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Clinical results of OPT-302 (VEGF-C/D ‘Trap’) Combination Treatment in nAMD and DME

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Megan Baldwin PhD, CEO & Managing Director

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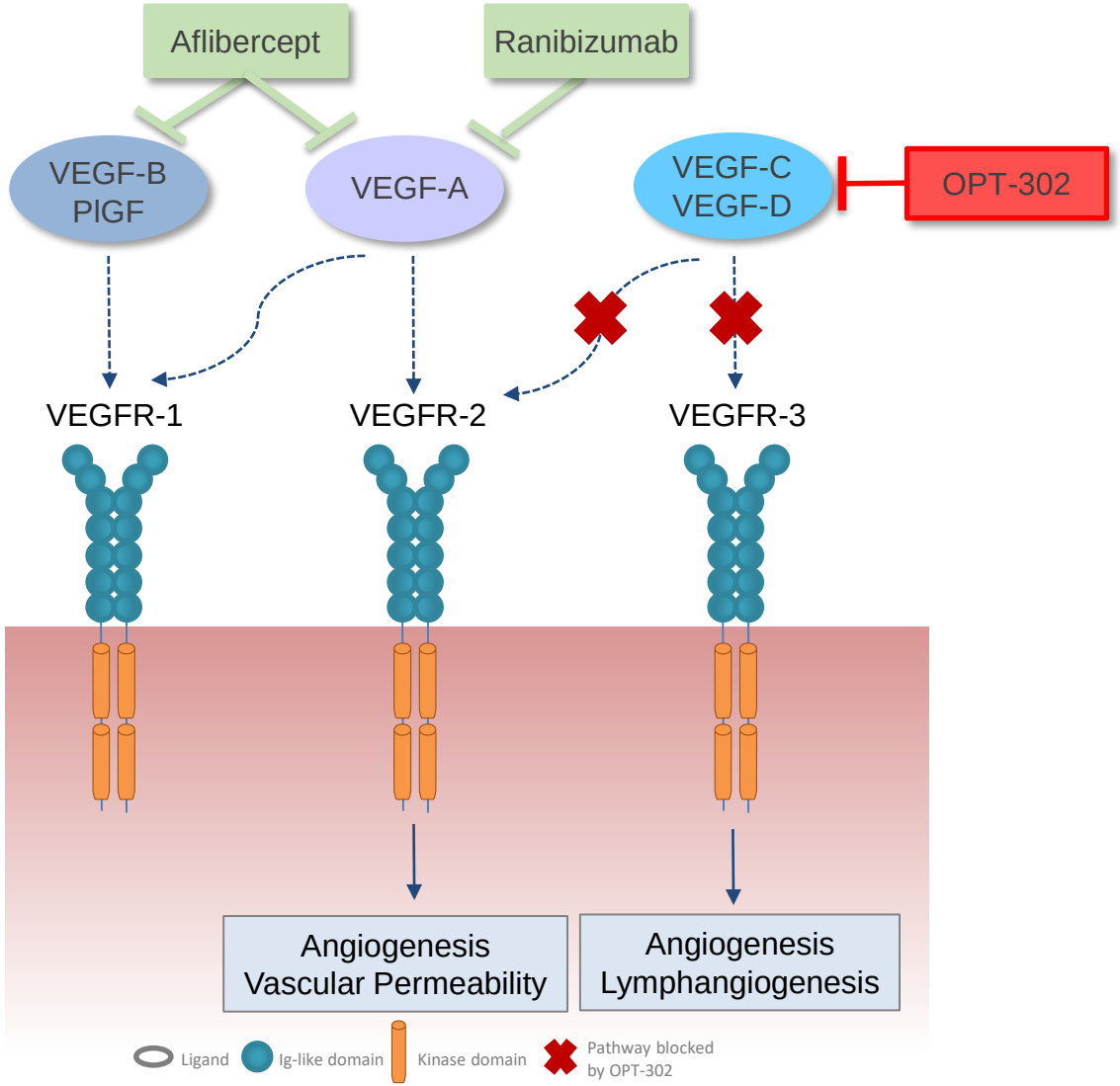
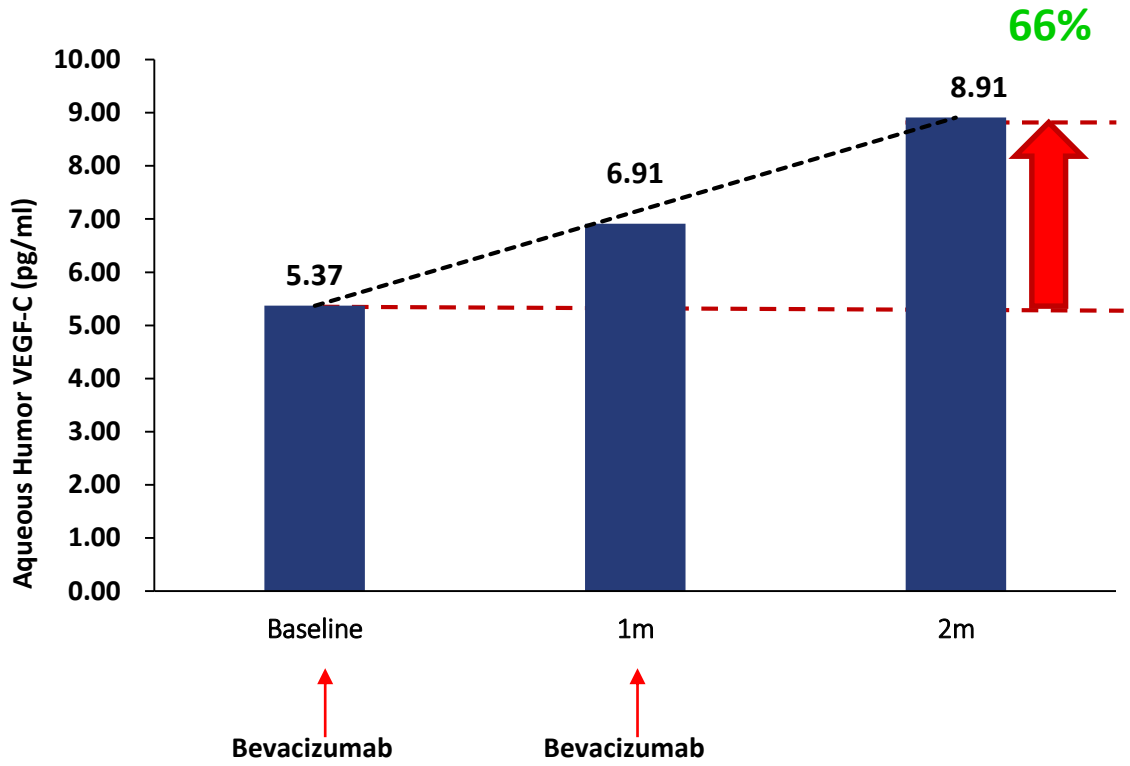
OPT-302 Inhibits VEGF-C and VEGF-D



