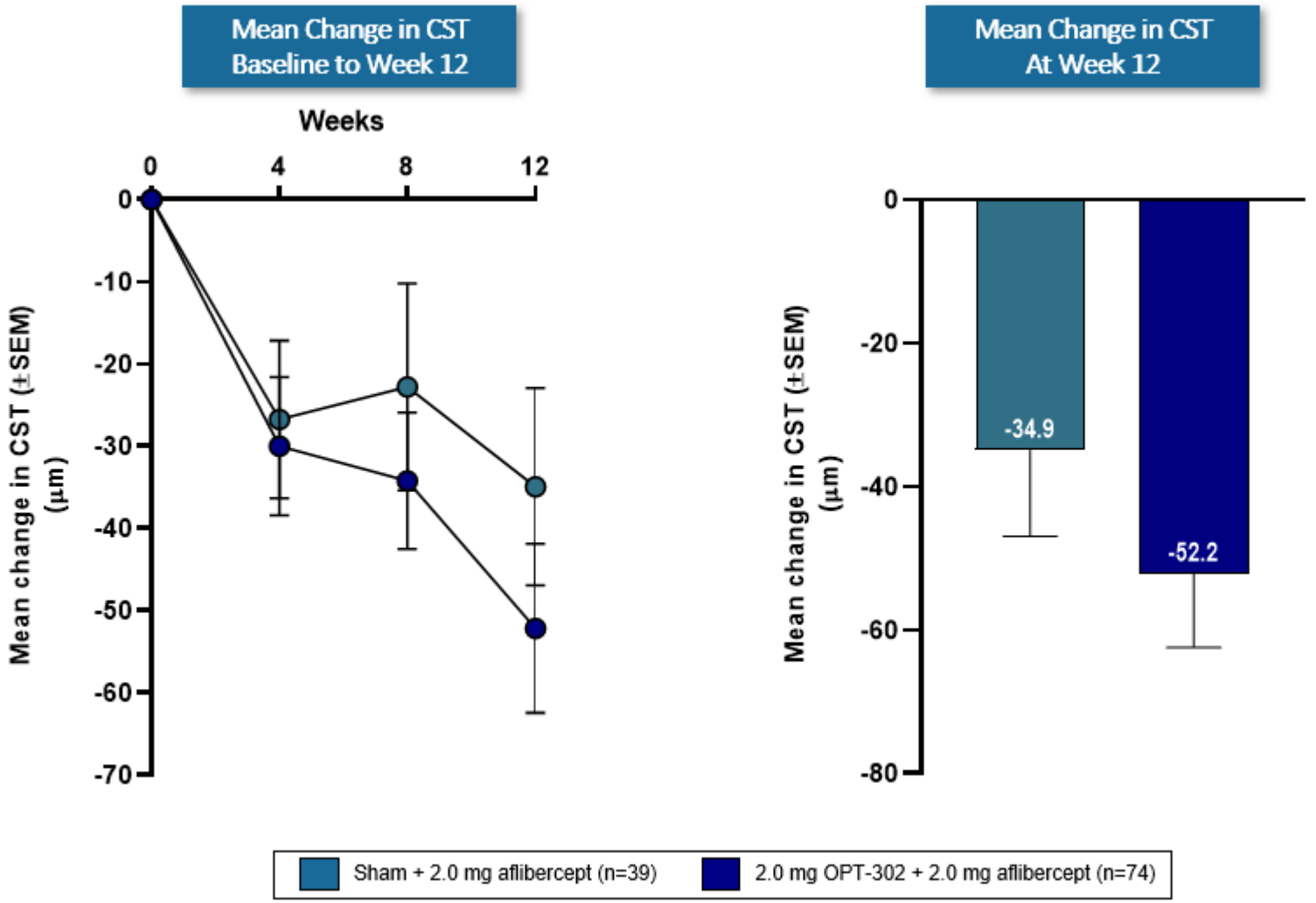
Persistent DME patients: Prior anti-VEGF-A therapy of aflibercept /ranibizumab / bevacizumab



Per Protocol population (n=115), must have received all 3 intravitreal study treatments and evaluable at Baseline through Week 12 and sufficiently compliant with the protocol.

Mean Change in Central Subfield Thickness - Baseline to Week 12

Persistent DME patients: Prior anti-VEGF-A therapy of aflibercept /ranibizumab / bevacizumab

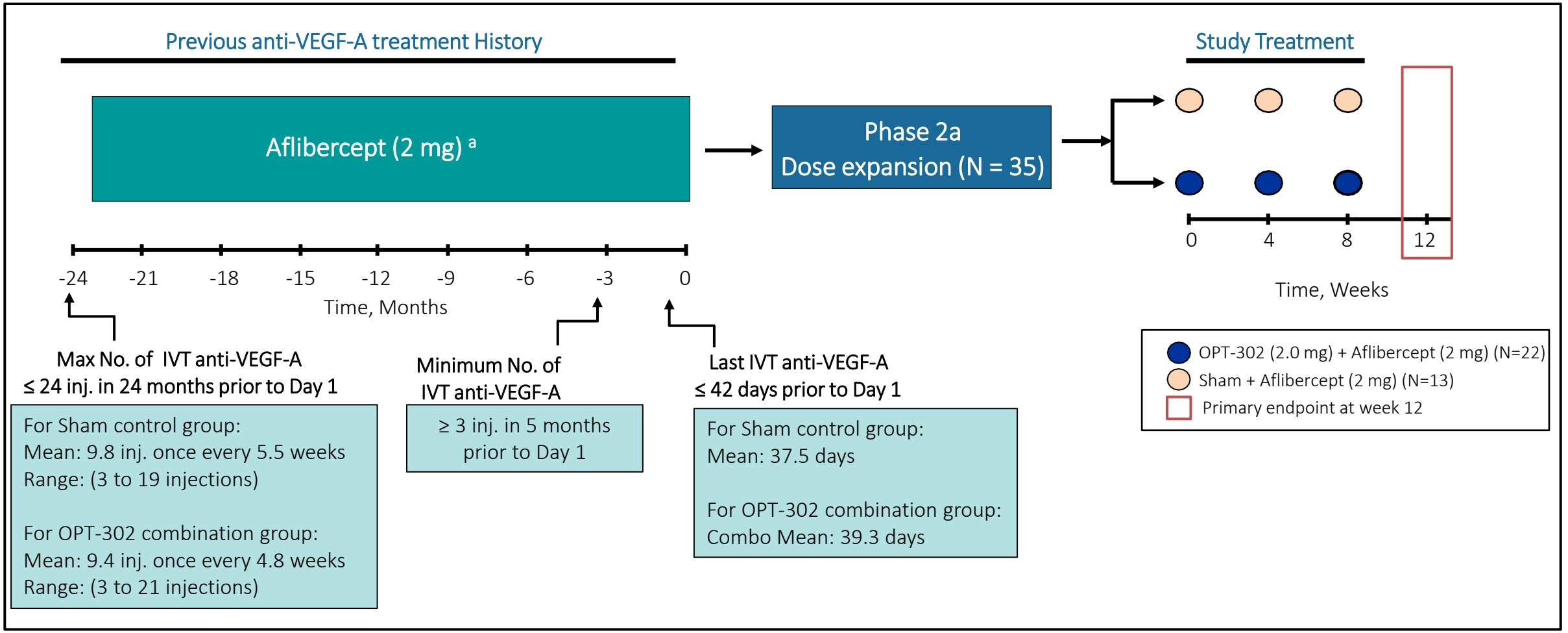


Per Protocol population (n=115), must have received all 3 intravitreal study treatments and evaluable at Baseline through Week 12 and sufficiently compliant with the protocol.
Error bars (± SEM)

OPT-302 Phase 2a DME Study

Exploratory subgroup analysis in patient population receiving previous aflibercept

- More homogeneous population of anti-VEGF-A prior treatment history of previous aflibercept in patients with persistent DME
  - Less variable prior treatment history & greater VEGF-A suppression at baseline
  - Most stringent and least variable patient population to test the ability of OPT-302 to provide additional benefit over VEGF-A inhibition

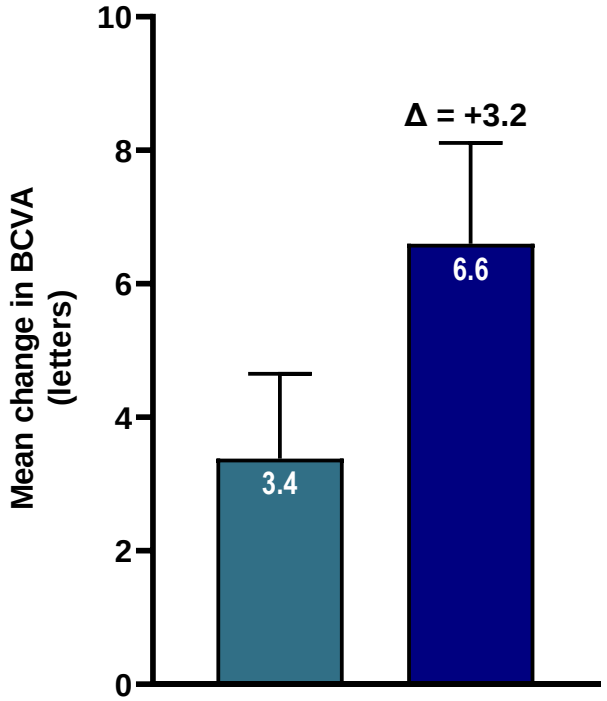


a Includes patients receiving only all Aflibercept or last 3 injections of Aflibercept prior to study entry
Sham = Sham + Aflibercept (2 mg); Combo = OPT-302 (2 mg) + Aflibercept (2 mg); inj. = injections;

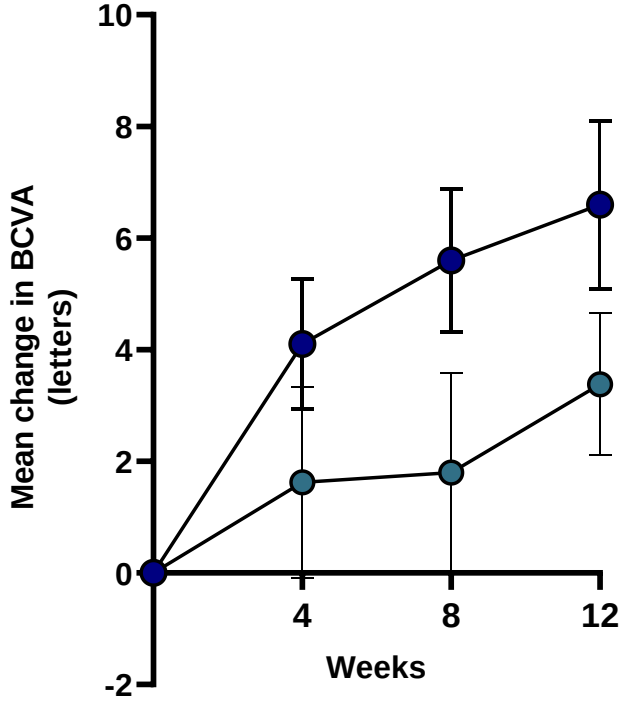
Visual Acuity Gain following OPT-302 combination therapy

Exploratory Subgroup Analysis in patient population with a prior treatment history of previous aflibercept

