



Switching to combination OPT-302 with aflibercept from prior anti-VEGF-A monotherapy in eyes with persistent diabetic macula edema (DME)

Clinical results from Opthea's Phase 1b/2a trial

Data presented at ASRS Virtual Meeting, July 25 2020

Disclaimer

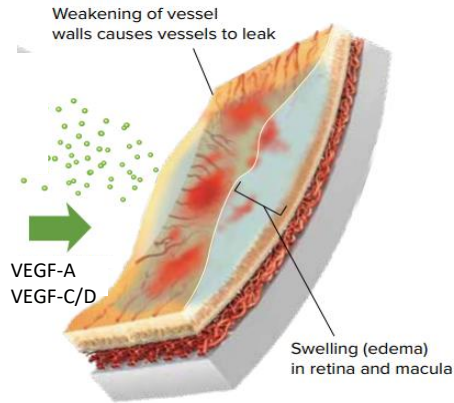
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Diabetic Macular Edema

Up to 10% diabetics develop DME which is responsible for most of the central vision loss in the diabetic population



Central-involved Diabetic Macular Edema

Driver: • Sustained hyperglycaemia

Prevalence: • Increasing due to diabetes epidemic
• ~1.3M – 2M people worldwide

Primary macular site: • Intra-retinal layers

Pathogenesis: • Sustained hyperglycemia
• Upregulation VEGF-A, -C, -D and inflammatory mediators
• Inflammation
• Hyperpermeability & retinal swelling

Standard of Care Treatments & An Unmet Medical Need

- VEGF-A inhibitors are first-line standard of care therapy for DME
 - Aflibercept (Eylea) & ranibizumab (Lucentis) are approved
 - Bevacizumab (Avastin) often used off-label
- Many patients experience sub-optimal gains in visual acuity & persistent retinal fluid despite receiving anti-VEGF-A therapy
- OPT-302 in combination with anti-VEGF-A therapy achieves broader inhibition of the VEGF/VEGFR pathway by targeting VEGF-A, VEGF-C and VEGF-D and has the potential to improve clinical outcomes for DME patients
- The two VEGF-A inhibitors approved for the treatment of DME, aflibercept and ranibizumab, generated annual worldwide sales of over USD 11.9 billion in 2019
- Approximately 22% of these sales are attributable to DME

Patients With Persistent DME Are a Significant Unmet Need

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

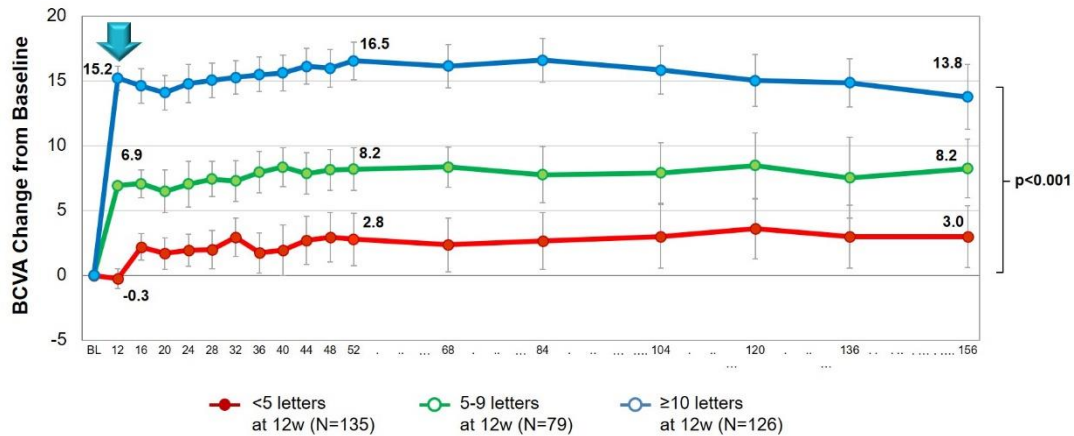
Many patients have limited gains despite regular anti-VEGF-A monotherapy*

In Protocol I, patients with DME received ranibizumab + sham injections every 4 weeks to week 12, then as needed

- 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

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

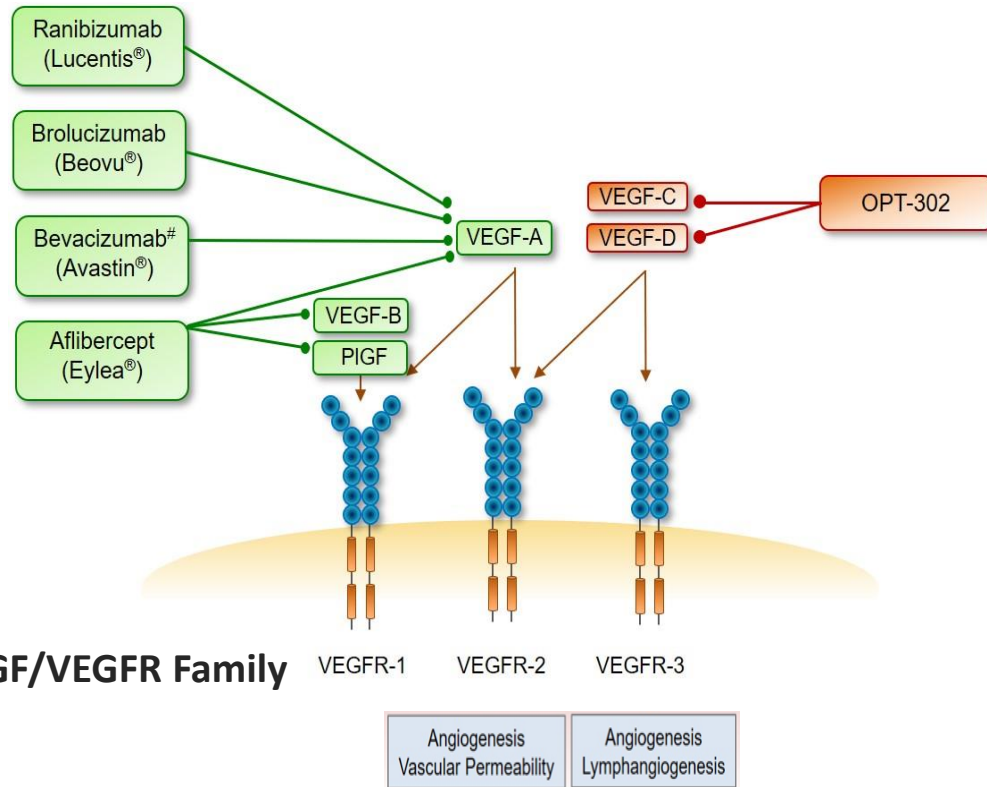
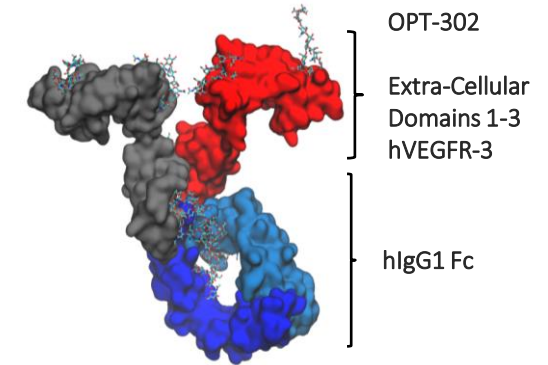
Combination therapy targeting alternative mediators of the disease such as VEGF-C/-D may lead to improved outcomes