Neovascular AMD [1]



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

An Unmet Medical Need for nAMD & DME

Despite receiving a VEGF-A inhibitor (Ranibizumab, Aflibercept or Bevacizumab)*:

nAMD	>50%	Do not achieve significant vision gains
	2/3	Will continue to have fluid at the back of the eye
	25%	Will have further vision loss at 12 months
DME	2/3	Do not achieve significant vision gains#
	25%	Continue to have macula thickening/swelling^

Opportunity: New Products that Improve Efficacy and Durability

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

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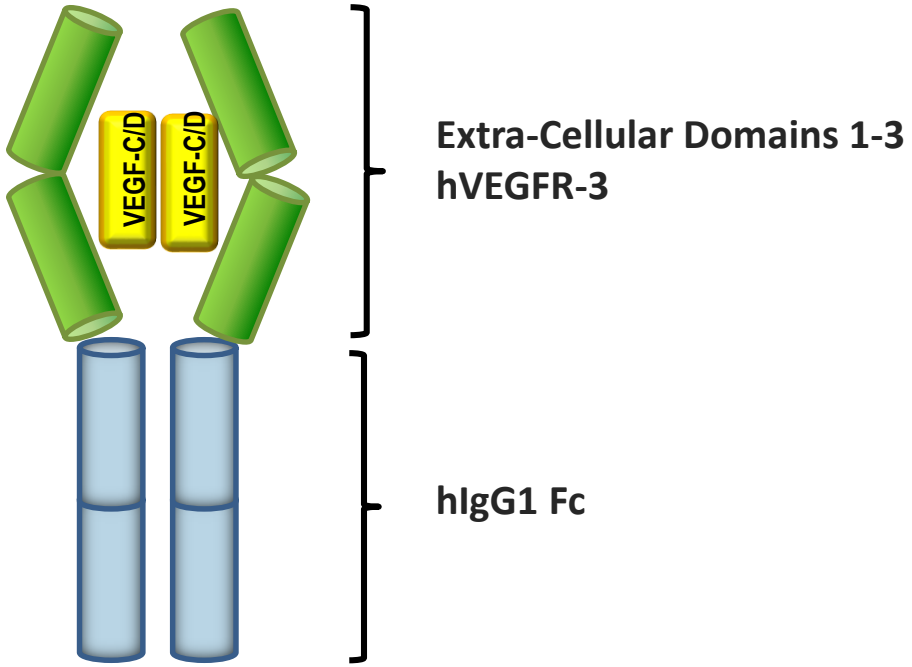
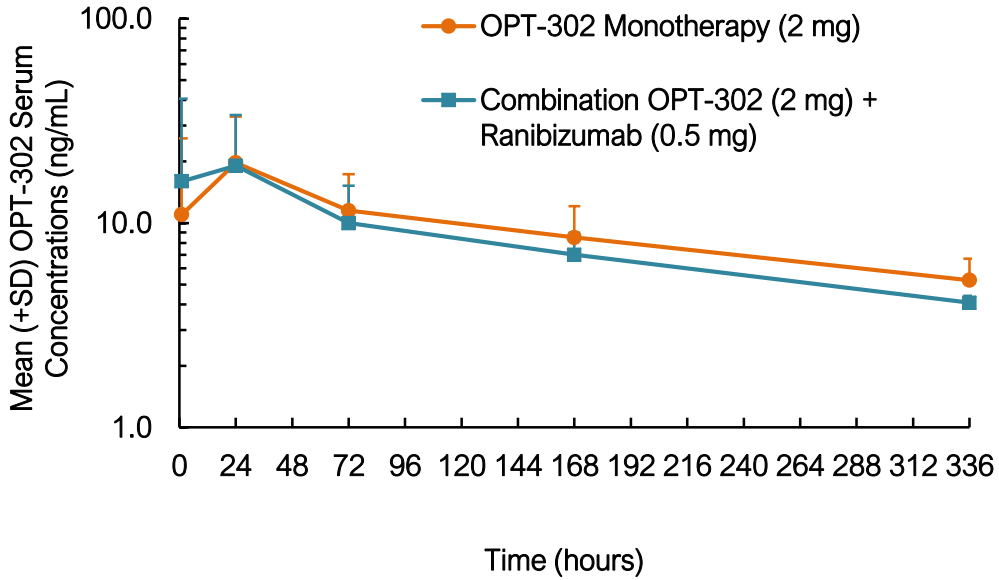
OPT-302

- Potent inhibitor of VEGF-C (~5pM) and VEGF-D (~0.5 nM)
- A ‘trap’ that blocks VEGF-C and VEGF-D binding to the receptors VEGFR-2 and VEGFR-3