Mean Change in BCVA
Baseline to Week 12



Mean Change in BCVA
Baseline to Week 12



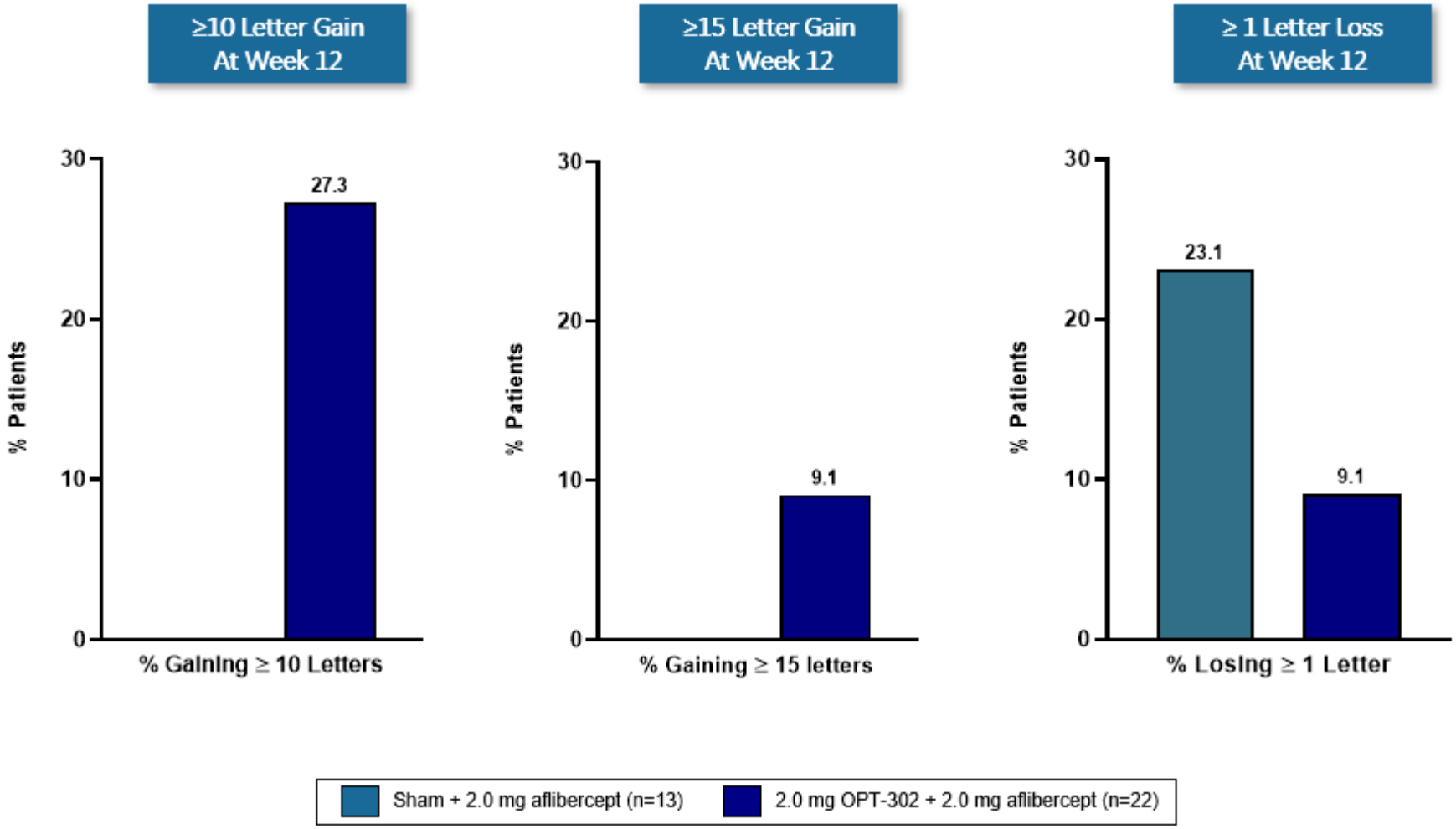
Sham + 2.0 mg aflibercept (n=13)

2.0 mg OPT-302 + 2.0 mg aflibercept (n=22)

Per Protocol population prior aflibercept subgroup (n=35), must have received all 3 intravitreal study treatments and evaluable at Baseline through Week 12 and sufficiently compliant with the protocol.
Error bars (± SEM)

Gains in Visual Function, Reduced Vision Loss with OPT-302

Exploratory Subgroup Analysis in patient population with a prior treatment history of previous aflibercept

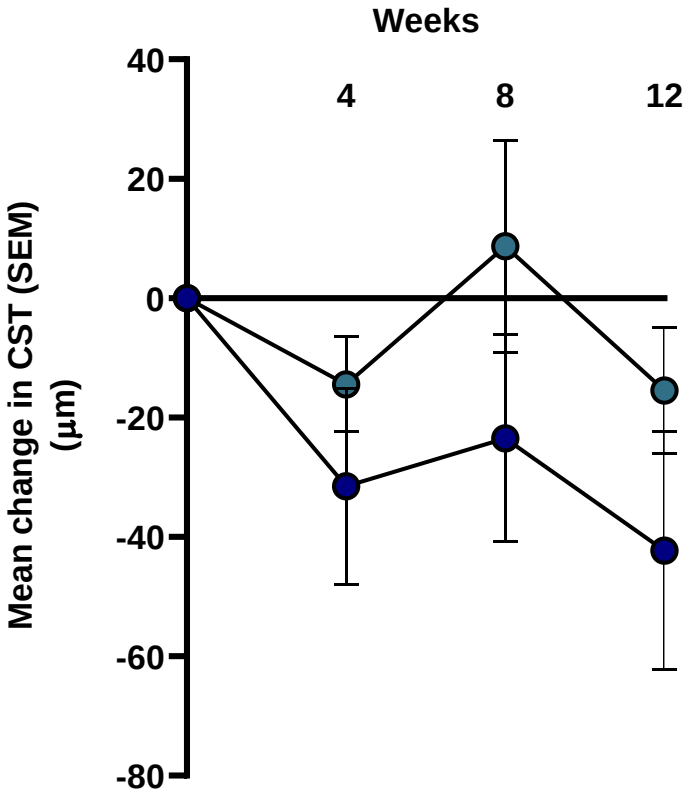


Per Protocol population prior aflibercept subgroup (n=35), must have received all 3 intravitreal study treatments and evaluable at Baseline through Week 12 and sufficiently compliant with the protocol.

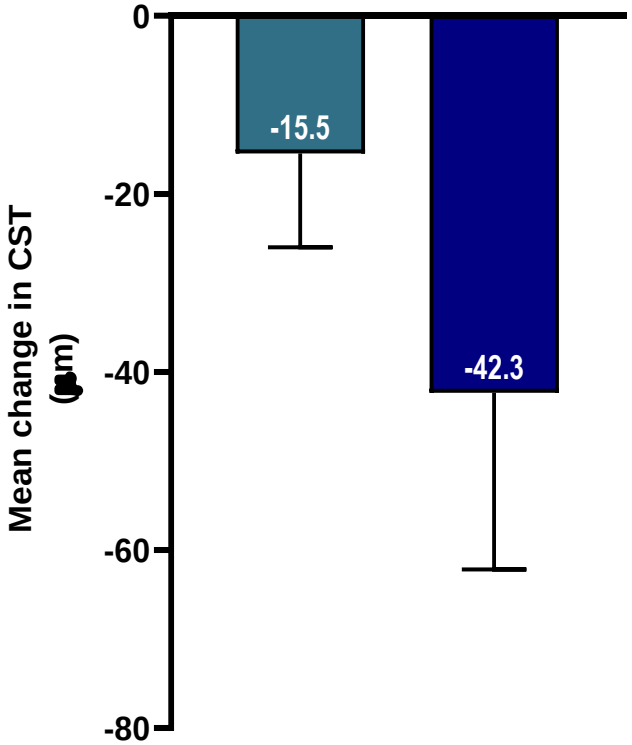
Reduced Retinal Thickness with OPT-302 Combination Therapy

Exploratory Subgroup Analysis in patient population with a prior treatment history of previous aflibercept

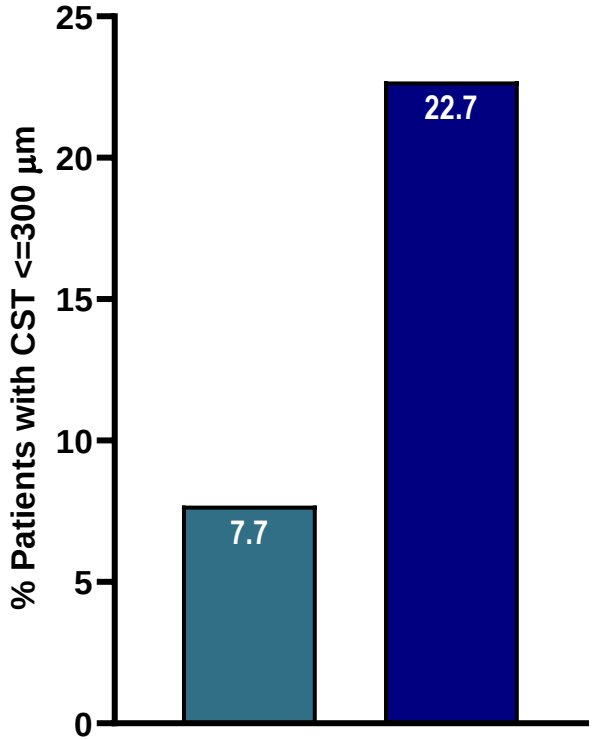
Mean Change in CST Baseline to Week 12



Mean Change in CST At Week 12



% Patients ≤300 µm CST At Week 12



Sham + 2.0 mg aflibercept (n=13) | 2.0 mg OPT-302 + 2.0 mg aflibercept (n=22)

Per Protocol population prior aflibercept subgroup (n=35), must have received all 3 intravitreal study treatments and evaluable at Baseline through Week 12 and sufficiently compliant with the protocol.
Error bars (± SEM)

Conclusions

OPT-302 Combination therapy in Previously Treated Patients with Persistent DME

- Primary safety endpoint met:
  - The safety profile of OPT-302 combination therapy is favorable and consistent across two eye indications where a total of >1850 intravitreal injections have been administered to patients with nAMD and DME
- Efficacy outcomes were assessed in a heterogenous previously treated all-comer's population with variable treatment history including number and frequency of prior intravitreal injections of anti-VEGF-A monotherapy
- The primary efficacy endpoint was achieved:
  - Totality of secondary functional and anatomical responses indicate biological effects for OPT-302 combination therapy
- Exploratory subgroup analysis in a difficult to treat patient population with a more homogenous prior treatment history of previous aflibercept indicates VEGF-C/D blockade with OPT-302 showed positive improvements and additive benefit to aflibercept anti-VEGF-A monotherapy
- These results in previously-treated patients warrant further evaluation of OPT-302 combination therapy in larger patient populations with DME

Wet AMD

Review & Opthea's Phase 2b wet AMD Trial

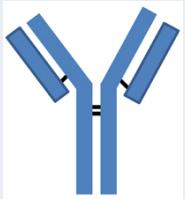
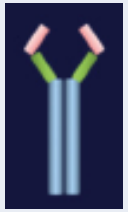
Jason Slakter, MD, Vitreous Retina Macula Consultants, New York City, NY

Practice Setting: Vitreous Retina Macula Consultants, New York

- Practice encompasses 3 Locations in Brooklyn, Manhattan & Westchester
- Multispecialty with 11 retinal physicians
- Strong research focus on the development of new diagnostic and therapeutic strategies
- Approximately 1500 anti-VEGF-A Intravitreal injections a month

Medical Director – Digital Angiography Reading Center

Most commonly used wet AMD therapies primarily target VEGF-A

	Bevacizumab[a] (Avastin)	**Ranibizumab** (Lucentis)	**Aflibercept** (Eylea)	**Brolucizumab**[b] (Beovu)
Format	Full antibody (IgG1)	Monoclonal humanized antibody fragment	VEGFR-1/2-Fc fusion protein	Single-chain antibody fragment (scFv)
Molecular structure				
Molecular weight	149 kDa	48 kDa	115 kDa	26 kDa
Clinical dose for nAMD	1.25 mg (unlicensed use)	0.5 mg	2.0 mg	6.0 mg

