The Novel 'Trap' Inhibitor of Vascular Endothelial Growth Factors C/D, OPT-302, and Ranibizumab, an anti-VEGF-A Agent, for Wet Age-Related Macular Degeneration:

Phase 1 Study Results

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Palmetto Retina Center

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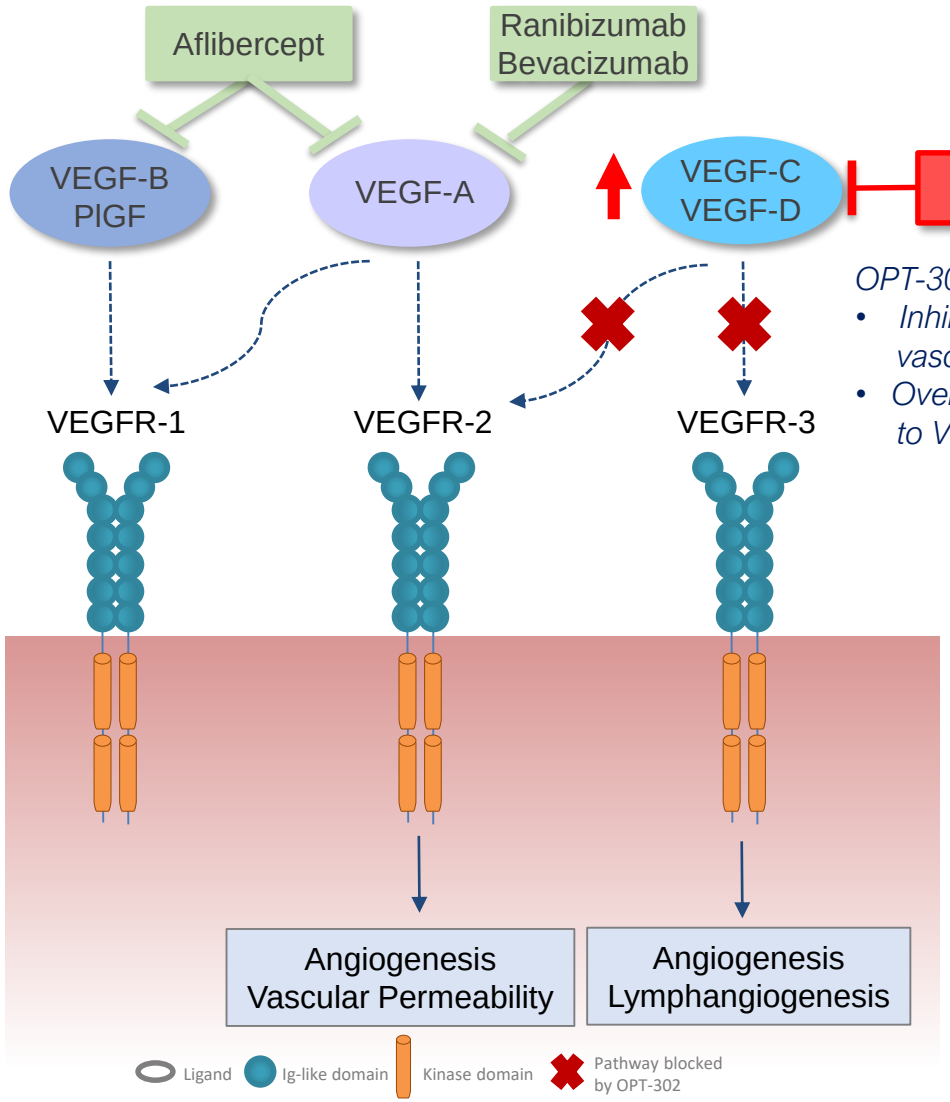
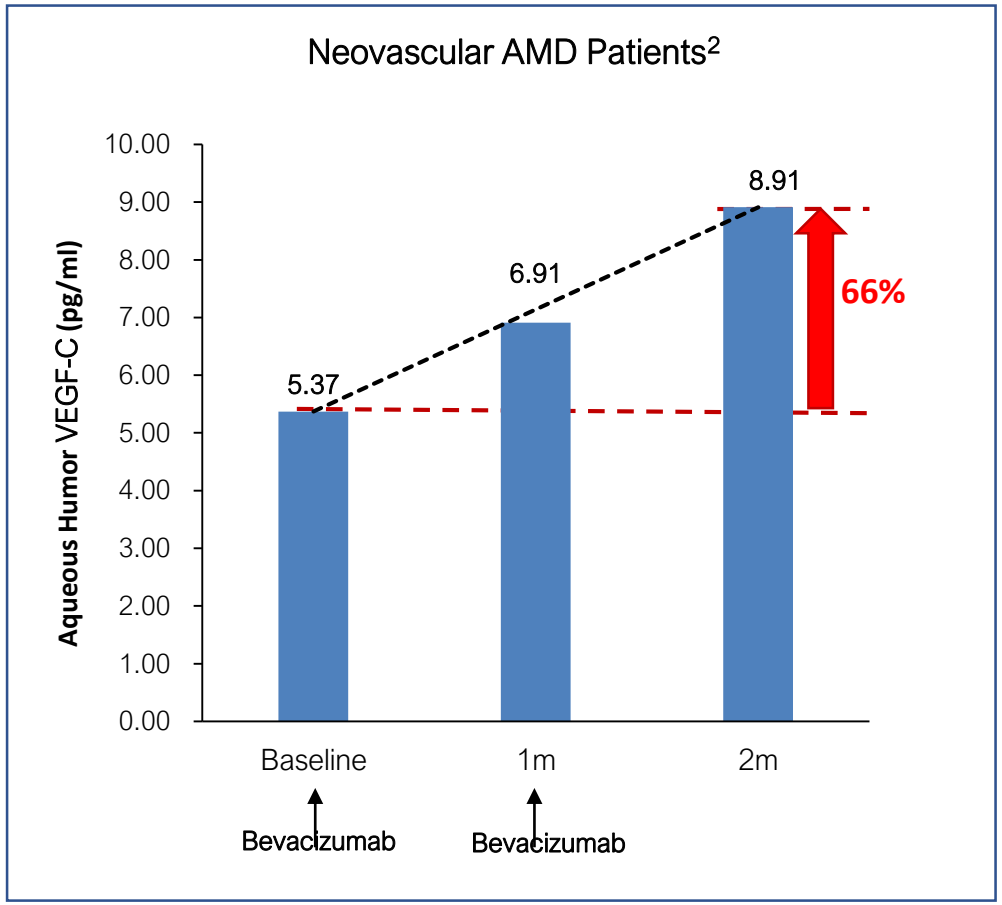
VEGF-A Inhibition Upregulates VEGF-C/D



OPT-302 (anti-VEGF-C/-D):

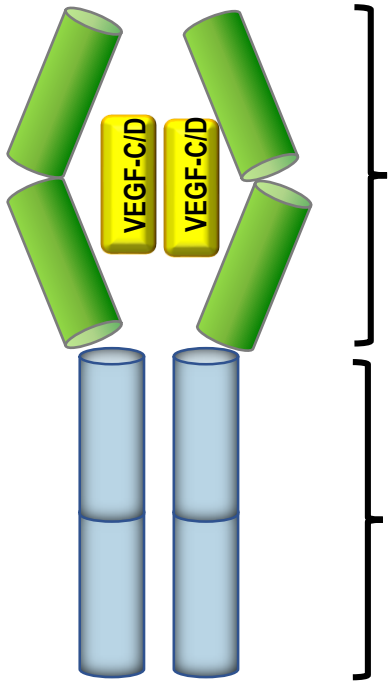
- *Inhibits angiogenesis & vascular leakage*
- *Overcomes escape mechanism to VEGF-A suppression*