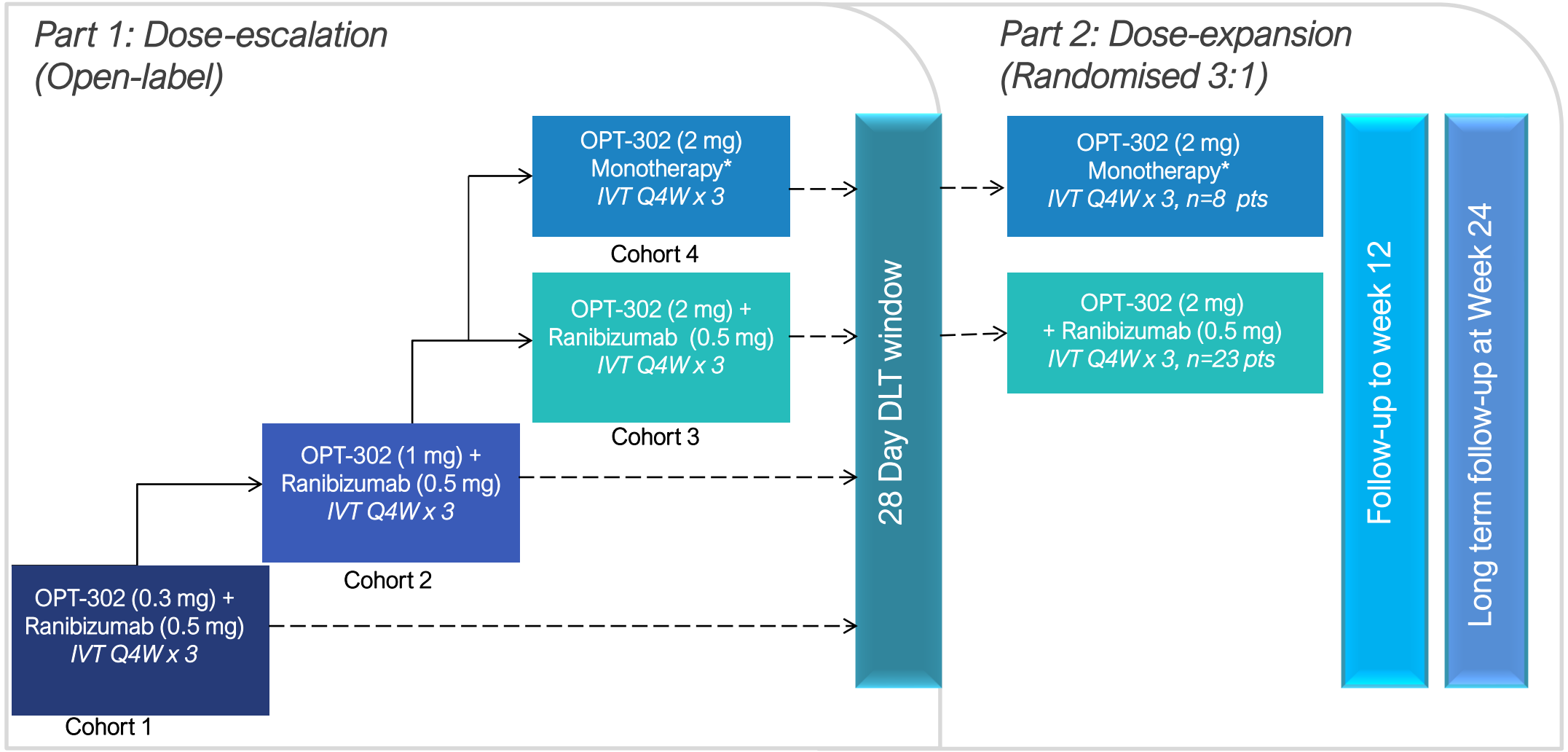


Mean OPT-302 serum concentrations



- Non-compartmental OPT-302 PK analysis indicated:
  - Low systemic exposure
  - 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.

OPT-302 Phase 1/2a First-in-Human Study in Neovascular AMD (n=51)



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

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

ClinTrials Identifier NCT 02543229

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OPT-302 +/- Ranibizumab - Phase 1/2a Safety Summary

OPT-302 ± Lucentis administered by repeat IVT injection (Baseline, Week 4, Week 8)

- No missed doses, safety experience with ~150 intravitreal (ocular) injections of OPT-302

OPT-302 at ocular doses up to 2 mg ± Lucentis (0.5 mg):

- No dose limiting toxicities (MTD was not reached)
- No drug-related serious adverse events or systemic adverse events

Majority of ocular emergent adverse events primarily related to IVT injection procedure

- (31 / 51 patients; 59%); majority Grade 1 / Mild or Grade 2 / Moderate and Manageable

Two patients (4%) had ocular adverse events related to OPT-302 study drug

- AEs were Grade 1 / Mild inflammation indicative of anterior uveitis in the low- and mid-dose combination groups
- No OPT-302 related AEs observed in the high dose (2mg) combination or monotherapy treated patients (n=41)