*Based on randomized, controlled clinical trial data; Fail to achieve ≥ 2 lines gain in BCVA; SD-OCT CST $\geq 300 \mu\text{M}$ or Time-Domain OCT CST $\geq 250 \mu\text{M}$
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.

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 wet AMD*

Phase 1b/2a Trial of OPT-302 Combination Therapy for Persistent DME

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

Phase 1b:

- Patients received escalating doses of OPT-302 (0.3, 1 or 2 mg) + aflibercept (2 mg) across 3 cohorts (total of 9 patients)
- Treatments administered by intravitreal (IVT) injections once every four weeks for a total of three doses

Phase 2a:

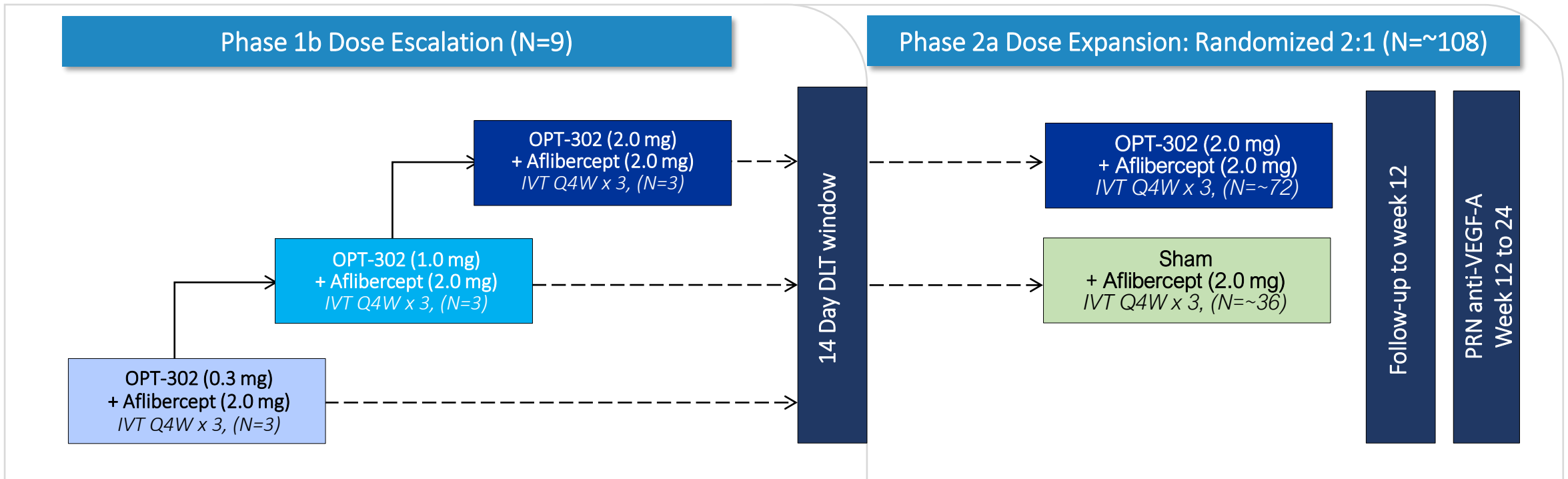
- Randomised, double-masked, dose expansion trial conducted at 53 sites in U.S., Israel, Australia and Latvia
- Patients were randomised 2:1 to receive either 2.0 mg OPT-302 in combination with 2.0 mg aflibercept, or a sham injection and 2.0 mg aflibercept
- Treatments administered by IVT injections once every four weeks for a total of three doses, primary analysis conducted at week 12, four weeks after the final dose
- 144 patients were randomised into the trial; 115 patients conformed sufficiently with the trial protocol (Per Protocol population)
- Primary endpoint analysis was based on pre-specified response rate in 72 patients who conformed sufficiently with the protocol and received OPT-302 combination therapy

Clinical Analyses:

- **All patients in the Per Protocol Population**
 - Heterogeneous all comers' population for prior anti-VEGF-A history (aflibercept / ranibizumab / bevacizumab)
 - Variable treatment history including number and frequency of prior intravitreal anti-VEGF-A injections
- **Patients who had received prior aflibercept therapy** (exploratory subgroup analysis)
 - 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 DME Trial Design