1 *ARVO (Association for Research in Vision & Ophthalmology) Annual Meeting 2016, Cabral et al., Program 3341, Poster D0144*

OPT-302 a Novel 'Trap' Inhibitor of VEGF-C/D

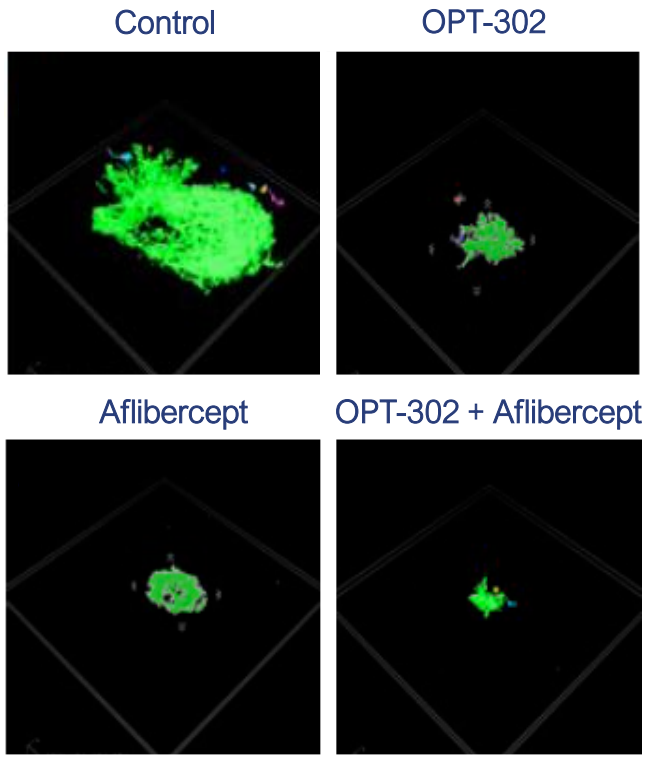
- OPT-302 (Opthea Ltd, Melbourne, Australia)
- A 'trap' molecule that binds and neutralises the activity of VEGF-C/-D, blocking binding to the receptors VEGFR-2 and VEGFR-3
- Potent inhibitor of VEGF-C (~5pM) and VEGF-D (~0.5 nM)

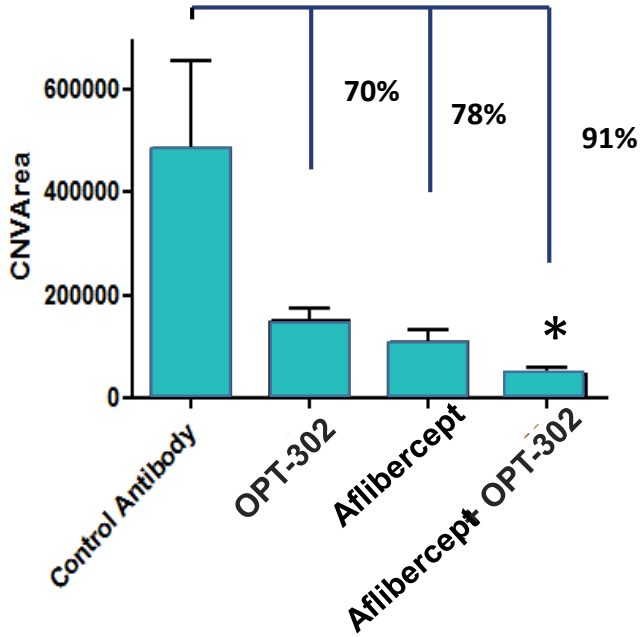


Extra-Cellular Domains 1-3 hVEGFR-3

hIgG1 Fc

OPT-302 Inhibition of CNV in Rodent Model of AMD





** Pairwise comparison: OPT-302 vs Aflibercept + OPT-302 (p<0.02)*
Aflibercept vs Aflibercept + OPT-302 (p<0.05)

Combined inhibition of VEGF-A (Aflibercept) and VEGF-C/-D (OPT-302) is more effective than inhibition of VEGF-A alone

OPT-302 Phase 1 Study Design

A Phase 1 study was conducted to investigate OPT-302 ± ranibizumab in patients with wet AMD

Patients ≥ 50 years with wet AMD and persistent CNV activity were enrolled:

- Treatment-naïve or
- with prior exposure to multiple anti-VEGF-A therapies and suboptimal therapeutic response
  - despite ≥ 3 intravitreal anti-VEGF-A injections in the prior 6 months

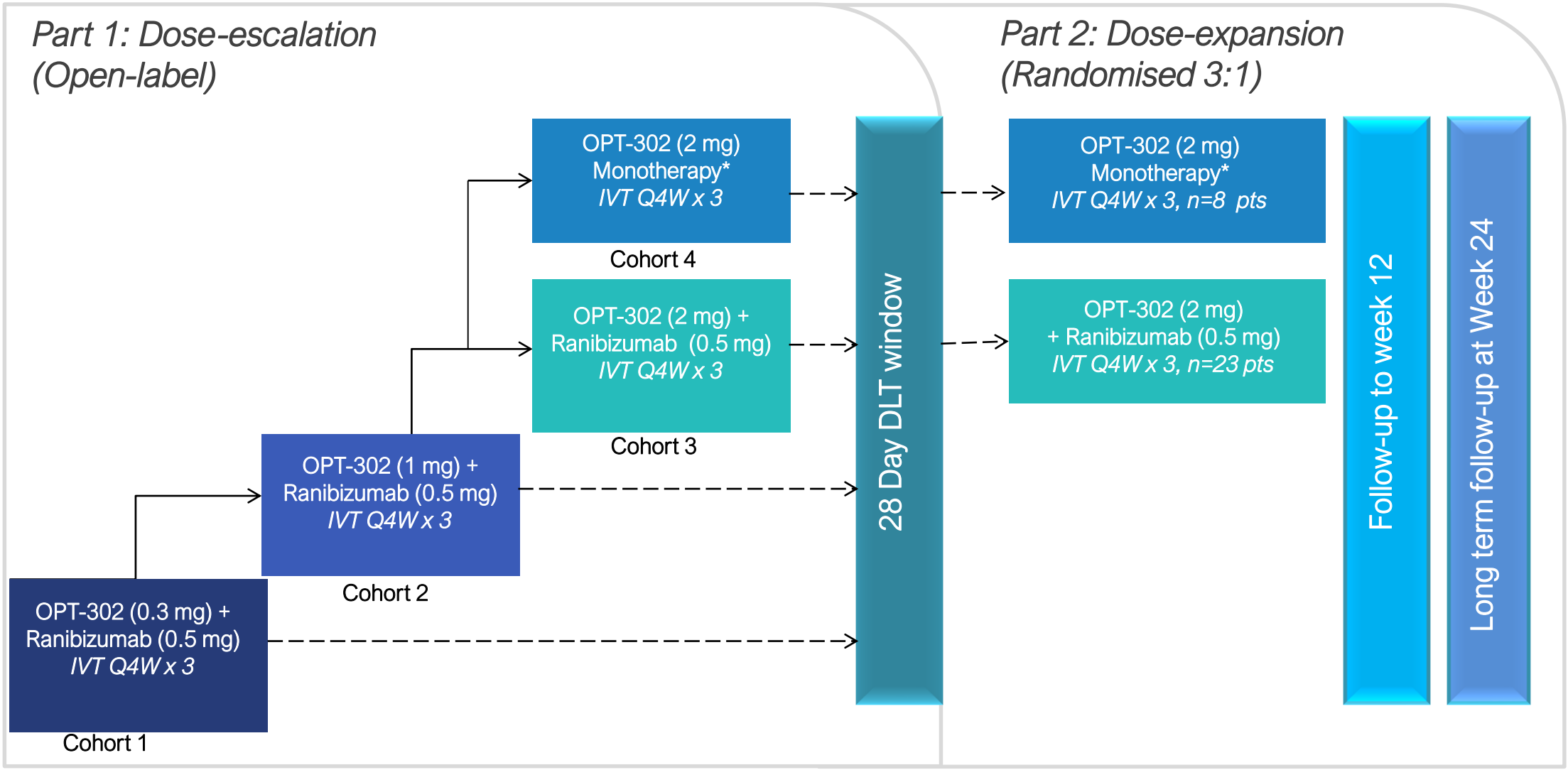
Two-part study design:

- Part 1 Dose escalation
  - The multiple ascending dose enrolled four cohorts each with 5 patients consisting of OPT-302 (0.3, 1 or 2 mg) in combination with ranibizumab (0.5 mg) or OPT-302 monotherapy (2 mg)
- Part 2 randomized dose expansion
  - The dose expansion randomized 31 patients in a 3:1 ratio to either OPT-302 (2 mg) + ranibizumab (0.5 mg) or OPT-302 (2 mg) monotherapy.

All patients received a total of 3 treatments at 4 weekly intervals

Masking: Visual acuity testers and OCT/FA image readers at Independent Reading Center

OPT-302 First-in-Human Study in wet AMD Patients (n=51)

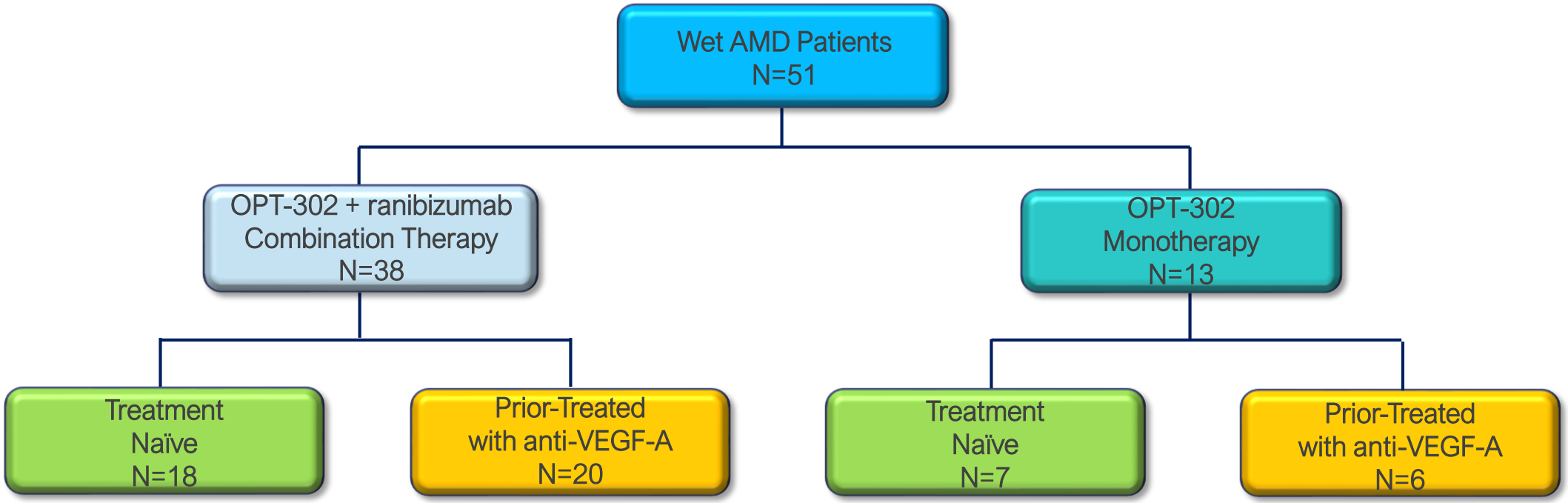


- *Comprises of 4 treatment cohorts of 5 subjects each*

**Access to rescue anti-VEGF-A Tx*

ClinTrials Identifier NCT 02543229

Treatment Groups



- Mean Age: 77.4 years
- 32/51 (63%) female and 19 (37%) were male
- 49% treatment-naive
- 51% were difficult to treat patients who were heavily pre-treated and sub-responsive to prior anti-VEGF-A therapy
  - Mean number prior anti-VEGF-A injections = 17
- Lesions: 73% Occult, 23% Minimally Classic, 4% Predominantly Classic