Current Management of wet AMD and Major Unmet Medical Need

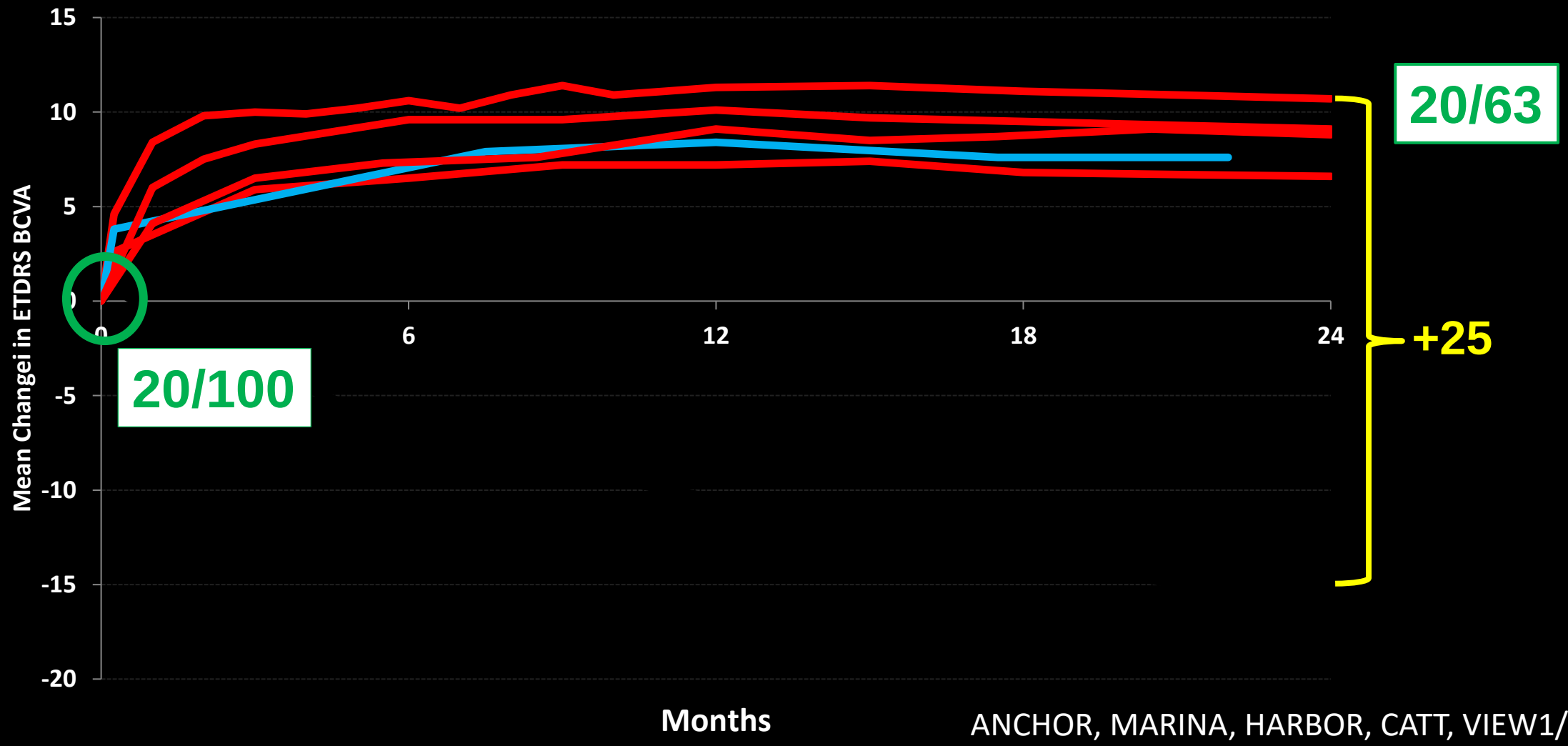
Current management: Anti-VEGF-A therapy individualized for patients:

- Most commonly used are ranibizumab, aflibercept and bevacizumab
  - Each have similar efficacy and safety
  - Mean gain in visual acuity is ~9 letters for wet AMD
  - Only a ~third of patients achieve 3 or more lines of vision improvement
  - Best outcomes with frequent dosing regimens
  - Treat and extend is often utilized in attempt to reduce treatment burden
  - "Real World" experience: Undertreatment = suboptimal outcomes > 2 years

Major unmet need:

- Need for **better efficacy** resulting in improved visual outcomes
  - Immediate and long-term VA gains to help with patient interest and compliance
  - Decreased burden
- New treatment modalities including **combination therapy** are needed to improve vision outcomes and/or durability of responses

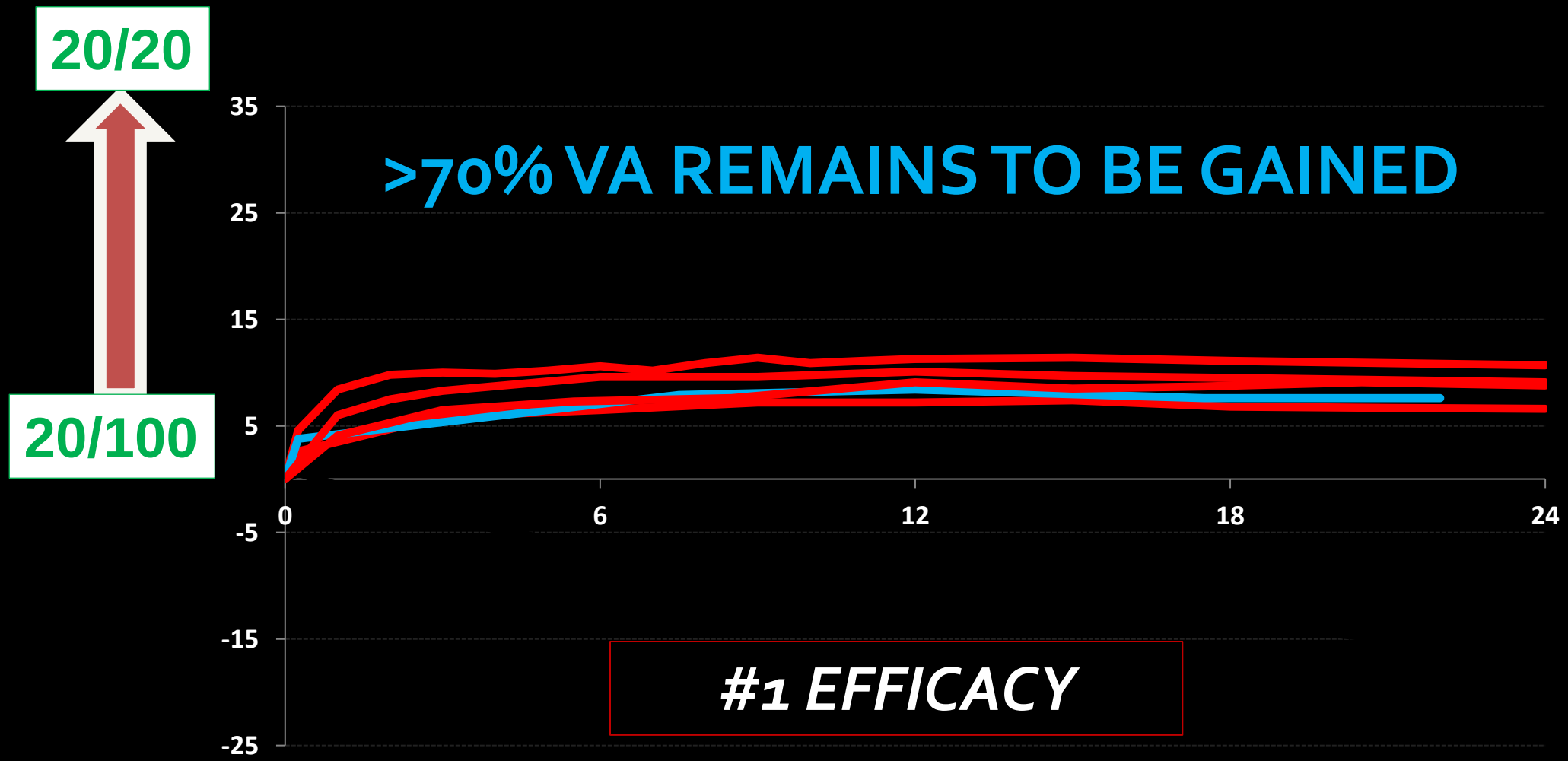
Further Vision Gains Possible with VEGF- A Blockade in wet AMD



ANCHOR, MARINA, HARBOR, CATT, VIEW1/2

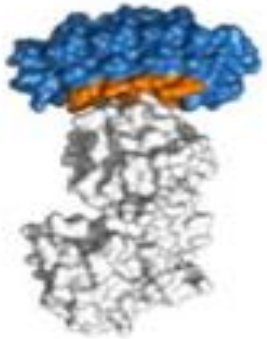
Brown DM, et al. *Ophthalmology*. 2009 Jan;116(1):57-65.e5; Rosenfeld PJ, et al; *N Engl J Med*. 2006;355:1419-1431; Ho AC, et al. *Ophthalmology*. 2014 Nov;121(11):2181-92; Martin DF, et al. *Ophthalmology*. 2012; 119(7):1388-98; Heier JS, et al. *Ophthalmology*. 2012 Dec;119(12):2537-48

Wet AMD – Shortcomings of VEGF-A Blockade

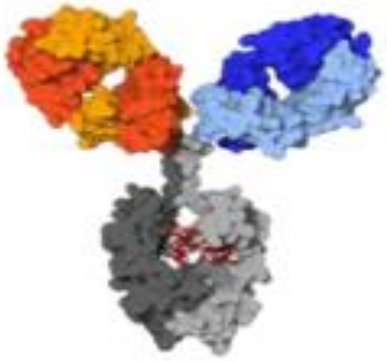


Brown DM, et al. *Ophthalmology*. 2009 Jan;116(1):57-65.e5; Rosenfeld PJ, et al; *N Engl J Med*. 2006;355:1419-1431; Ho AC, et al. *Ophthalmology*. 2014 Nov;121(11):2181-92; Martin DF, et al. *Ophthalmology*. 2012; 119(7):1388-98; Heier JS, et al. *Ophthalmology*. 2012 Dec;119(12):2537-48

Investigational treatments in pipeline also mostly targeting VEGF-A and aimed at improving durability

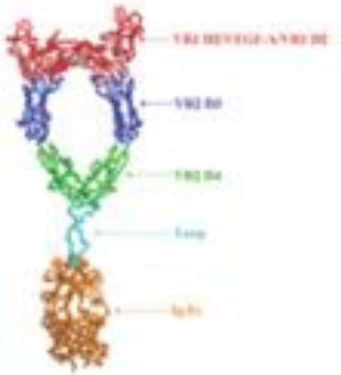


Abicipar



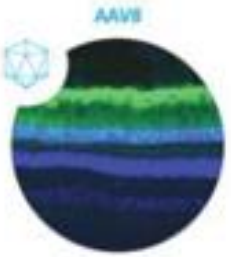
Faricimab

Portal Delivery System (PDS)

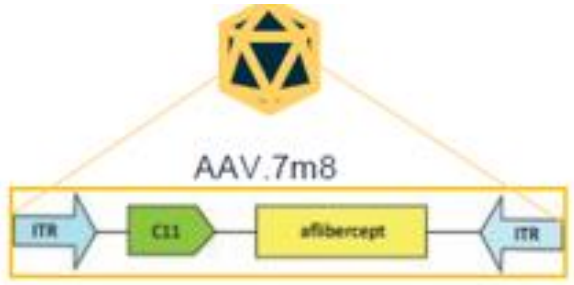


Conbercept

KSI-301



RGX-314



ADVM-022

Intraocular Safety of Newer Longer-acting anti-VEGF-A agents

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use BEOVU safely and effectively. See full prescribing information for BEOVU.