No clinically significant changes in IOP, ECG's, blood pressure, vitals

No evidence of OPT-302-related immunogenicity

OPT-302 has consistently demonstrated a favourable safety profile +/- ranibizumab

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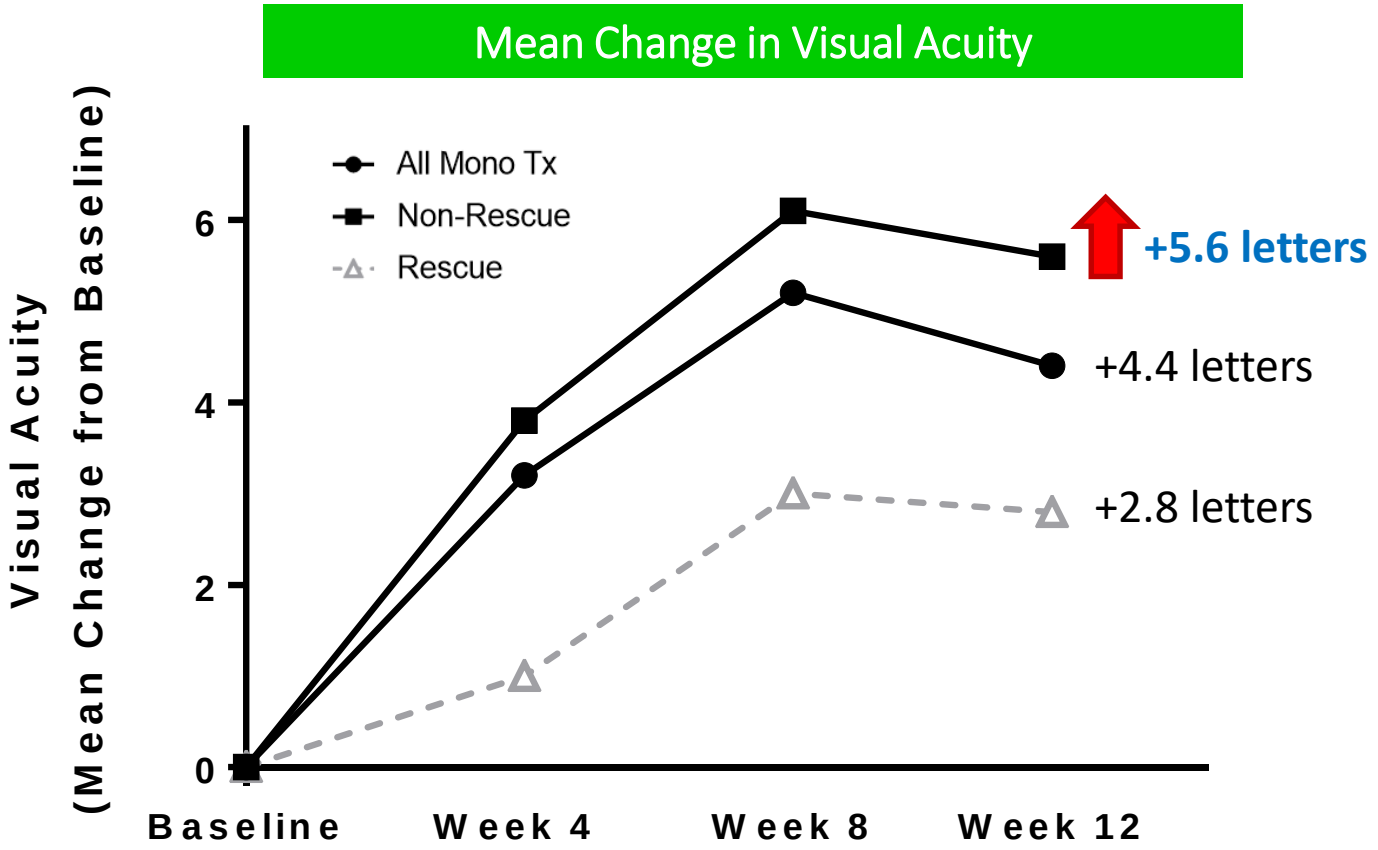
Evidence of biological activity in patients treated with intravitreal OPT-302 (2 mg) monotherapy