OPT-302 ± Ranibizumab Safety Results

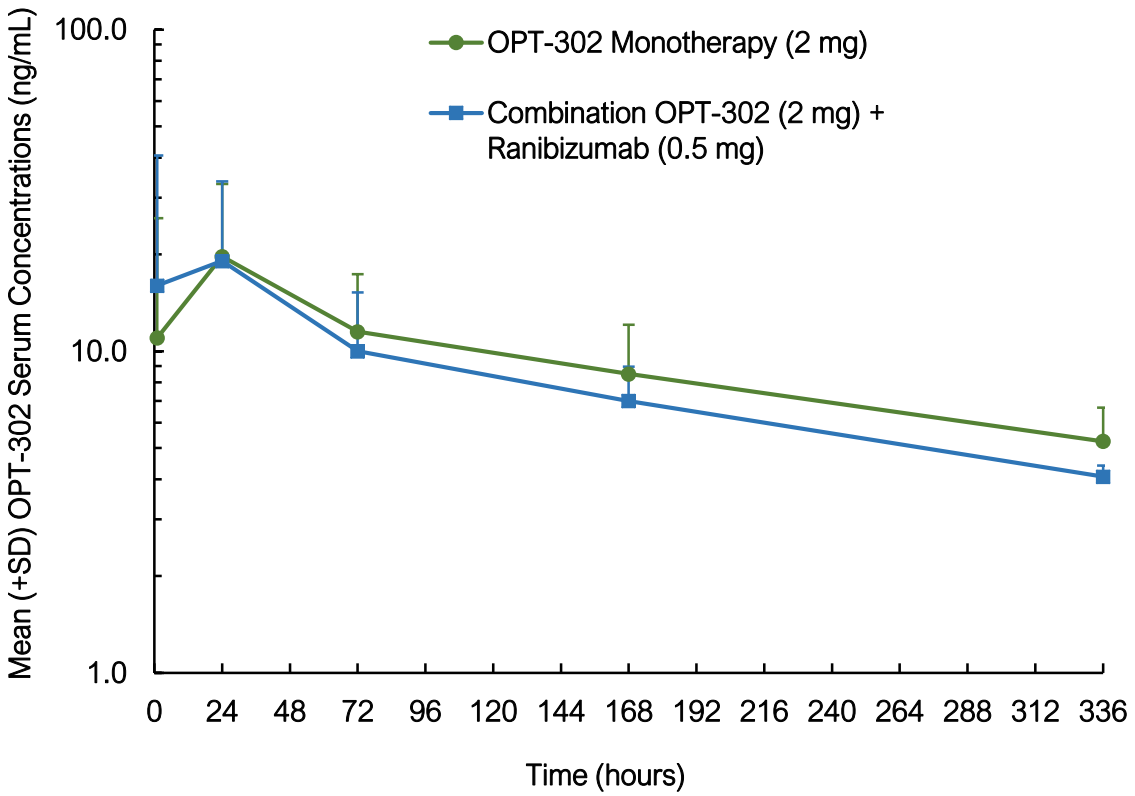
- OPT-302 ± ranibizumab administered by IVT injection (Baseline, Week 4, Week 8)
  - No missed doses, safety experience with ~150 intravitreal (ocular) injections of OPT-302
- OPT-302 intravitreal doses up to 2 mg ± with ranibizumab 0.5 mg
  - No dose limiting toxicities (MTD not reached)
  - No study drug related serious adverse events or systemic AEs
- AEs primarily related to IVT injection procedure (*Mild/moderate, manageable*)
- Two patients (3.9%) had treatment-related AEs of Grade 1/Mild anterior chamber inflammation / anterior uveitis in the low and mid-dose combination groups
  - No OPT-302 related AEs observed in high dose (2mg) combination or monotherapy patients (n=41)
- No clinically significant changes in IOP, ECG's, blood pressure, vitals
- No evidence of OPT-302-related immunogenicity
- OPT-302 was generally safe and well tolerated ± with ranibizumab

Summary of Adverse Events Reported in ≥ 5% of all Subjects

	OPT-302 (0.3 mg) + RBZ (0.5 mg) (n=5)	OPT-302 (1 mg) + RBZ (0.5 mg) (n=5)	OPT-302 (2 mg) + RBZ (0.5 mg) (n=28)	OPT-302 (2 mg) Monotherapy (n=13)	Total Number of Subjects (N=51)
Total pts with at least one AE	5	4	22	9	40 (79%)
Total pts with at least 1 Ocular AE	5	4	18	8	35 (69%)
Ocular AEs					
Conjunctival Haemorrhage	4	3	9	4	20 (39%)
Punctate Keratitis	1	2	6	2	11 (22%)
Eye pain	2	2	5	2	11 (22%)
Retinal haemorrhage	1	-	1	2	4 (8%)
Eye irritation	-	1	2	-	3 (6%)
Ocular discomfort	1	-	2	-	3 (6%)
Vitreous floaters	-	1	-	2	3 (6%)
Total pts with at least 1 Non-Ocular AE	3	3	13	4	23 (45%)
Non-Ocular AEs					
Nasopharyngitis	1	-	1	1	3 (6%)

OPT-302 Serum Pharmacokinetic Profile (± Ranibizumab)

Mean OPT-302 serum concentrations

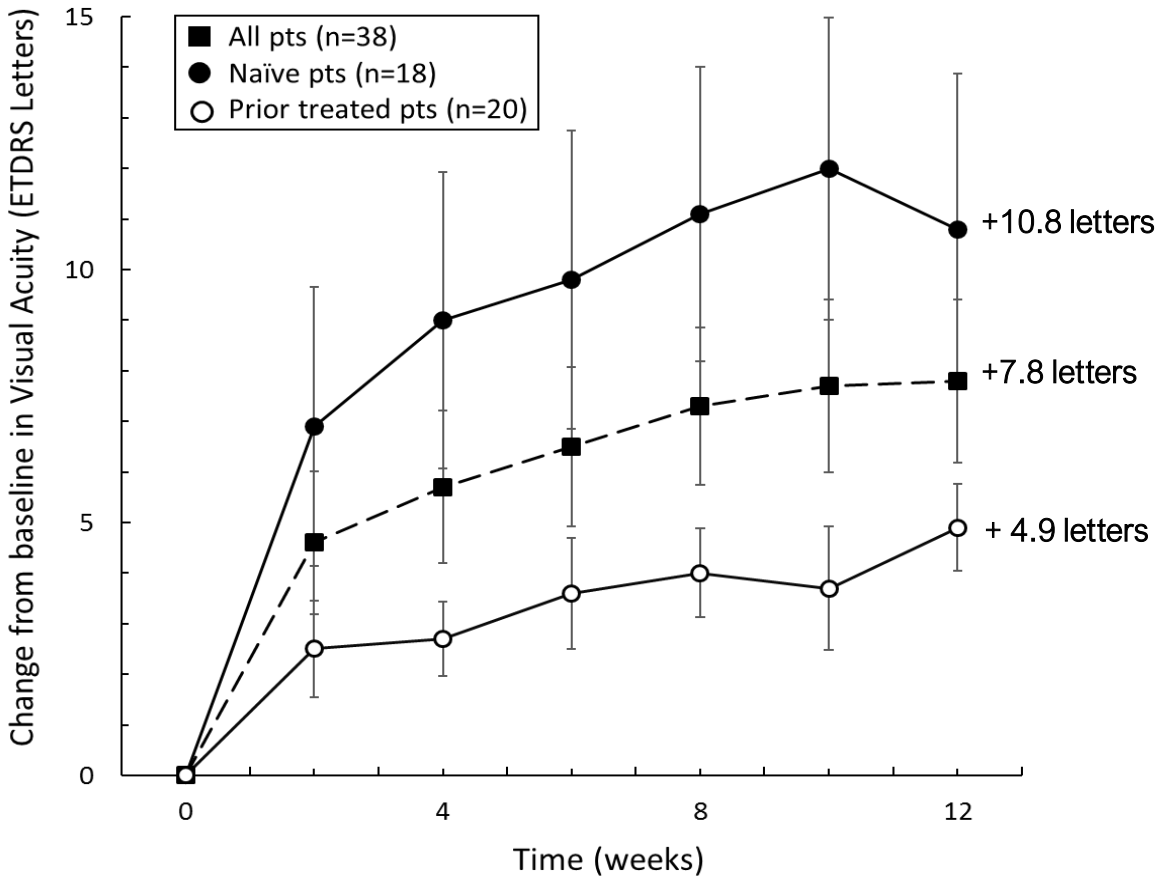


- Non-compartmental OPT-302 PK analysis indicated:
  - low systemic exposure
  - a half-life of 8 ± 2 days
  - mean C_{max} of ~21 ng/mL at ~31 hours post IVT injection at a dose of 2 mg
  - no accumulation
  - no influence from ranibizumab on the PK profile.