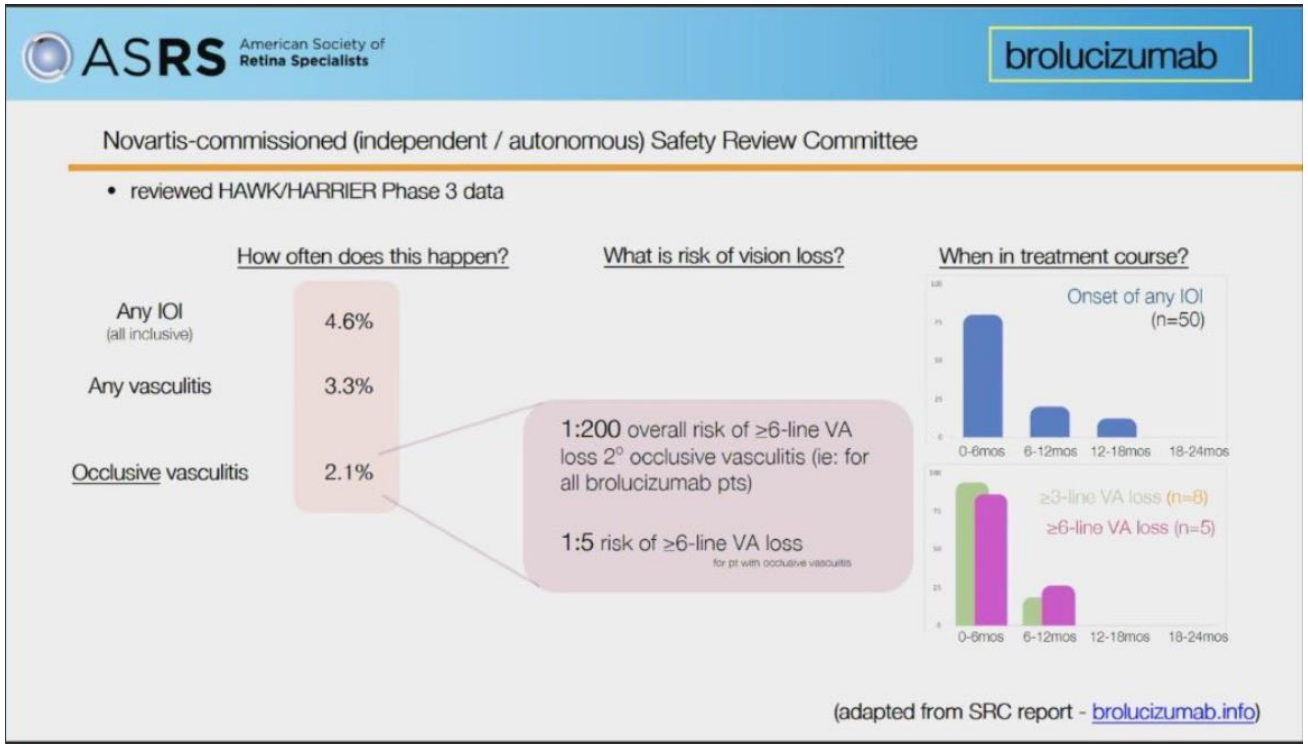
BEOVU® (brolucizumab-dbll) injection, for intravitreal use
Initial U.S. Approval: 2019

----------WARNINGS AND PRECAUTIONS----------

- Endophthalmitis and retinal detachment may occur following intravitreal injections. Patients should be instructed to report any symptoms suggestive of endophthalmitis or retinal detachment without delay (5.1).
- Retinal vasculitis and/or retinal vascular occlusion, typically in the presence of intraocular inflammation, have been reported following BEOVU injections. Patients should be instructed to report any change in vision without delay (5.2).
- Increases in intraocular pressure (IOP) have been seen within 30 minutes of an intravitreal injection (5.3).
- There is a potential risk of arterial thromboembolic events (ATE) following intravitreal use of VEGF inhibitors (5.4).

----------ADVERSE REACTIONS----------

The most common adverse reactions (≥ 5%) reported in patients receiving BEOVU are vision blurred (10%), cataract (7%), conjunctival hemorrhage (6%), eye pain (5%), and vitreous floaters (5%) (6.1).



https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/761125s004lbl.pdf accessed 7/26/20; ASRS Annual Meeting 2020; #ASRS2020 Accessed 7/26/20

Intraocular Safety of Newer Longer-Acting anti-VEGF-A agents

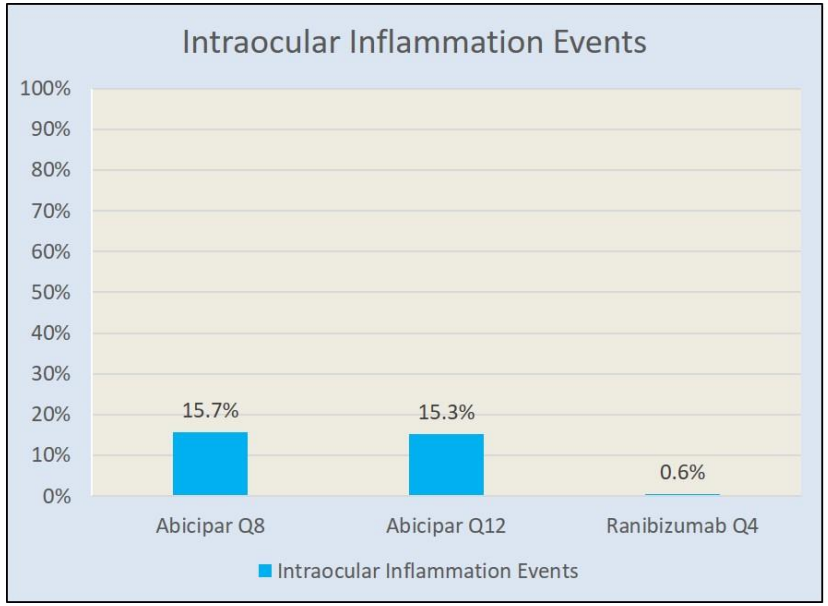
June 26, 2020

Allergan, an AbbVie Company, and Molecular Partners Receive Complete Response Letter from FDA on Biologics License Application for Abicipar pegol

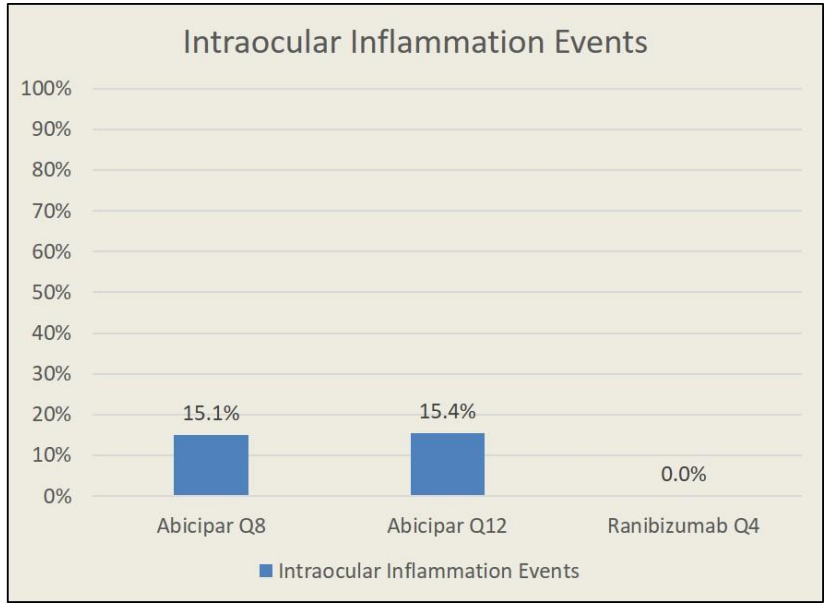
NORTH CHICAGO, Ill., June 26, 2020 /PRNewswire/ -- Allergan, an AbbVie Company (NYSE: ABBV), and Molecular Partners (SIX: MOLN), a clinical-stage biotechnology company developing a new class of custom-built protein therapeutics known as DARPin® therapeutics, today announced that the U.S. Food and Drug Administration (FDA) has issued a Complete Response Letter to the Biologics License Application (BLA) for Abicipar pegol, a novel, investigational DARPin® therapy for patients with neovascular (wet) age-related macular degeneration (nAMD).

The letter from the FDA indicates that the rate of intraocular inflammation observed following administration of Abicipar pegol 2mg/0.05 mL results in an unfavorable benefit-risk ratio in the treatment of neovascular (wet) age-related macular degeneration (AMD). AbbVie plans to meet with the FDA to discuss their comments and determine next steps.

SEQUOIA STUDY



CEDAR STUDY



https://news.abbvie.com/news/press-releases/allergan-an-abbvie-company-and-molecular-partners-receive-complete-response-letter-from-fda-on-biologics-license-application-for-abicipar-pegol.htm

Phase 2b

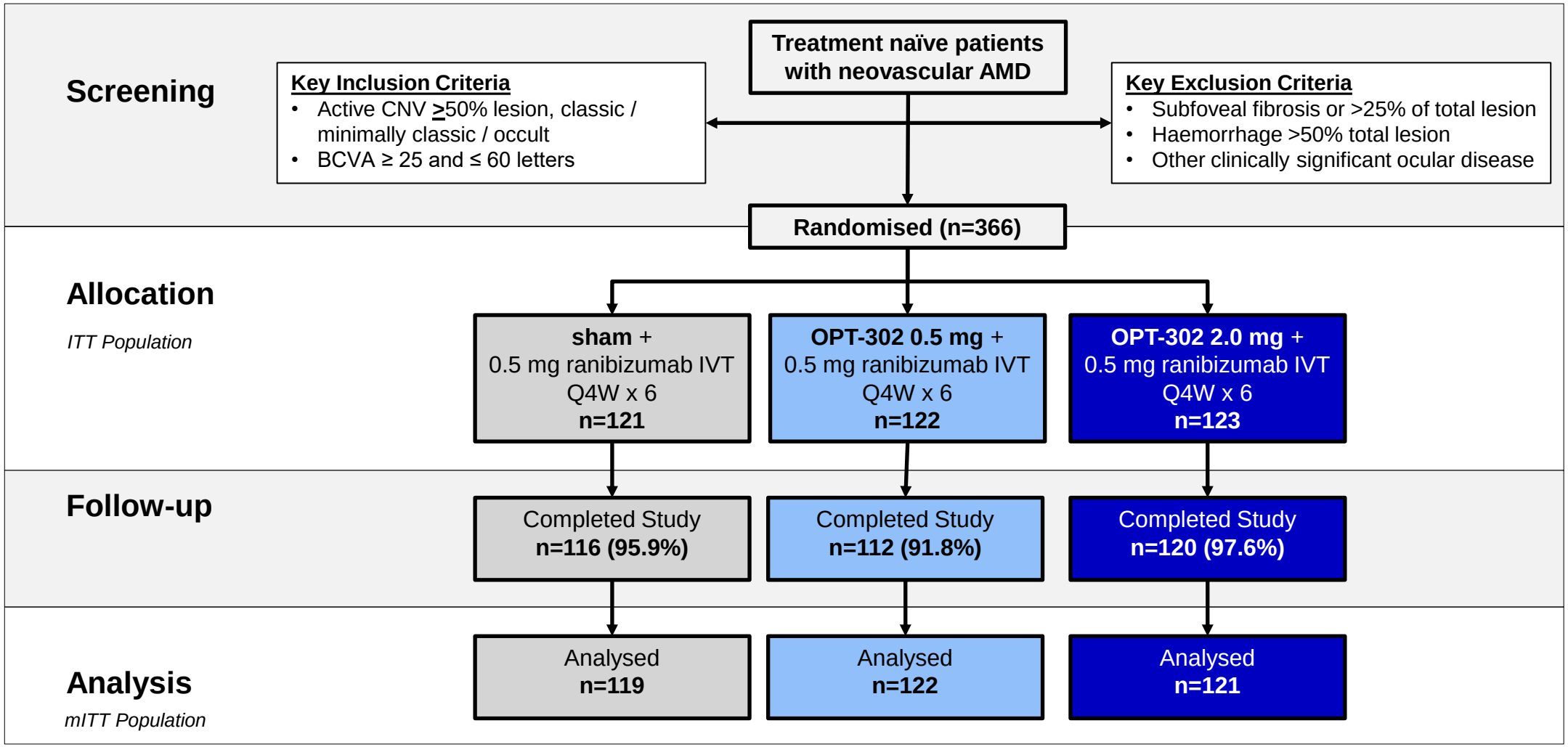
A multicenter, randomized, double-masked, sham controlled study of intravitreal OPT-302 in combination with ranibizumab, in participants with neovascular (wet) AMD

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

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

OPTHEA

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 Demographics and Baseline Characteristics