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



Key Inclusion Criteria

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

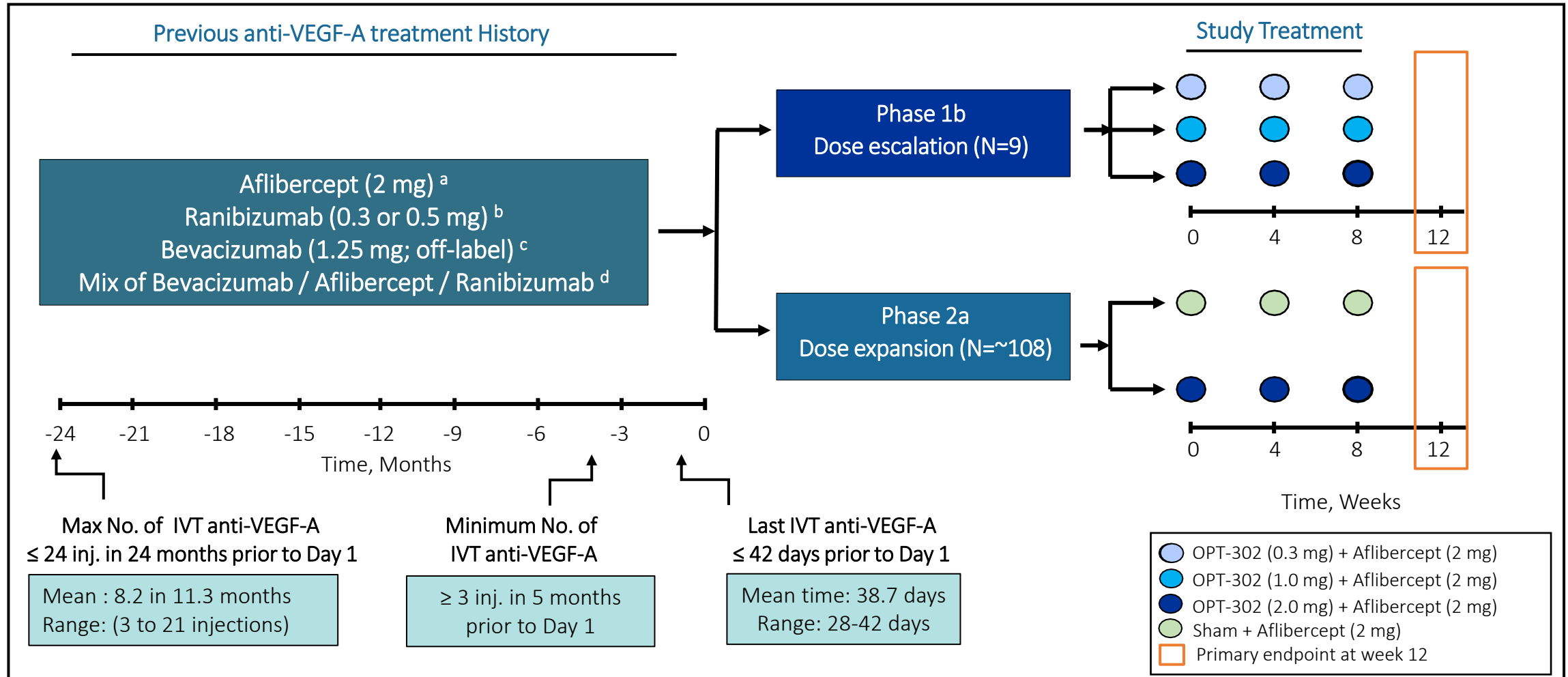
Key Exclusion Criteria

- HbA1c \geq 12%
- Uncontrolled hypertension \geq 180 mmHg systolic or \geq 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 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

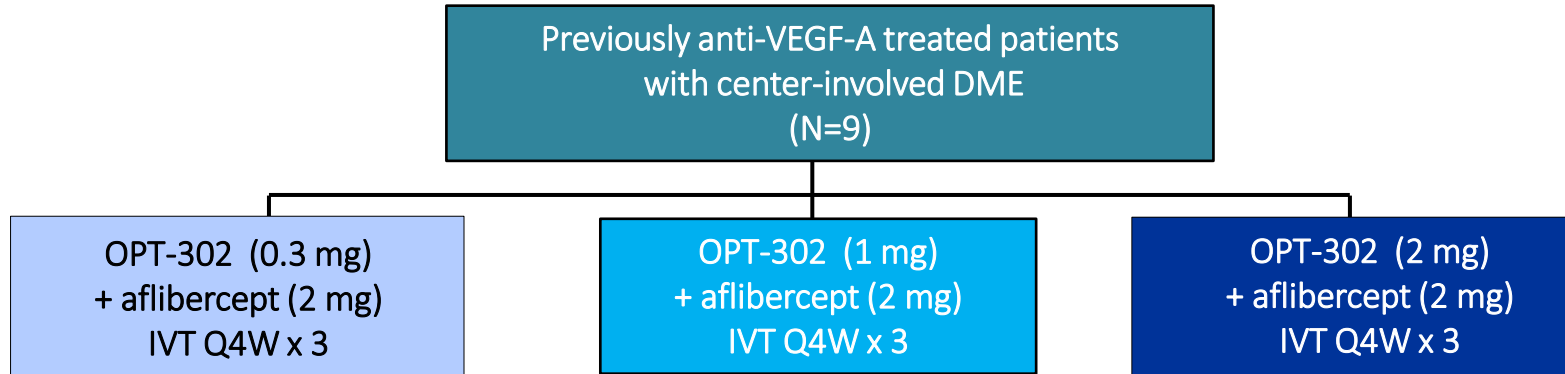
d Includes patients receiving multiple switching of anti-VEGF-A therapy. For last injection prior to study entry patients must be switched to 1 injection of either Aflibercept or Ranibizumab

Phase 1b Dose Escalation

Dose-responsive gains in visual acuity following OPT-302 combination therapy and reductions in retinal thickness