Intravitreal OPT-302 (2 mg) (± 0.5 mg ranibizumab)	C_{max} (ng/mL)	T_{max} (hours)	$AUC_{0–last}$ (ng·h/mL)	$T_{1/2}$ (days)
Mean ± SD (n)	21.1 ± 17.3 (n = 41)	31 ± 24 (n = 41)	2760 ± 1110 (n = 30)	8 ± 2 (n = 10)

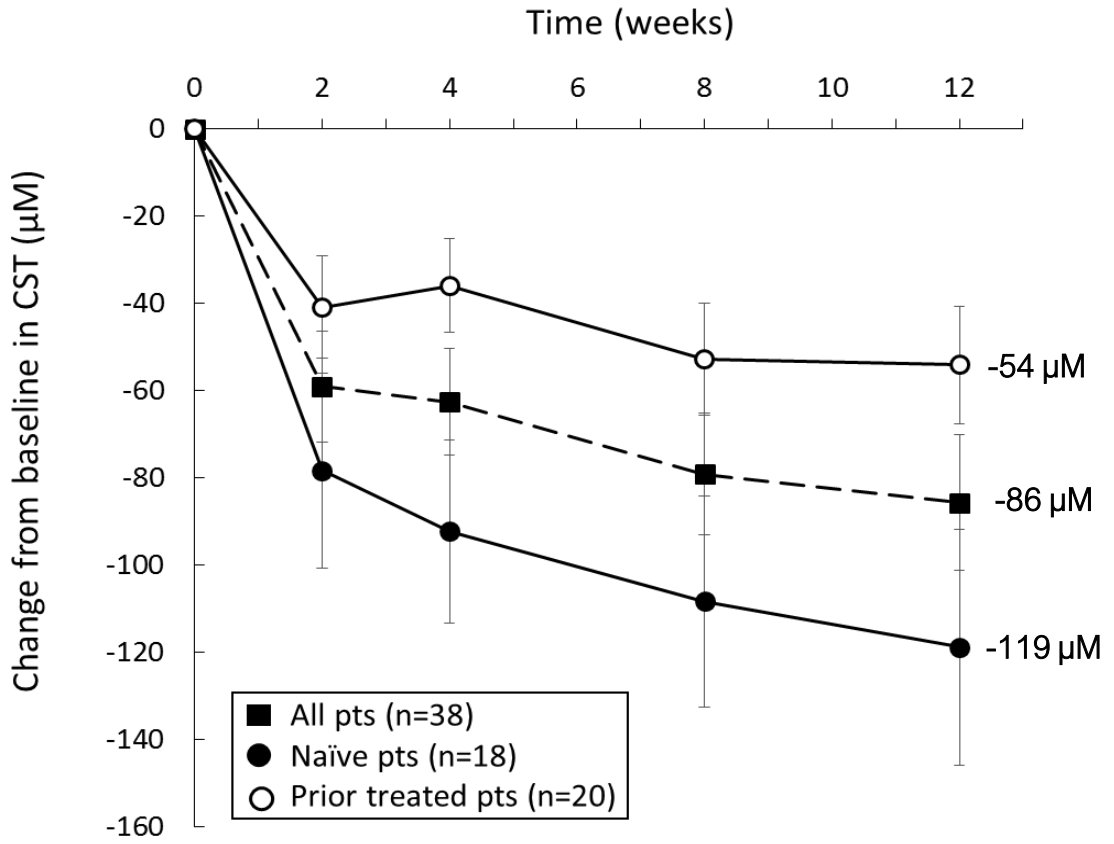
OPT-302 + Ranibizumab: Gains in BCVA & Reduced Retinal Thickness

Change in mean BCVA



Treatment Naïve Patients:
n = 18; OPT-302 (0.3, 2.0 mg) + ranibizumab (0.5 mg)
Mean Baseline VA = 56.5 Letters

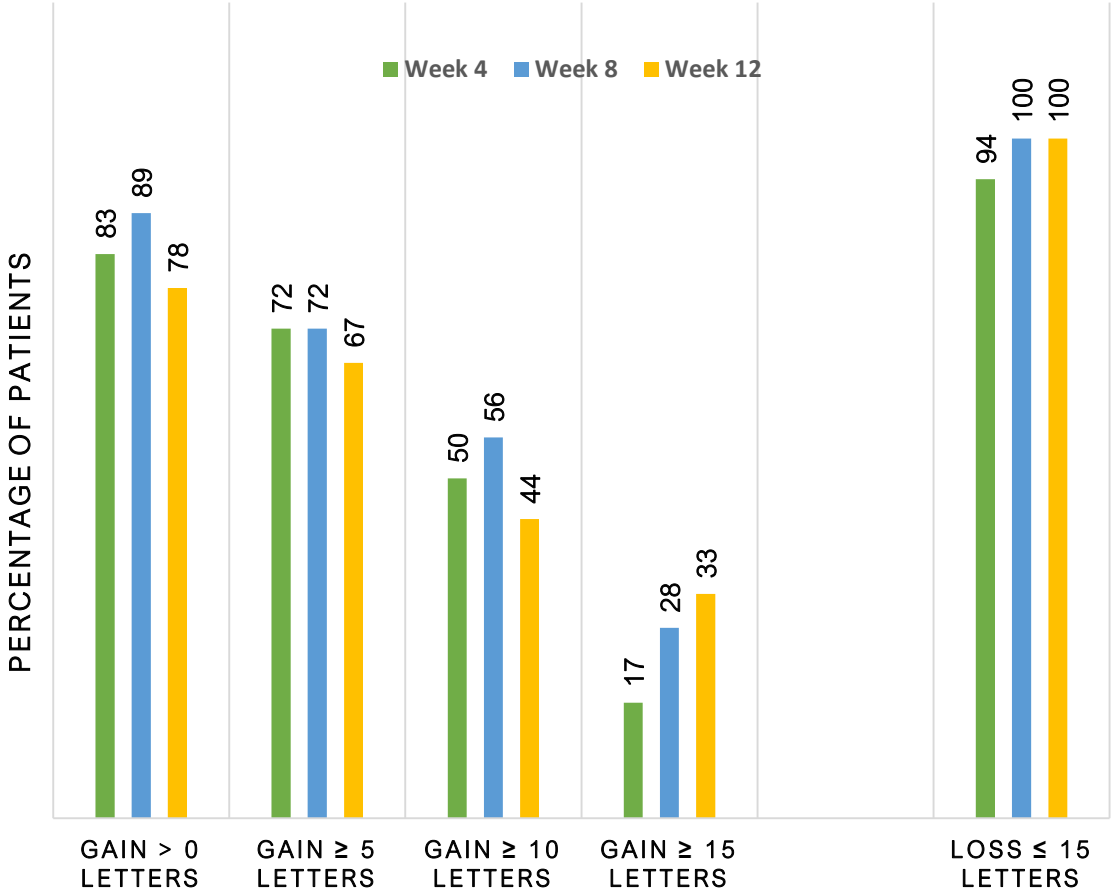
Change in mean Central Subfield Thickness



Prior-Treated Patients:
n = 20 (wk 4, 8), 19 (wk 12); OPT-302 (0.3-2.0 mg) + ranbizumab (0.5 mg)
Mean Baseline VA = 64.5 Letters