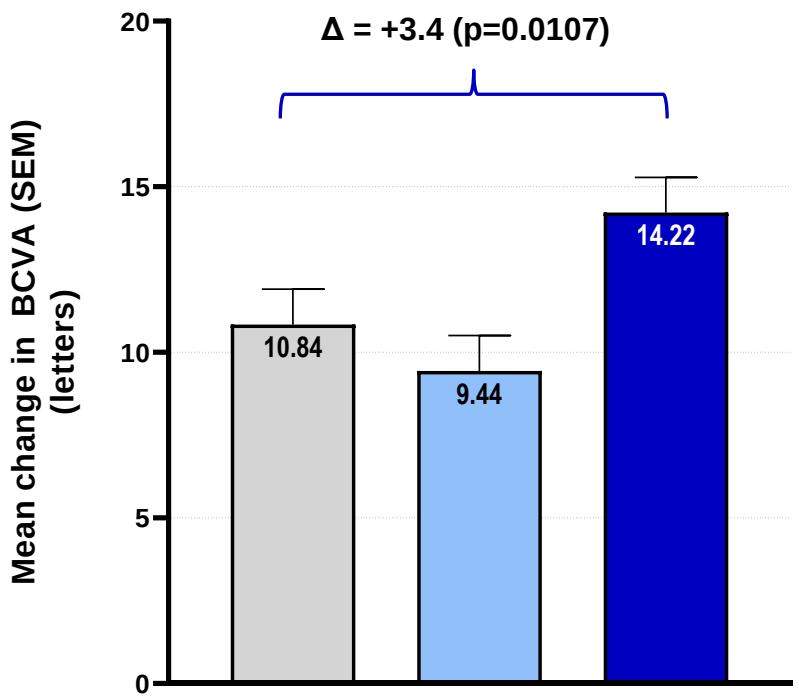
Demographic / Baseline Disease Characteristic		Sham + ranibizumab N=121	0.5 mg OPT-302 + ranibizumab N=122	2.0 mg OPT-302 + ranibizumab N=123
Mean Age – years ± SD		76.1 ± 9.48	78.8 ± 8.16	77.8 ± 8.82
Sex – n (%)	Male	48 (39.7%)	49 (40.2%)	45 (36.6%)
	Female	73 (60.3%)	73 (59.8%)	78 (63.4%)
Caucasian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

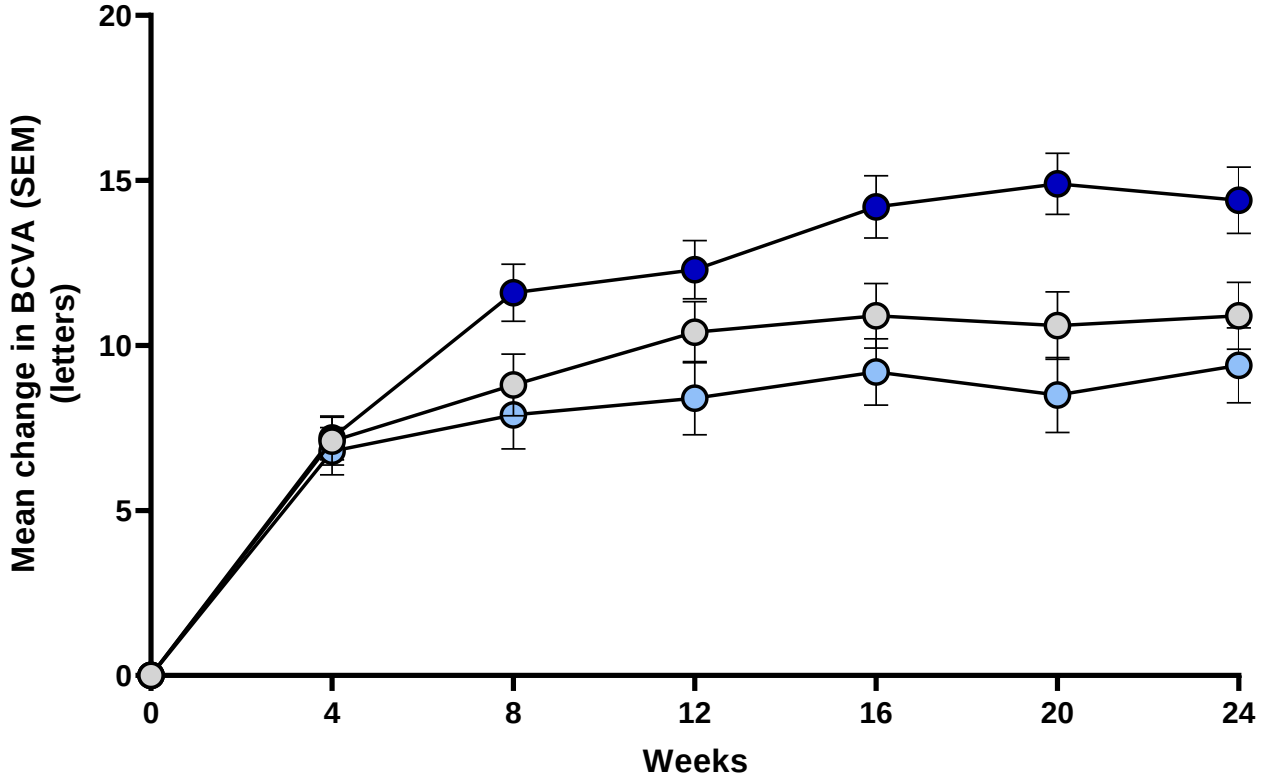
Intent-to-Treat (ITT) population; SD: standard deviation; BCVA: Best Corrected Visual Acuity
[1]PCV - polypoidal choroidal vasculopathy, detected by SD-OCT, FA and fundus photography
[2]RAP - retinal angiomatous proliferation, detected by SD-OCT, FA and fundus photography

OPTHEA

Superior Vision Gain at Week 24 with OPT-302 (2mg) Combination Therapy

Primary Endpoint Achieved:
Mean Change in Best Corrected Visual Acuity Baseline to Week 24

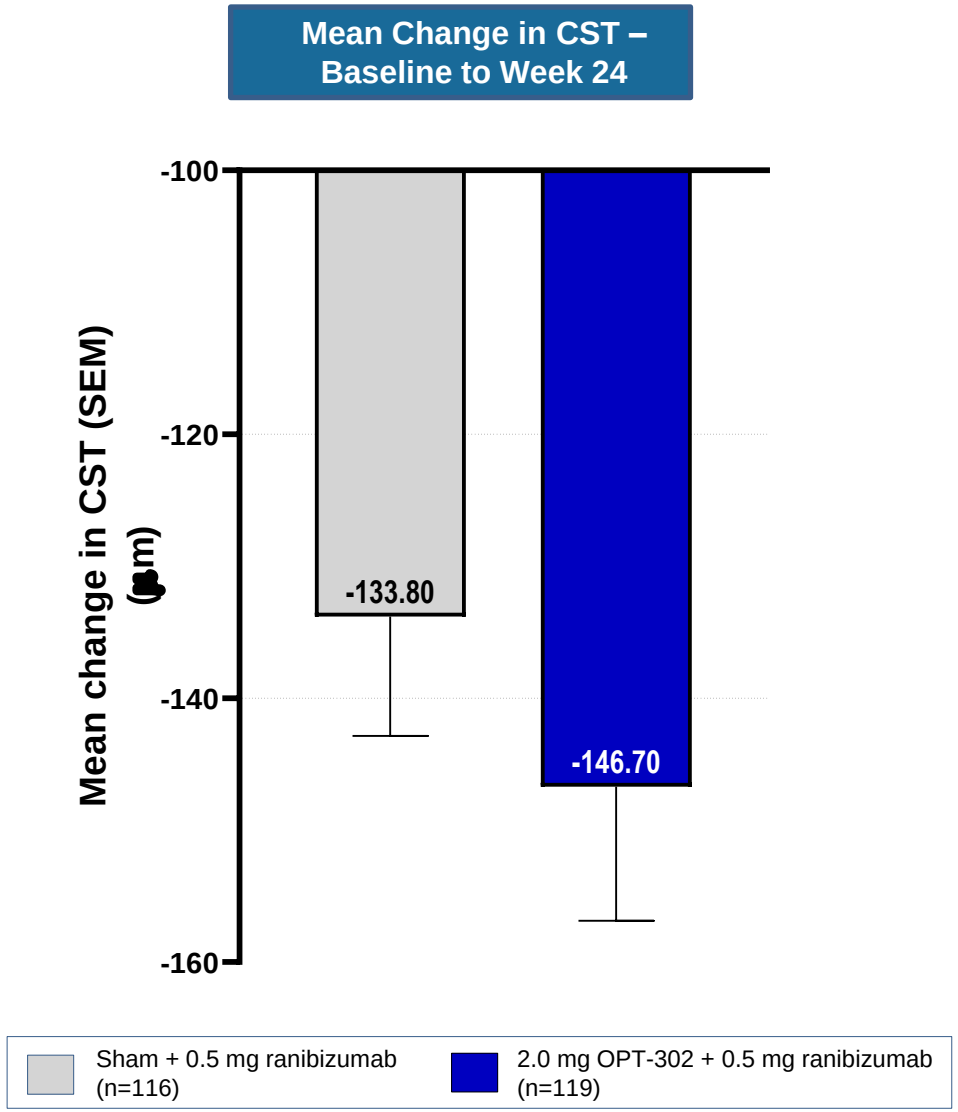




Sham + 0.5 mg ranibizumab (n=119)
0.5 mg OPT-302 + 0.5 mg ranibizumab (n=122)
2.0 mg OPT-302 + 0.5 mg ranibizumab (n=121)

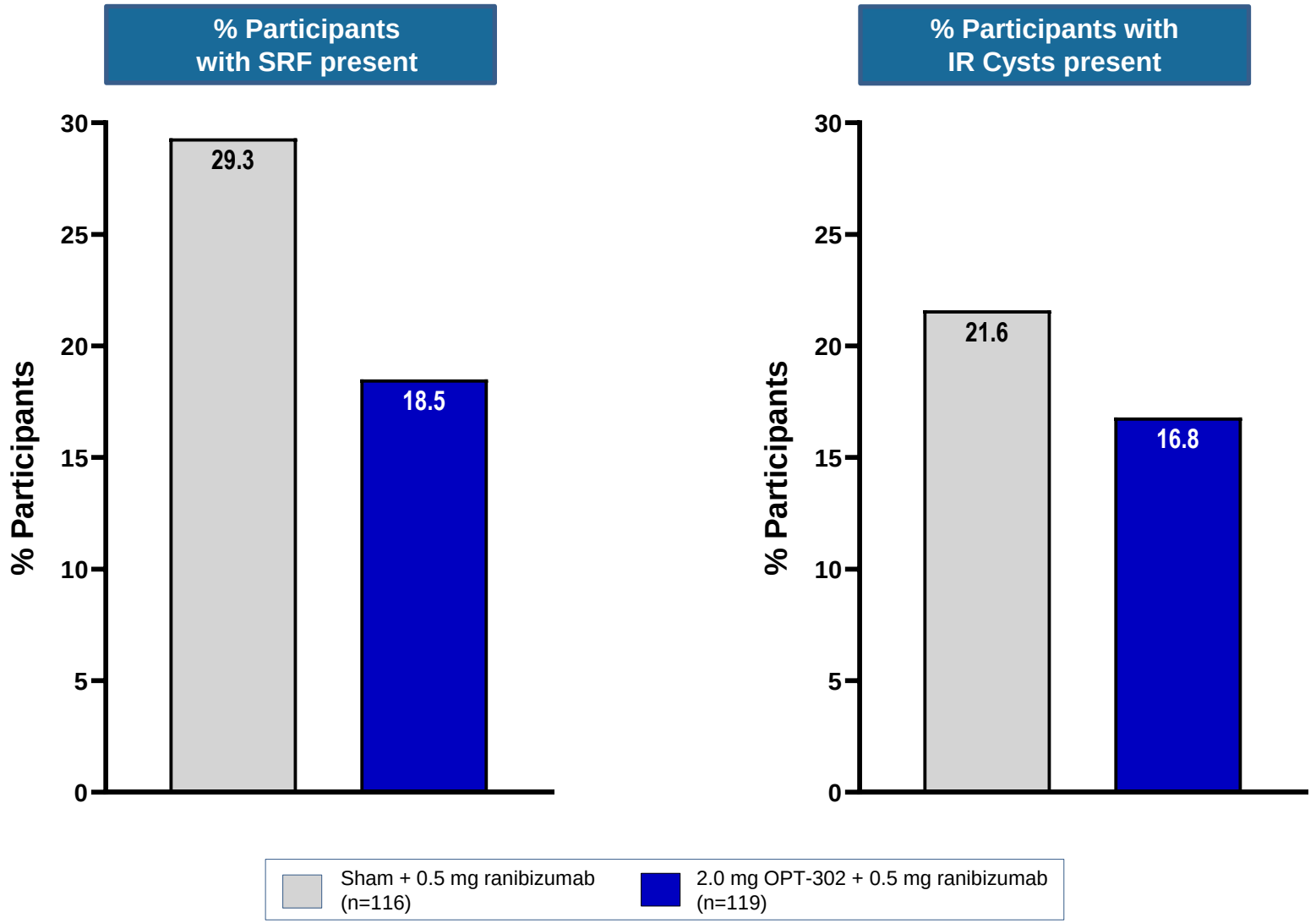
mITT; BCVA – best corrected visual acuity
Left: Difference in Least Square Means, using Model for Repeated Measures (MRM) analysis. Right: Graph represents "as observed" data and SEM