Phase 1b Dose Escalation of OPT-302 Combination Therapy

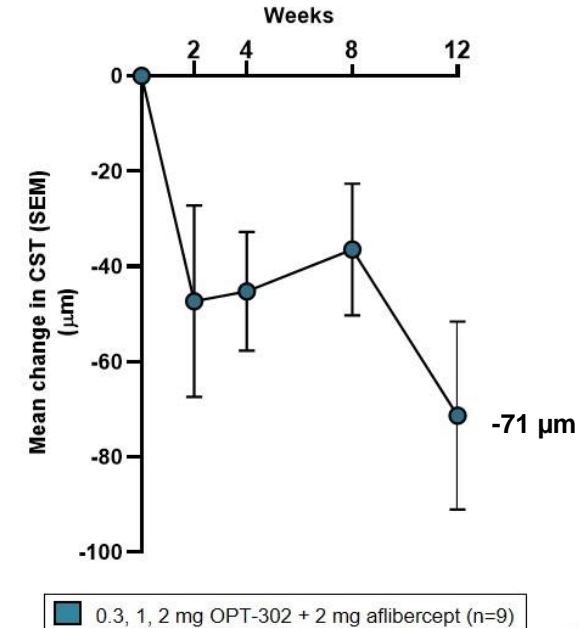
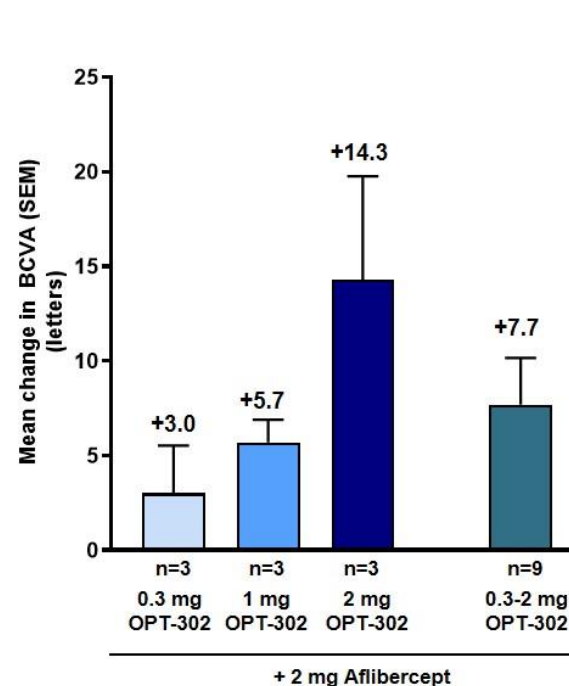
Summary of results



- 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



Phase 2a Trial of OPT-302 Combination Therapy for Persistent DME

Total “Per Protocol” patient population with variable prior anti-VEGF-A treatment history
of aflibercept / ranibizumab / bevacizumab

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	0 (0%)	0 (0%)
Asian	1 (2.1%)	1 (1.0%)
Black or AfricanAmerican	8 (16.7%)	8 (8.3%)
White	37 (77.1%)	87 (90.6%)
Other	2 (4.2%)	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)

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 (\pm SD)	63.9 (9.44)	63.3 (8.31)
>55 letters vision - n (%)	41 (85.4%)	81 (84.4%)
\leq 55 letters vision - n (%)	7 (14.6%)	15 (15.6%)
Anatomic		
Mean central subfield thickness (CST) - μ m (\pm SD)	427.3 (99.7)	433.8 (104.5)
CST >450 μ m - n (%)	17 (35.4)%	30 (31.3)%
CST \leq 450 μ m - 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) ; NPDR: Non-Proliferative Diabetic Retinopathy; PDR: Proliferative Diabetic Retinopathy

Prior Treatment History Study Eye

Approximately one third of patients received regular prior aflibercept therapy

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 (\pm SD)	1.6 (1.70)	1.3 (1.30)
Mean Number of Prior IVT Anti-VEGF-A Injections for CI-DME (\pm SD)	8.4 (4.56)	8.0 (4.35)
Mean Duration of Prior IVT Anti-VEGF-A injections – months (\pm SD)	12.4 (6.43)	10.7 (5.95)
Mean time from Prior Treatment to Day 1 – days (\pm 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.

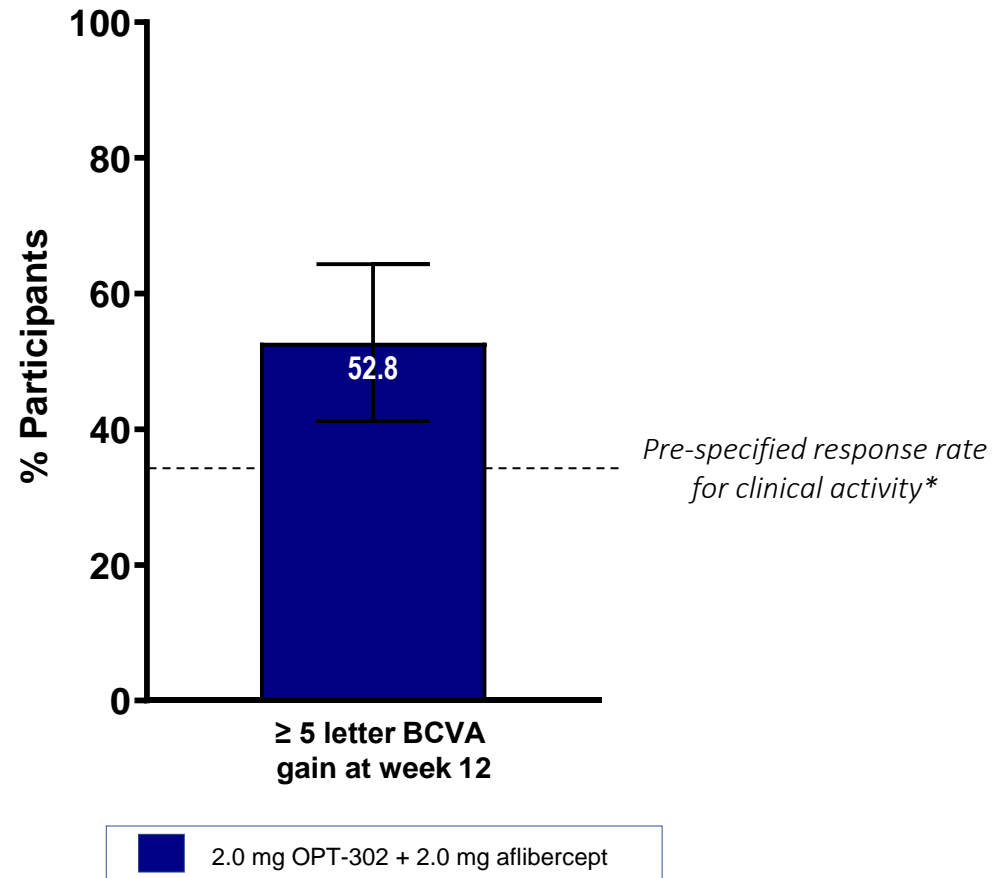
[^]Changes in IOP were transient and there were no sustained changes to post-treatment mean IOP values compared to baseline.