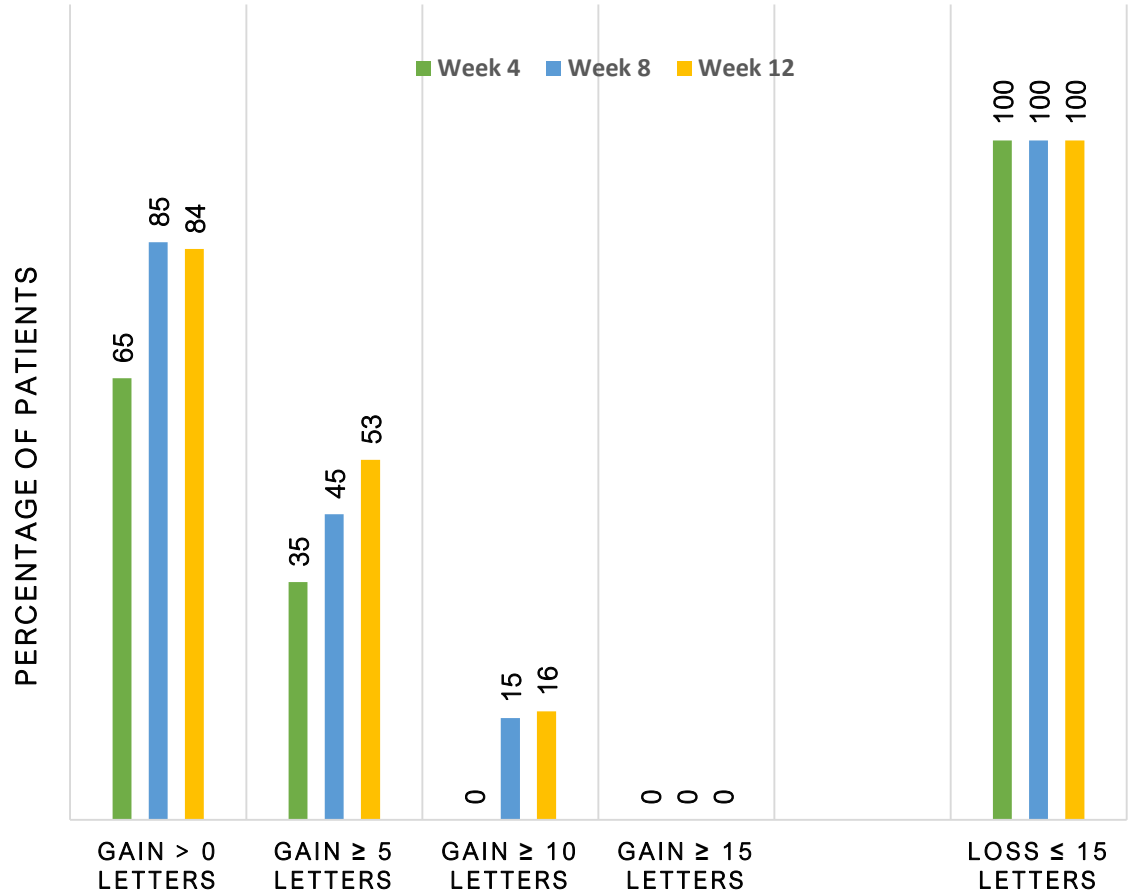
OPT-302 + Ranibizumab: % Patients with BCVA gains

Treatment-Naïve



Treatment Naïve Patients:
n = 18; OPT-302 (0.3, 2.0 mg) + ranibizumab (0.5 mg)
Mean Baseline VA = 56.5 Letters

Previously treated

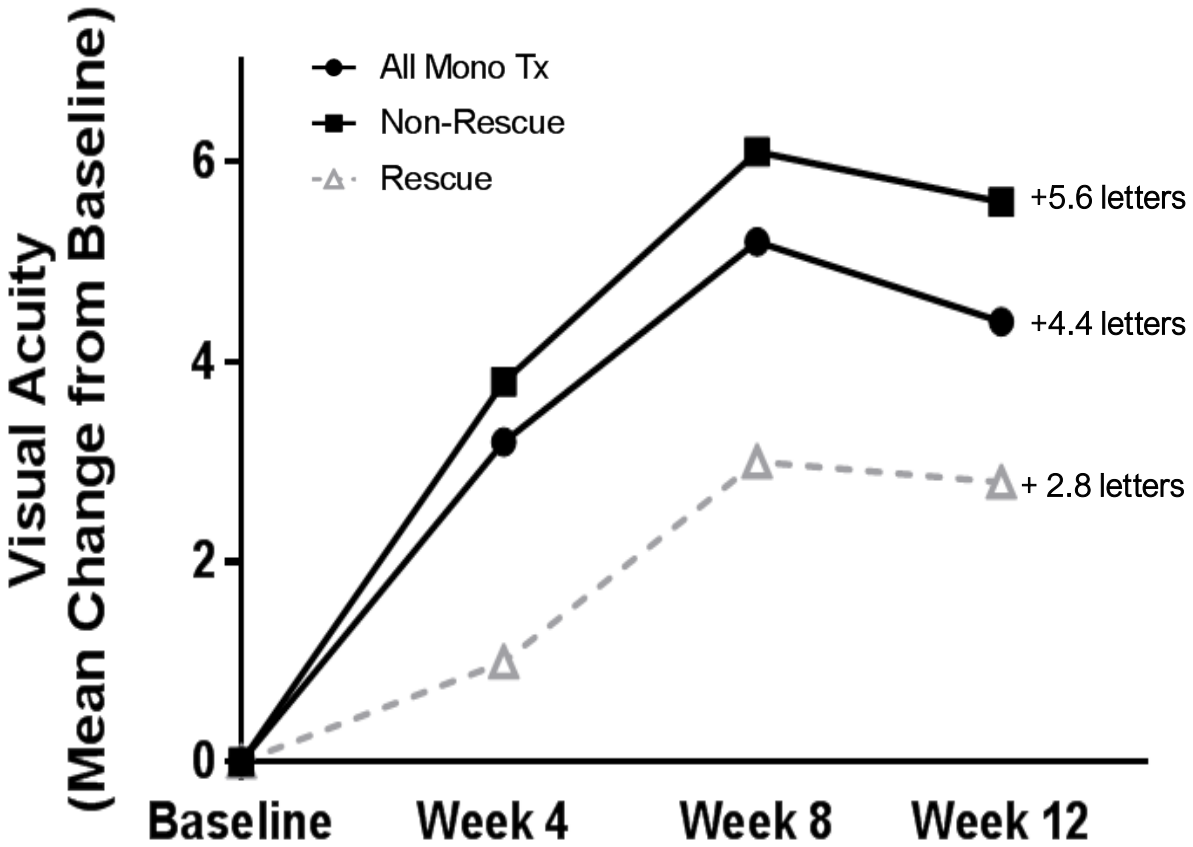


Prior-Treated Patients:
n = 20 (wk 4, 8), 19 (wk 12); OPT-302 (0.3-2.0 mg) + ranbizumab (0.5 mg)
Mean Baseline VA = 64.5 Letters