Greater Reduction in Retinal Thickness with OPT-302 Combination Therapy



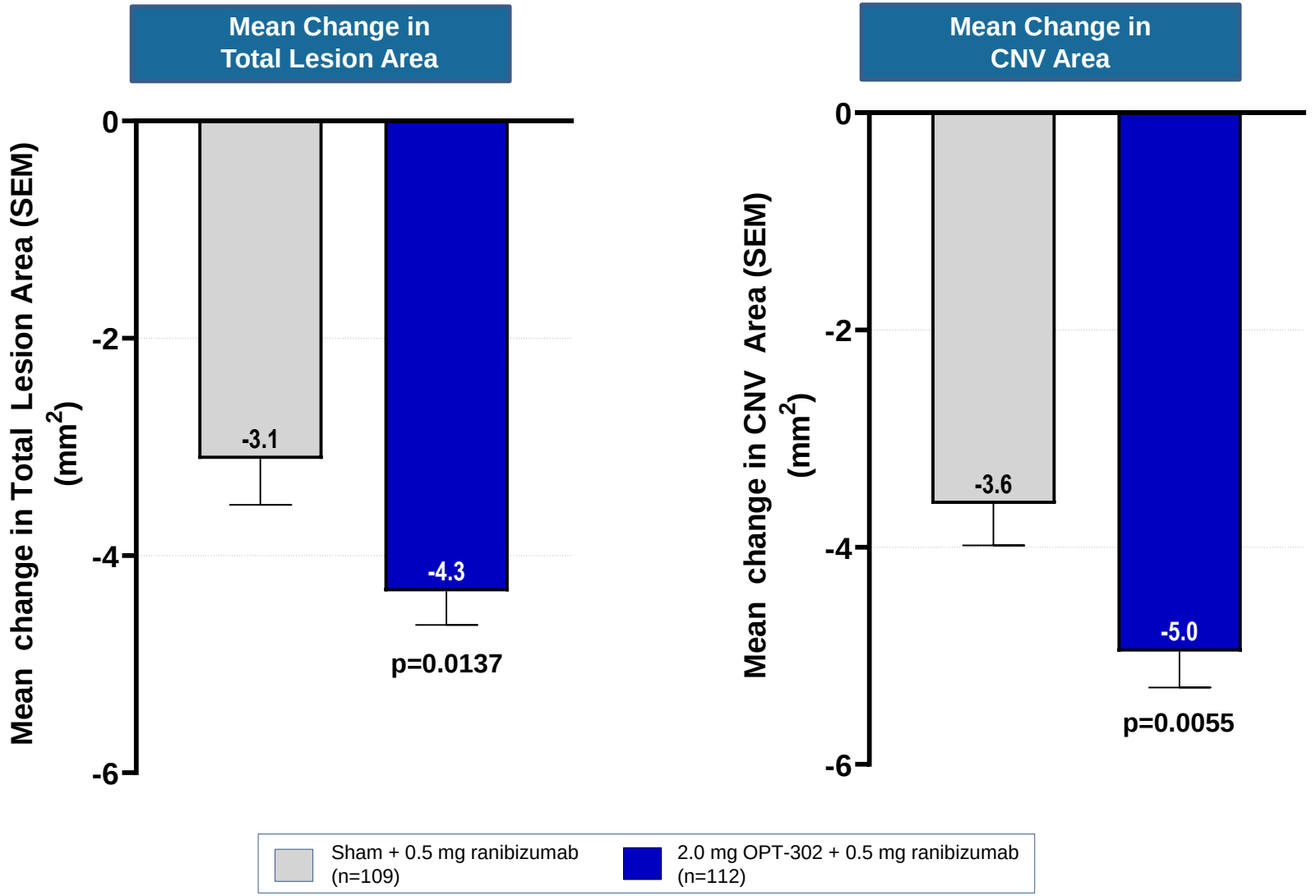
Modified Intent-to-Treat (mITT) population; as observed; CST – central subfield thickness

Better ‘Retinal Drying’ with OPT-302 Combination Therapy



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

Greater Reduction in Total Lesion and CNV Area



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

Phase 2b

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

Pre-Specified Subgroup Analyses

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

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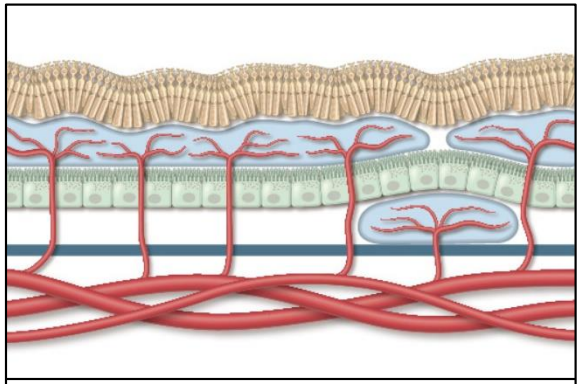
Neovascular (wet) AMD Lesion Types

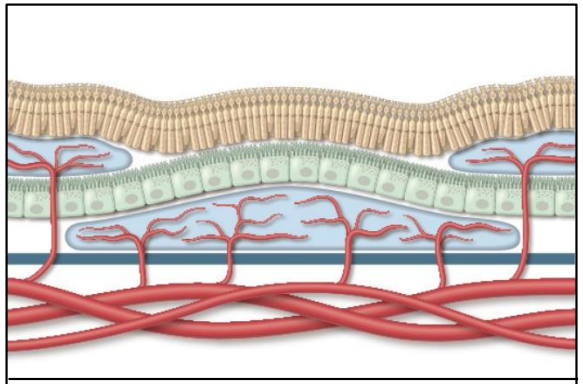
Differ in vessel location, leakiness and responsiveness to VEGF-A inhibitors

PREDOMINANTLY CLASSIC



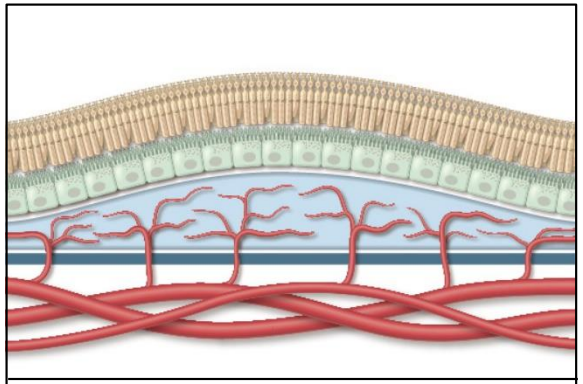
- ≥50% vessels above RPE
- **Highly responsive to VEGF-A inhibition**

MINIMALLY CLASSIC



- <50% vessels above RPE
- **Moderately responsive to VEGF-A inhibition**

OCCULT



- 100% beneath RPE
- **Least responsive to VEGF-A inhibition**

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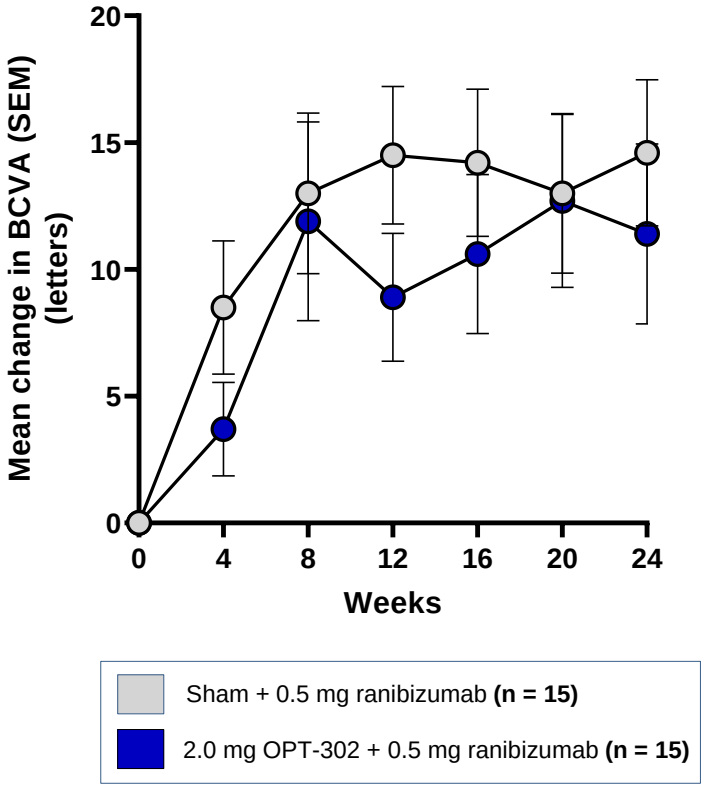
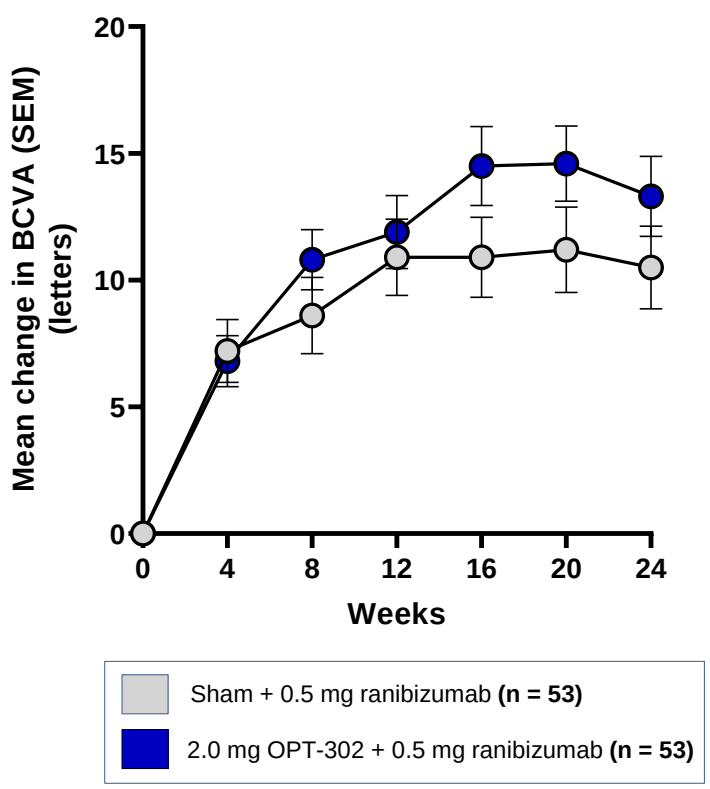
Mean Change in BCVA Over Time by Lesion Type