*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



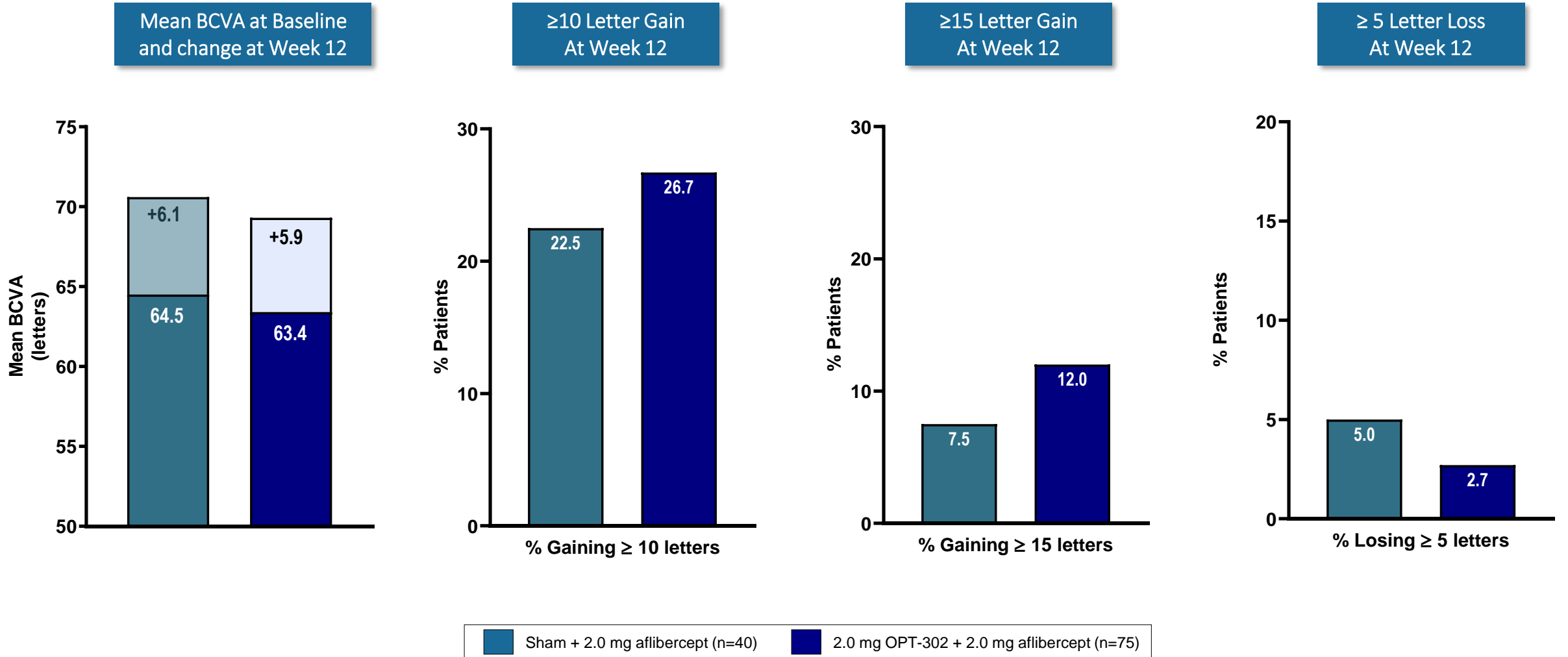
* A one stage design was used (Sargent, Control Clin Trials 2001;22:117–125) based on the pre-specified response rate primary outcome of a total of 72 evaluable patients receiving aflibercept + OPT-302, in Per Protocol population, must have received all 3 intravitreal study treatments and evaluable at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