Intravitreal OPT-302 (2 mg) monotherapy

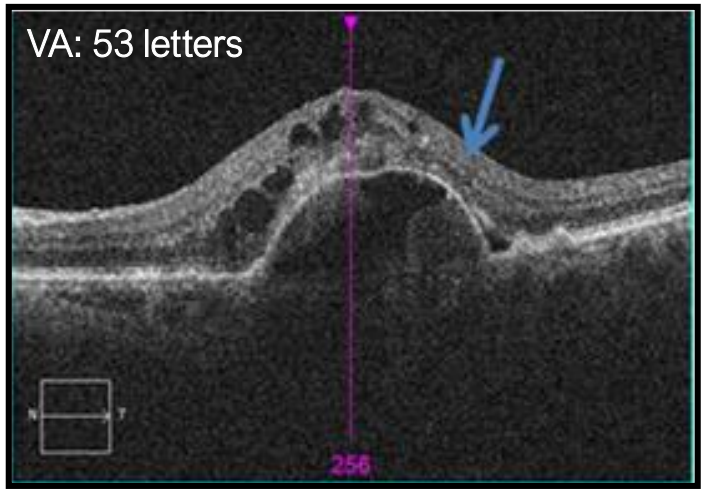
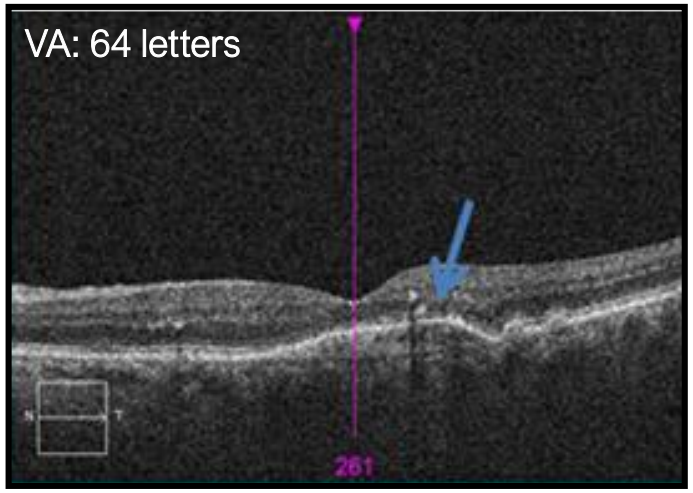
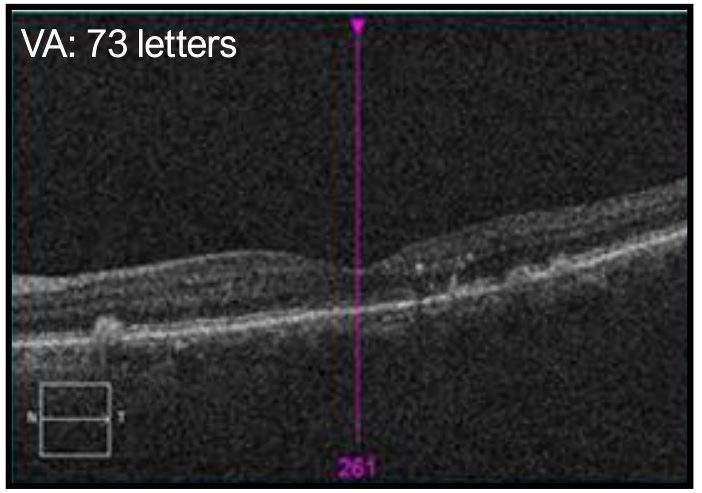
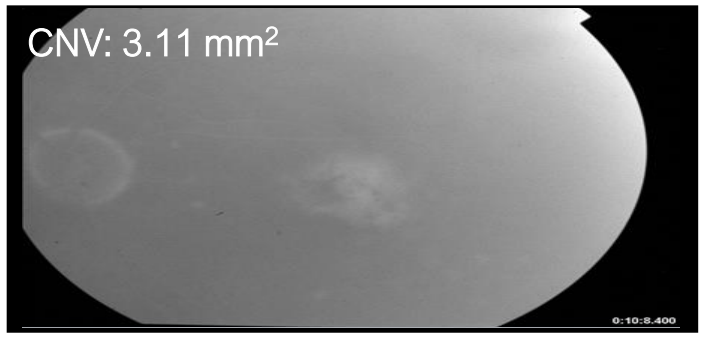
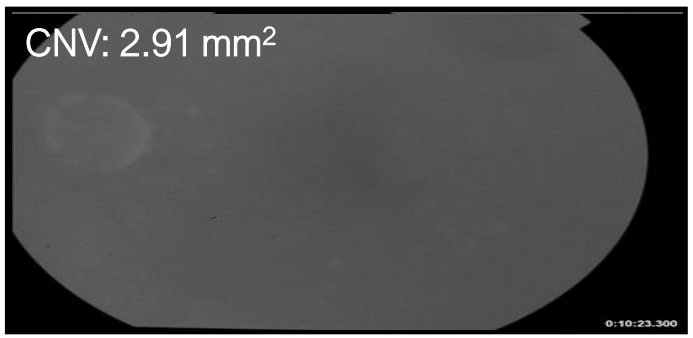
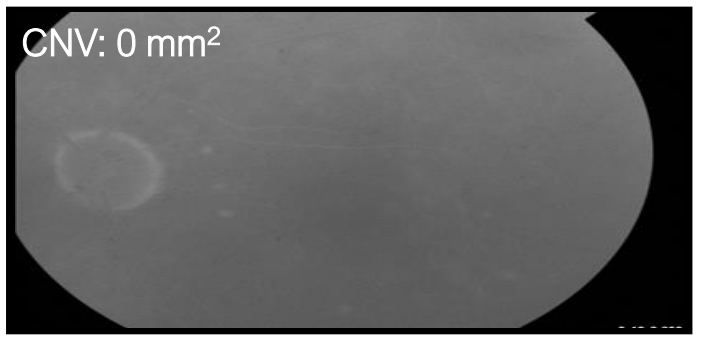
- OPT-302 monotherapy at 2 mg to assess biological activity in absence of standard of care
- Anti-VEGF-A (ranibizumab) rescue therapy was available to patients at week 2 through week 12 at investigator discretion or if patient met pre-defined criteria:
  - <10% decrease in CST and ≥ 5 letter loss of BCVA
- 7/13 (56%) patients (4 treatment-naïve, 3 prior treated) did not require 'rescue' therapy through week 12
- 6/13 (44%) patients (3 treatment-naïve, 3 prior treated) were rescued through week 12
  - 4/6 pts were rescued based on investigator discretion
  - 5/6 pts only required 1 rescue injection
  - 1/6 pts had 2 rescue injections
  - Mean time to rescue therapy was 57.7 days

Change in mean Best Corrected Visual Acuity from Baseline to week 12



OPT-302 Monotherapy Patients:
n = 13 (wk 4, 8), 12 (wk 12);
Mean Baseline VA = 55.7 Letters