Small number of predominantly classic patients

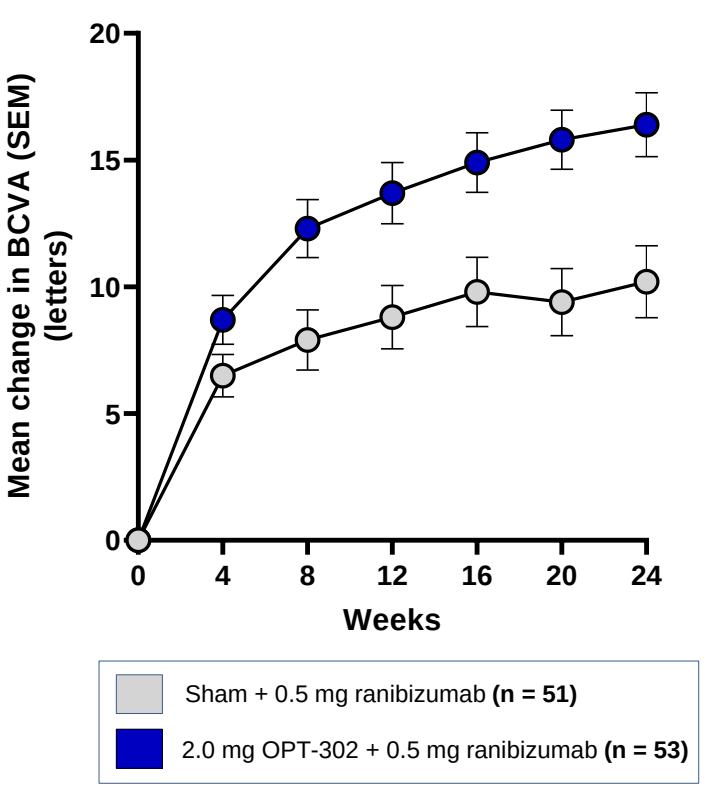
Predominantly Classic



Minimally Classic

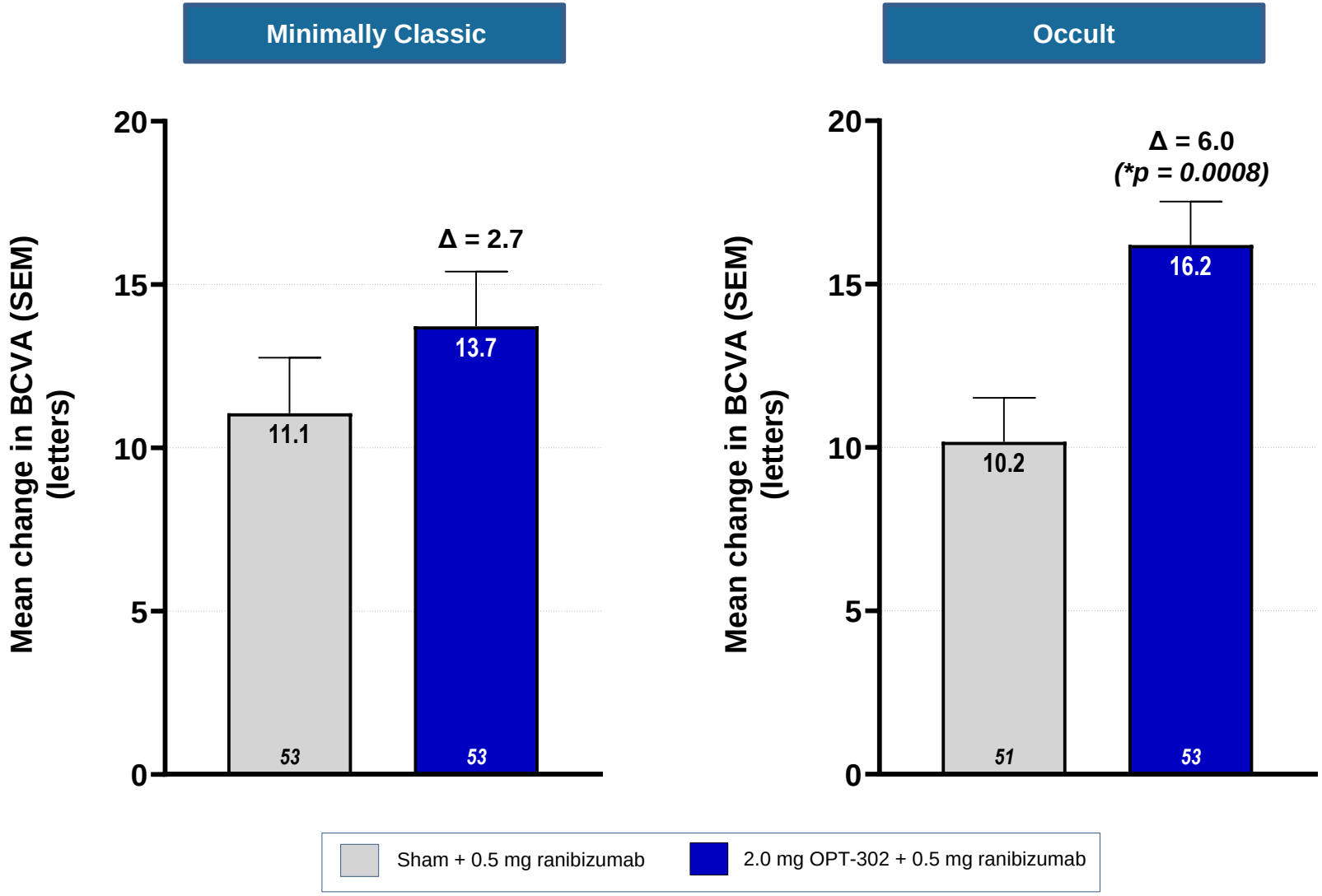


Occult



mITT; as observed

Greater Vision Gains 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).

Retinal Angiomatous Proliferation (RAP) Lesions

Have a distinct biology and vessel proliferation occurs within the retina (not the choroid)

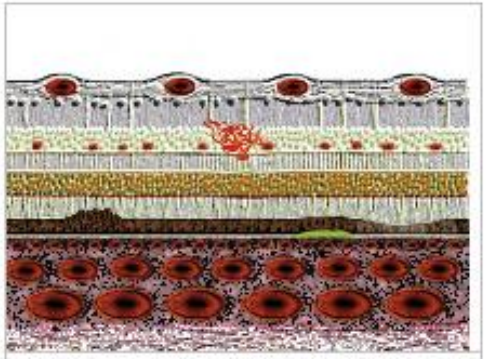


Figure 1: Retinal angiomatous proliferation (RAP) Stage I: intraretinal neovascularization.

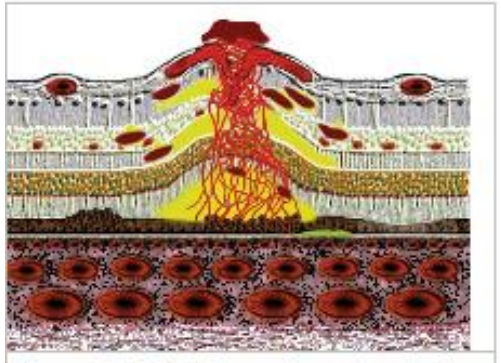


Figure 2: RAP Stage II: subretinal neovascularization with a retinal-retinal anastomosis.

Figure 3: RAP Stage II: subretinal neovascularization with a serous pigment epithelial detachment.

Figure 4: RAP Stage III: Choroidal neovascularization with a vascularized pigment epithelial detachment and a retinal-retinal anastomosis.

- No consensus of which treatment is optimal for RAP lesions*
- Favorable short-term results with anti-VEGF-A treatments but long-term results are conflicting

Nb. RAP lesions were excluded from: e.g. Phase 3 Ophthotech trials, Abicipar (Allergan) Phase 2 study, early conbercept studies

** Tsai AS et al., Surv Ophthalmology, 2017 Jul-Aug; 62(4):462-92. de Jong et al., Ophthalmologica 2019; 241:143-153.*

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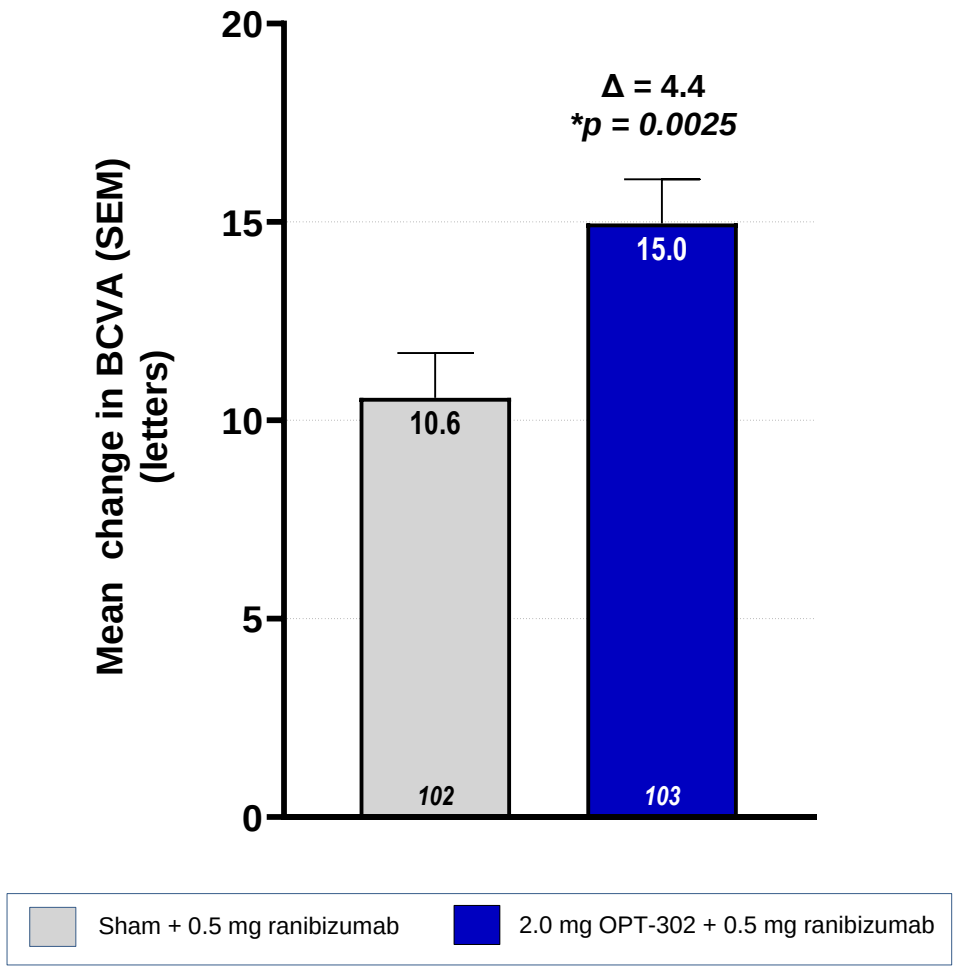
Improved Visual Acuity in OPT-302 + ranibizumab treated patients

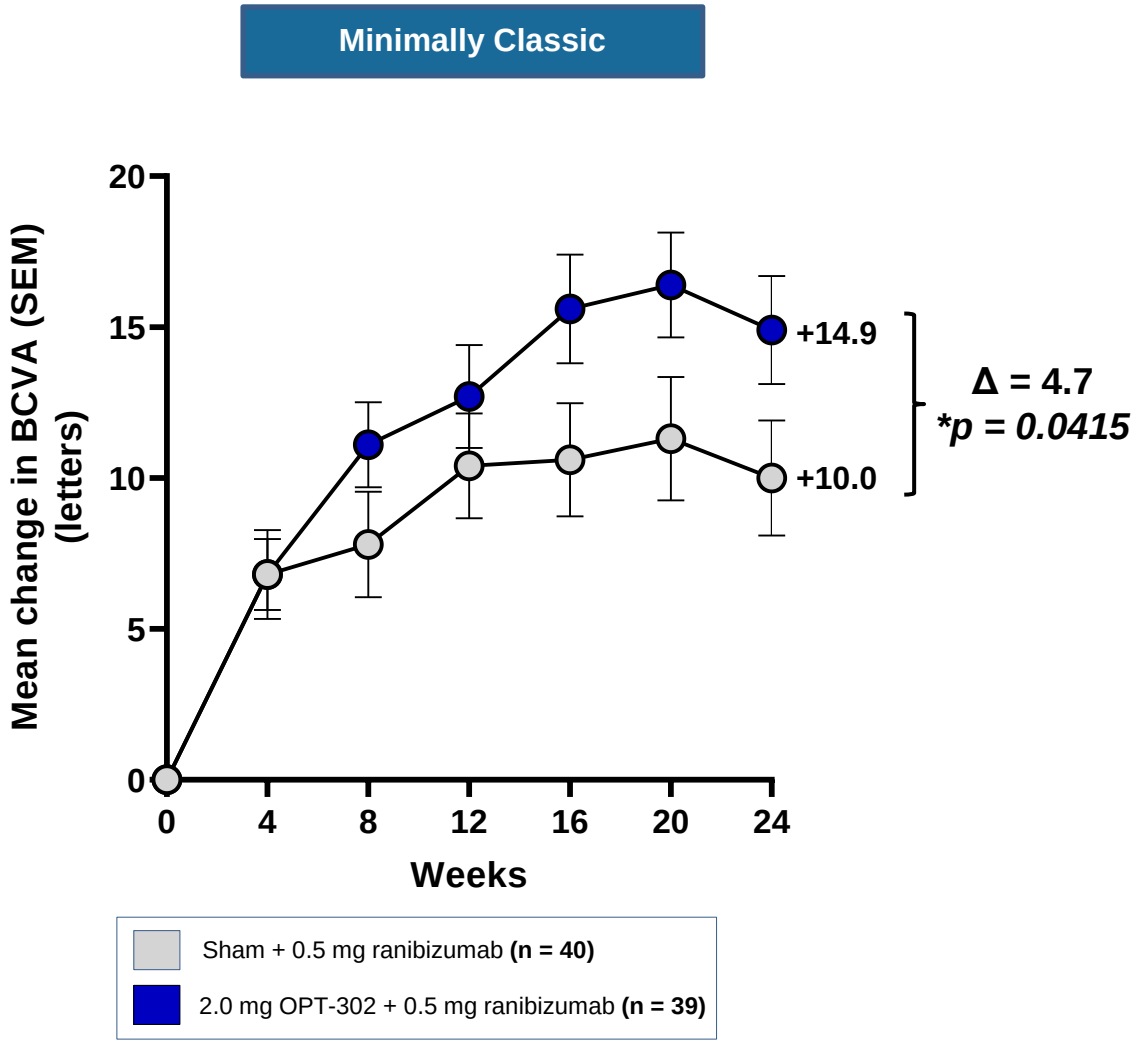
In participants <u>without</u> RAP at baseline (>86% study participants)