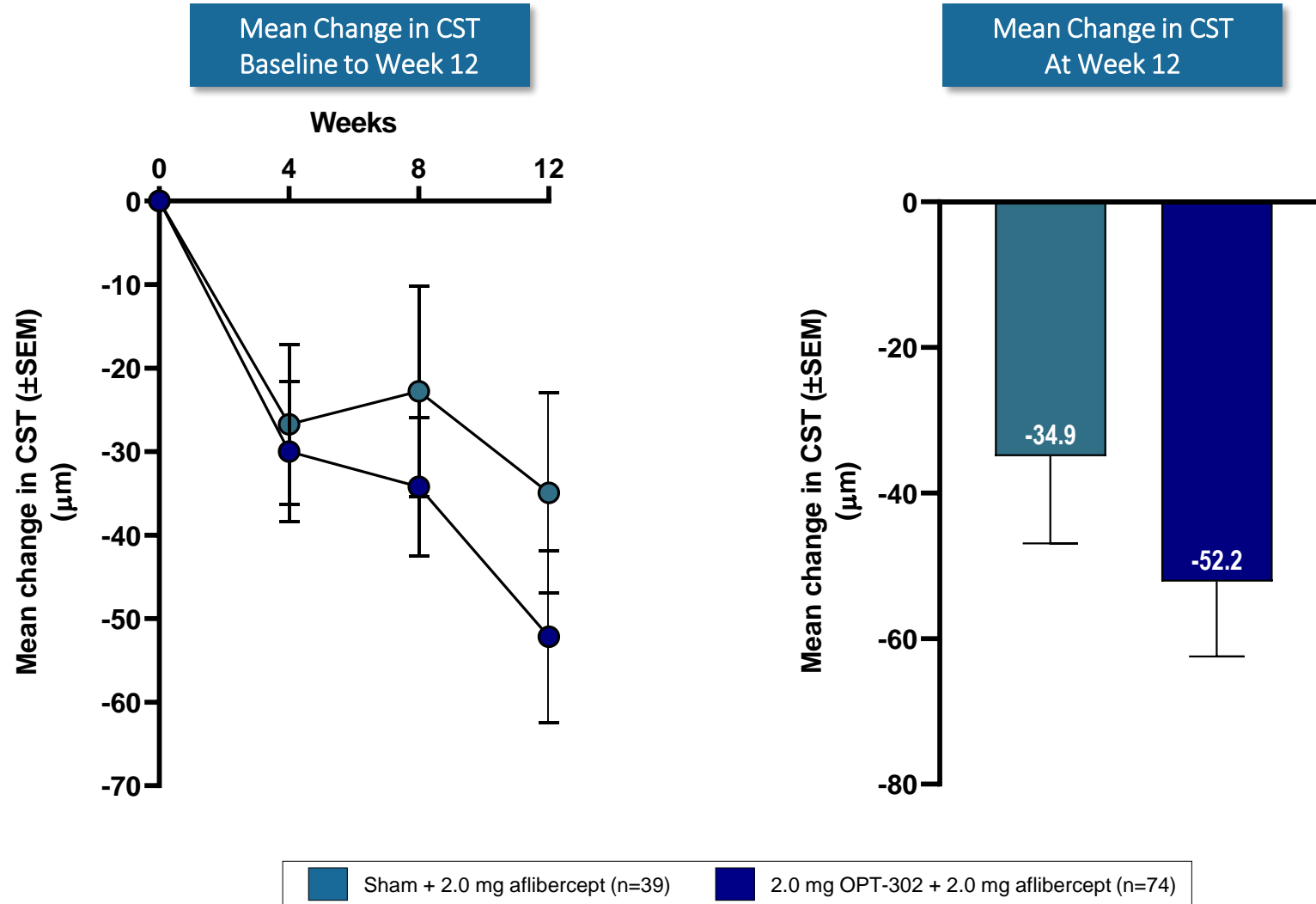
Measures of Visual Function

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



Mean Change in Retinal Thickness

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 (\pm SEM). Retinal Thickness measured by Spectral Domain-Optical Coherence Tomography (SD-OCT) as Central Subfield Thickness (CST)

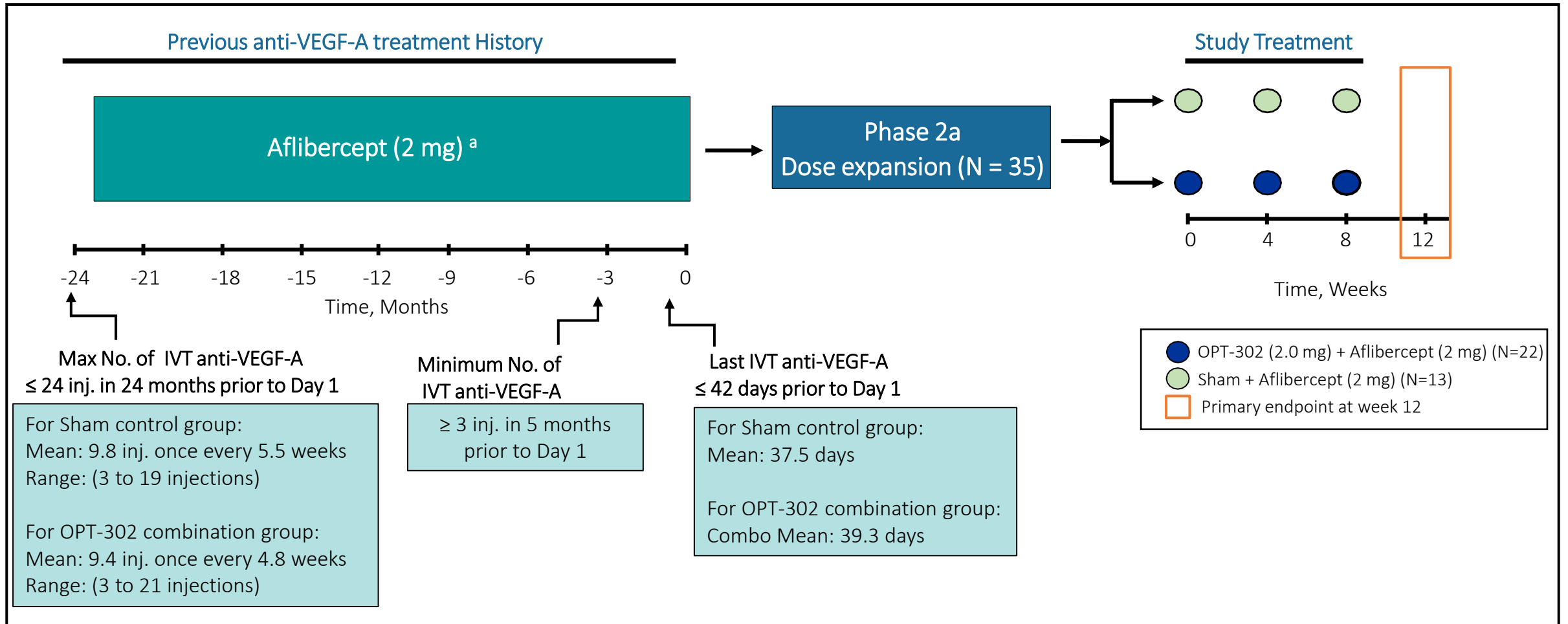
Phase 2a Trial of OPT-302 Combination Therapy for Persistent DME

Exploratory subgroup analysis in patient population receiving prior aflibercept therapy

OPT-302 Phase 2a DME Study

Exploratory subgroup analysis in patient population receiving previous aflibercept