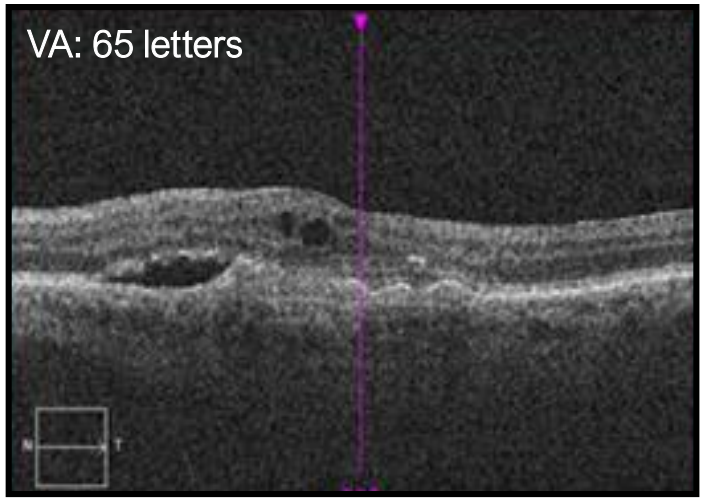
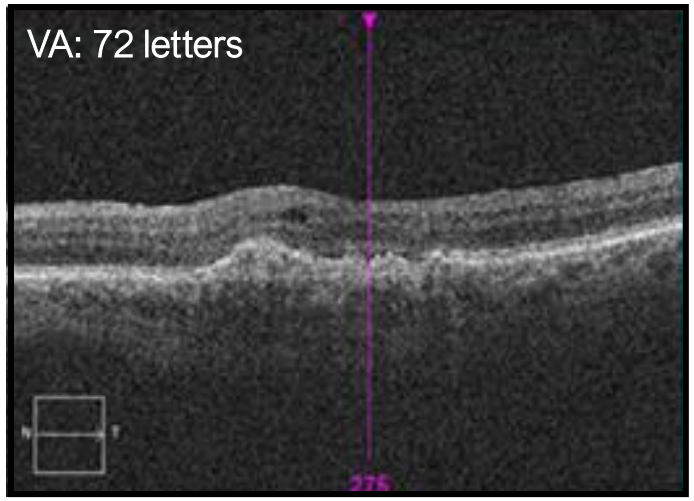
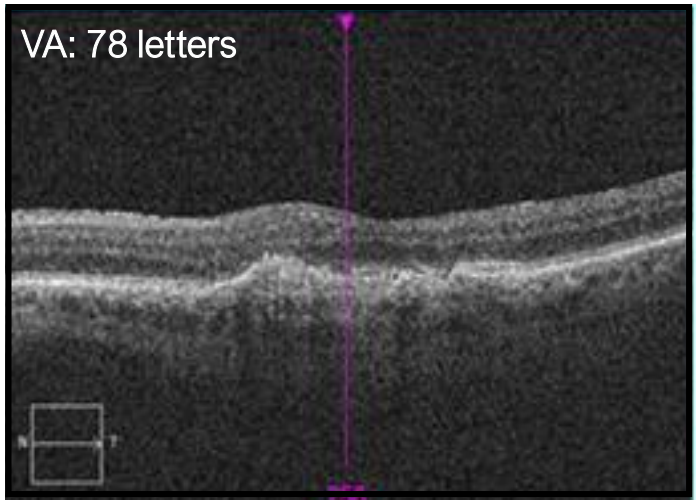
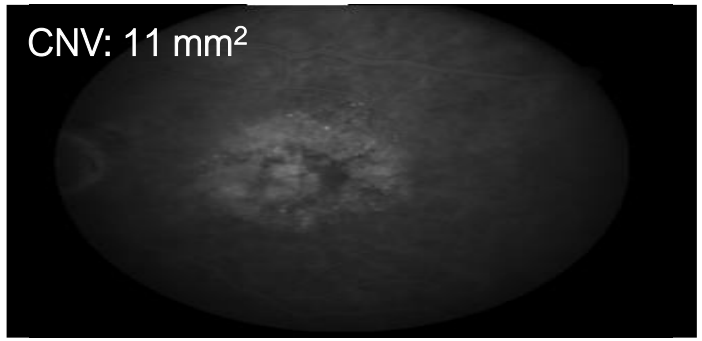
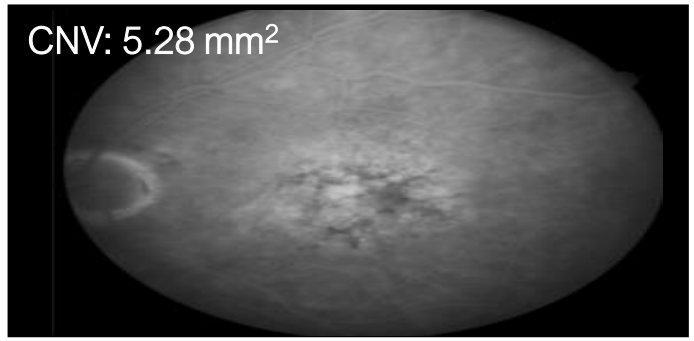
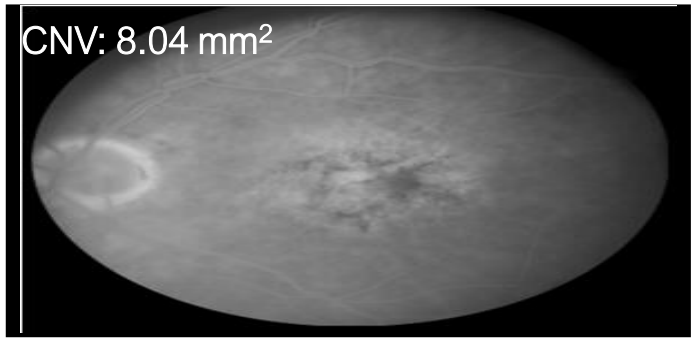
Case Study Naïve Patient (Occult): OPT-302 + Ranibizumab

Baseline	Week 4	Week 12
		
		
CST: 279 µM SRF: 192 µM SHRMw: 1053 µM SHRMh: 94 µM	CST: 217 µM SRF: 0 µM SHRMw: 0 µM SHRMh: 0 µM	CST: 233 µM SRF: 0 µM SHRMw: 0 µM SHRMh: 0 µM

OPT-302 (2 mg) + ranbizumab (0.5 mg)

Case Study Prior Treated Patient (Occult): OPT-302 + Ranibizumab

Patient was heavily pre-treated with Ranibizumab (0.5 mg) x 28 IVT injections

Baseline	Week 4	Week 12
		
		
CST: 303 µM SRF: 140 µM SHRMw: 1042 µM SHRMh: 133 µM	CST: 249 µM SRF: 41 µM SHRMw: 0 µM SHRMh: 0 µM	CST: 248 µM SRF: 0 µM SHRMw: 0 µM SHRMh: 0 µM

OPT-302 (2 mg) + ranbizumab (0.5 mg)

Conclusion

- Current treatments target primarily VEGF-A
- OPT-302 is a novel biologic that binds and neutralizes VEGF-C/-D
- Simultaneous targeting of VEGF-C/-D (with OPT-302) and VEGF-A signaling pathways may offer benefits that exceed the inhibition of either target alone.
- Multiple dosing with OPT-302 ± ranibizumab was well tolerated and an overall favourable safety profile was exhibited in the 51 patients enrolled.
- In eyes that were treatment-naïve or suboptimal responders on prior multiple anti-VEGF-A treatments, improvements in BCVA and key OCT / FA parameters were observed.
- Phase 2 studies are underway to evaluate OPT-302 in larger patient populations:
  - ~351 pts with wet AMD (ClinTrials Identifier: NCT 03345082)
  - ~117 pts with central-involved DME Edema (ClinTrials Identifier: NCT 03397264)

OPT-302-1001 Study Investigators

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