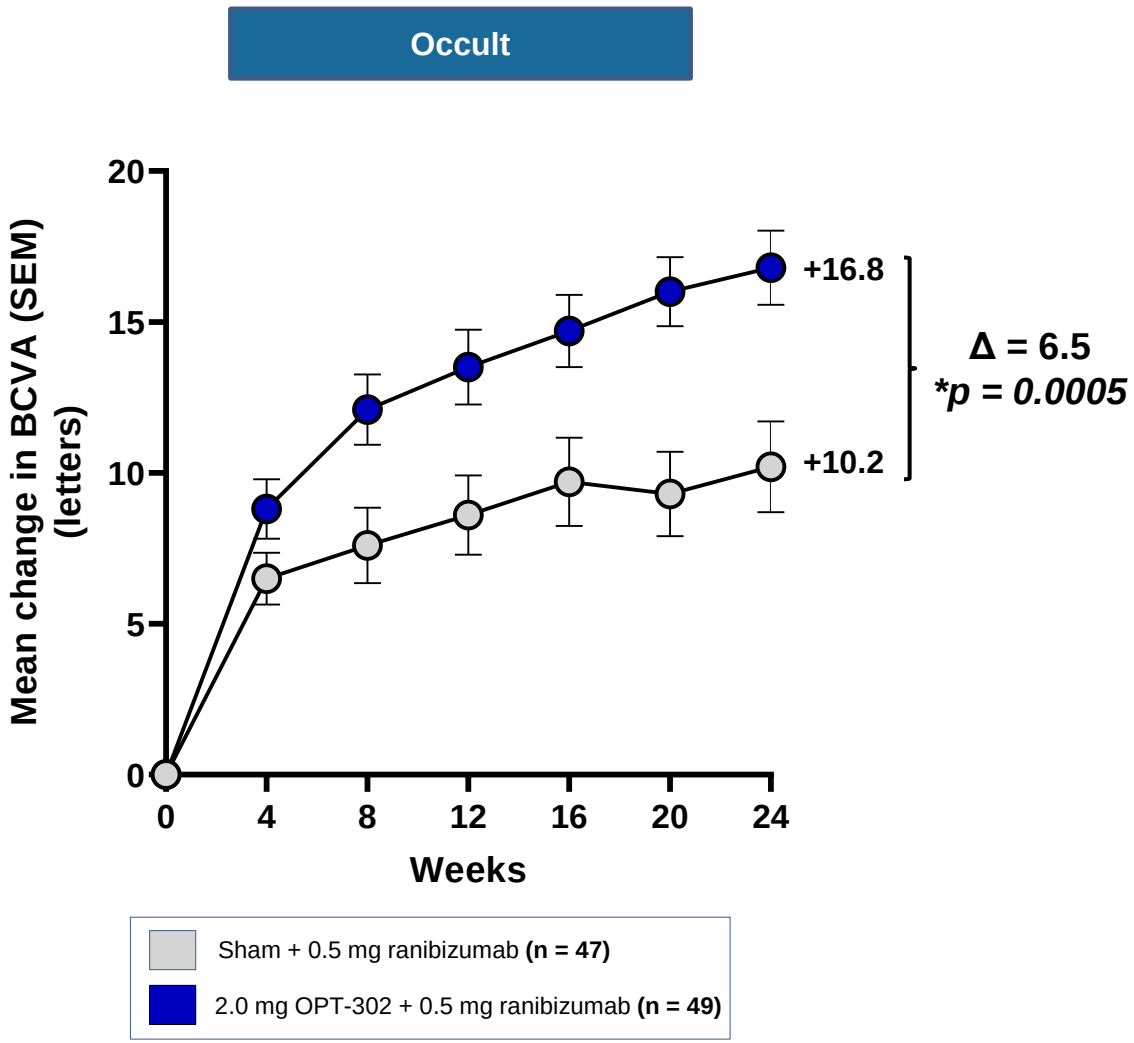


mITT; RAP – retinal angiomatous proliferation;
Least square means (LSM) determined using Model for Repeated Measures (MRM) analysis (adjusted for baseline vision and lesion type as used in the randomisation as covariates).

Mean Change in BCVA Over Time by Lesion Type (RAP Absent)

In participants without RAP at baseline, +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



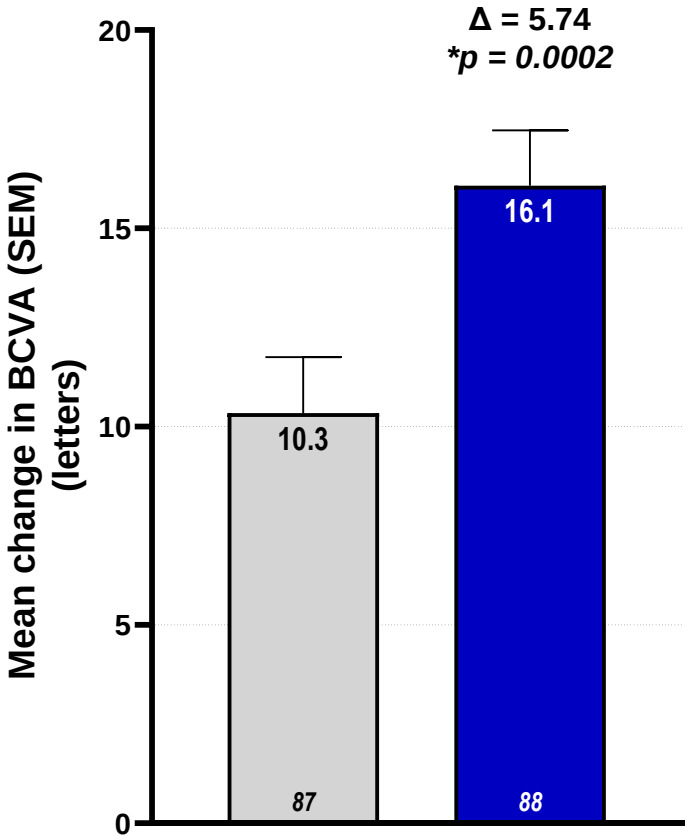


mITT, as observed, Δ based on least square means determined using Model for Repeated Measures (MRM) analysis (adjusted for baseline vision and lesion type (randomisation) as covariates).

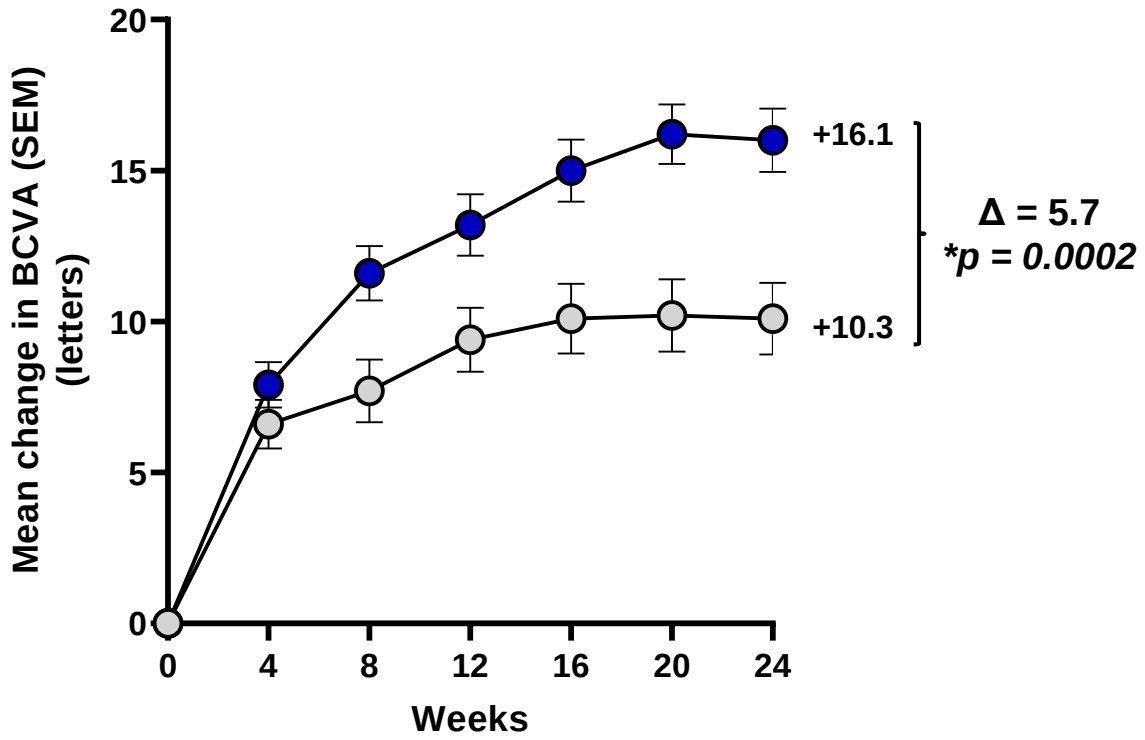
Improved Visual Acuity in patients with Min-Classic & Occult lesions (RAP Absent)

71% study participants had occult-containing lesions with RAP absent at baseline

Minimally Classic & Occult



Minimally Classic & Occult



Sham + 0.5 mg ranibizumab

2.0 mg OPT-302 + 0.5 mg ranibizumab

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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

OPT-302 well tolerated with very low incidence of ocular inflammation

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)

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Safety – Intraocular Inflammation – Study Eye (All OPT-302 Trials)

Incidence of intraocular inflammation similar to control

Study Eye **N Participants (%)**	**OPT-302 Any dose N=399 Inj=1,842**	**2.0 mg OPT-302 N=263 Inj=1,121**	**Sham + anti-VEGF-A control N=169 Inj=854**
Intraocular inflammation[1]	7 (1.8%)	3 (1.1%)	3 (1.8%)
OPT-302-1001	2	0	0
Uveitis with anterior chamber cell 1+ (6-10)	1	0	0
Uveitis with anterior chamber cell 2+ (11-20)	1	0	0
OPT-302-1002	3	1	2[2]
Endophthalmitis with anterior chamber cell 1+ (5-10) and hypopyon	1	0	0
Vitritis	1	0	0
Anterior chamber cell, trace (1-4 cells)	1	1	2[2]
OPT-302-1003	2	2	1
Iritis with keratic precipitates and anterior chamber cell 2+ (11-20)	1	1	0
Iritis with anterior chamber cell 2+ (11-20)	0	0	1
Anterior chamber cell, 4+ (>50 cells) associated with cataract extraction/intraocular lens implant and hyphema	1	1	0

Safety population; TEAEs reported to Week 12 for OPT-302-1003

[1] AEs and considered to be indicative of intraocular inflammation, defined prior to database lock : Iritis, anterior uveitis/Iritis, anterior chamber cells, endophthalmitis, vitritis and mutton fat keratic precipitate on endothelium

[2] Observed during ophthalmic examination, but not reported as TEAEs

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Conclusions – OPT-302 Phase 2b wet AMD 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

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