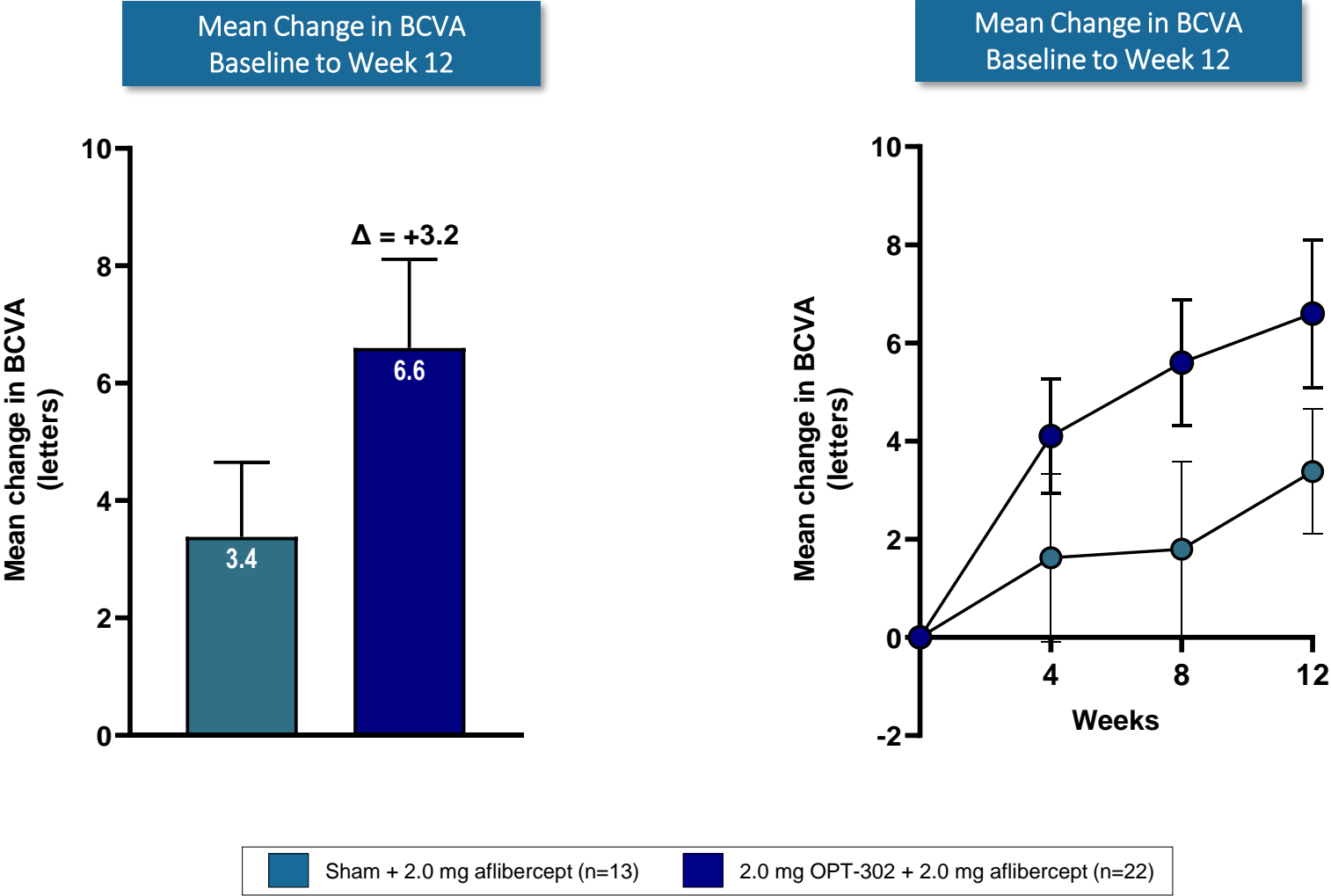
- More homogeneous population of anti-VEGF-A prior treatment history of previous aflibercept in patients with persistent DME
 - Less variable prior treatment history & greater VEGF-A suppression at baseline
 - Most stringent and least variable patient population to test the ability of OPT-302 to provide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

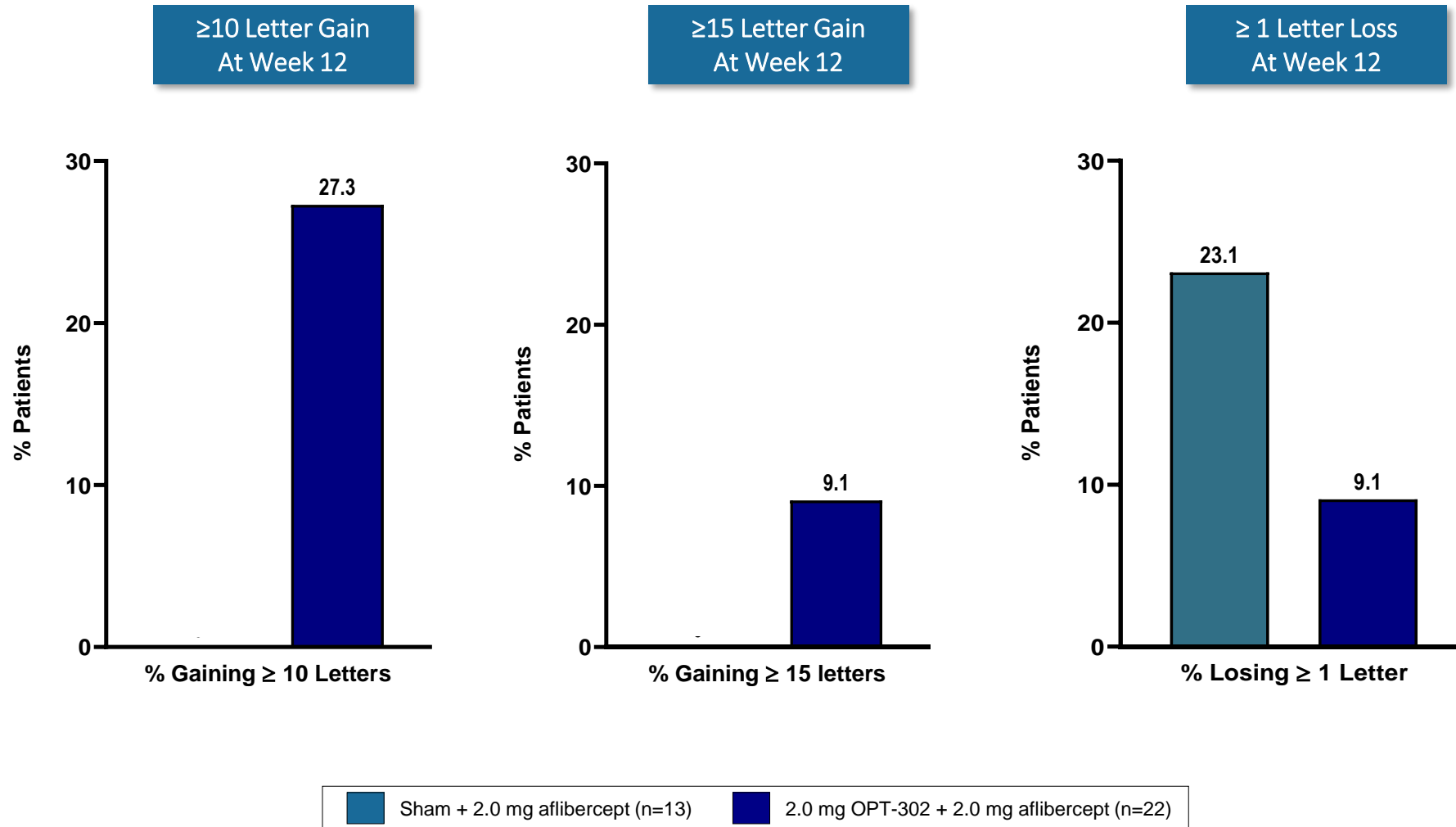
Exploratory Subgroup Analysis in patient population with a prior treatment history of aflibercept



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. Error bars (\pm SEM)

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

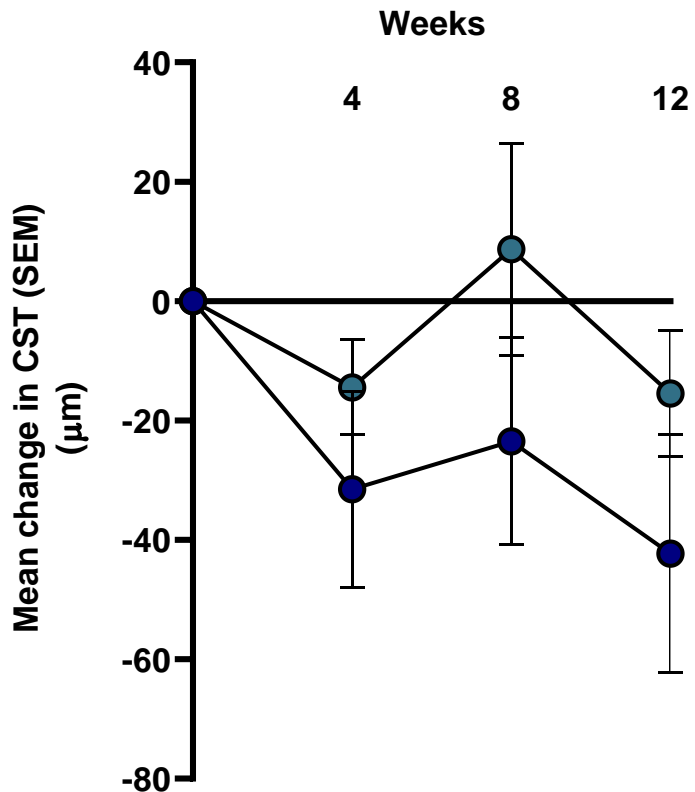
Exploratory Subgroup Analysis in patient population with a prior treatment history of aflibercept



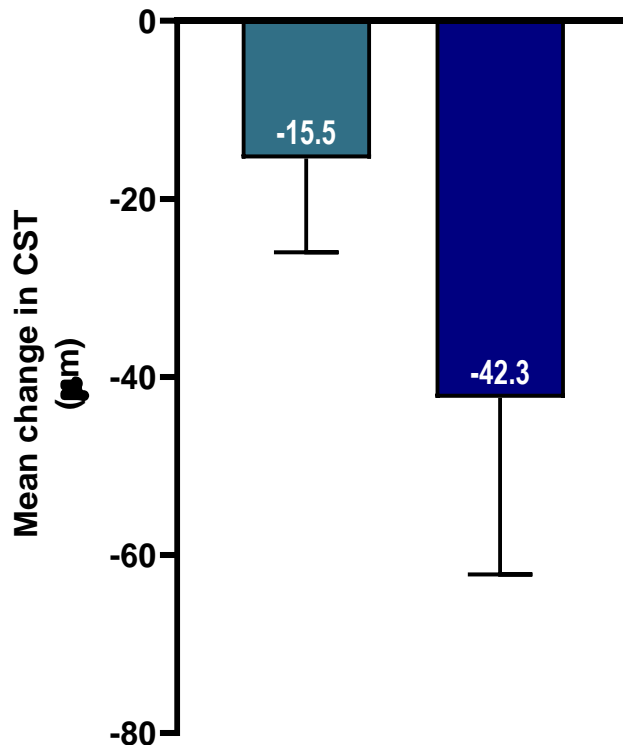
Reduction of Retinal Thickness

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

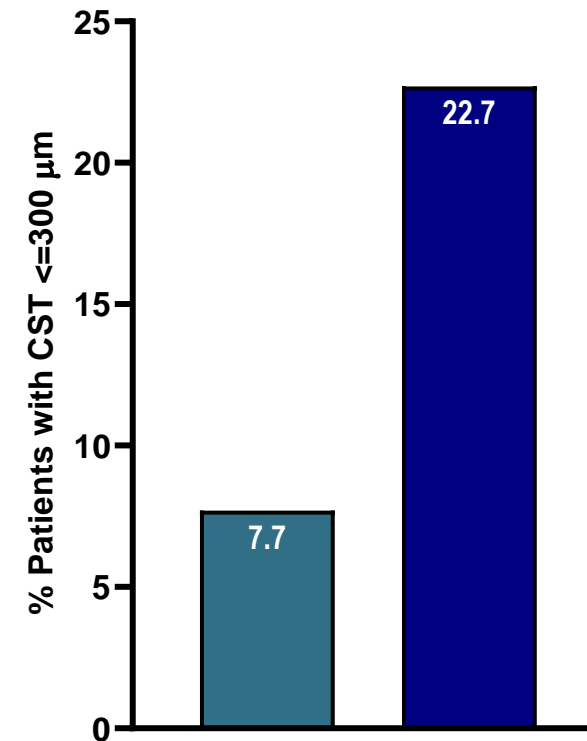
Mean Change in CST
Baseline to Week 12



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 (\pm SEM); Retinal Thickness measured by Spectral Domain-Optical Coherence Tomography (SD-OCT) as Central Subfield Thickness (CST)



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 wet AMD 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 for DME in larger, randomized, controlled clinical trials



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