- Of the 13 patients who received OPT-302 monotherapy treatment:
  - 7/13 (54%) did not receive anti-VEGF-A rescue therapy through week 12
  - An additional 5/13 (38%) received only 1 rescue injection through week 12
  - One subject (8%) received 2 rescue injections.
  - The mean time to rescue therapy was 58 days.
  - Use of rescue therapy in 4/6 cases was based on Investigator discretion



Mean Baseline VA = 55.7 Letters
Ranibizumab rescue therapy available week 2 through week 12 at investigator discretion or if patients met pre-defined criteria: <10% decrease in CST and ≥5 letter loss of BCVA

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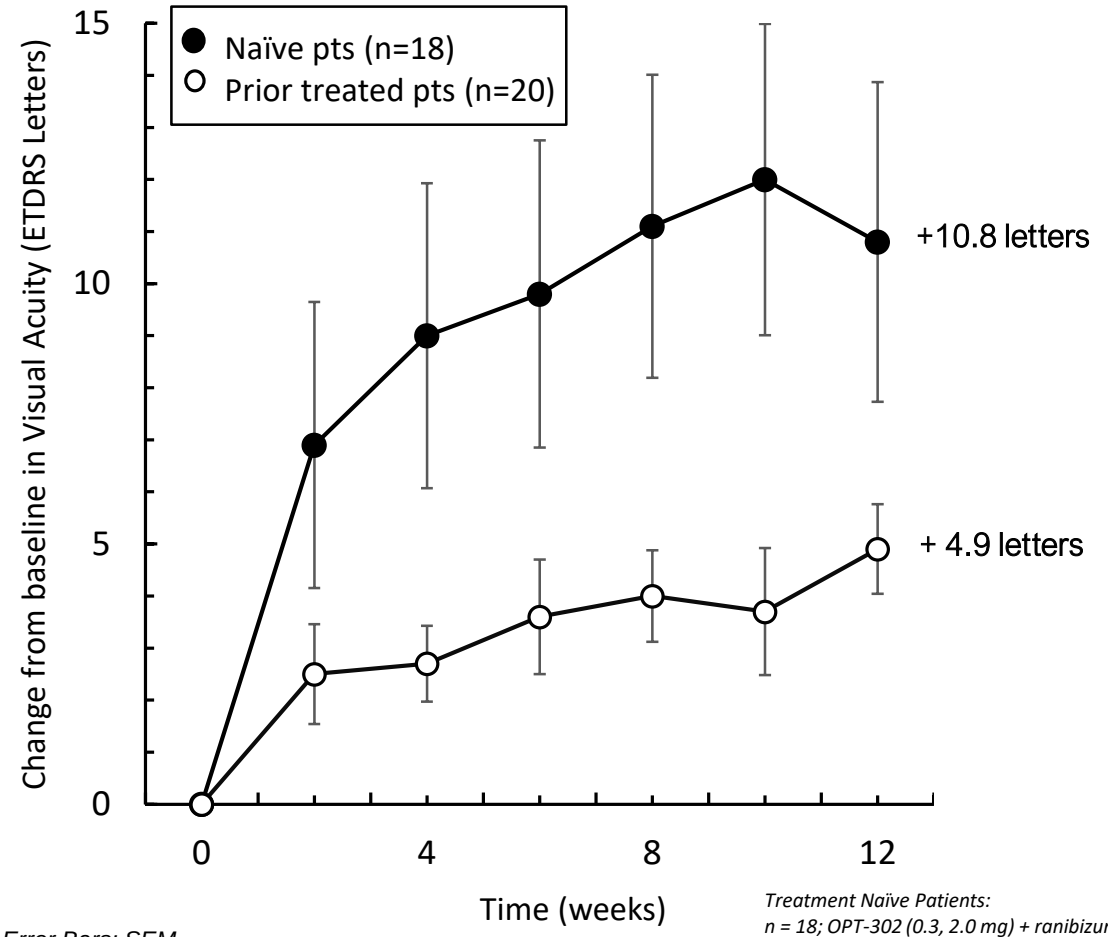
Gains in Visual Acuity and Reduced Retinal Thickness in Patients with OPT-302 + Ranibizumab Therapy

Change in mean BCVA



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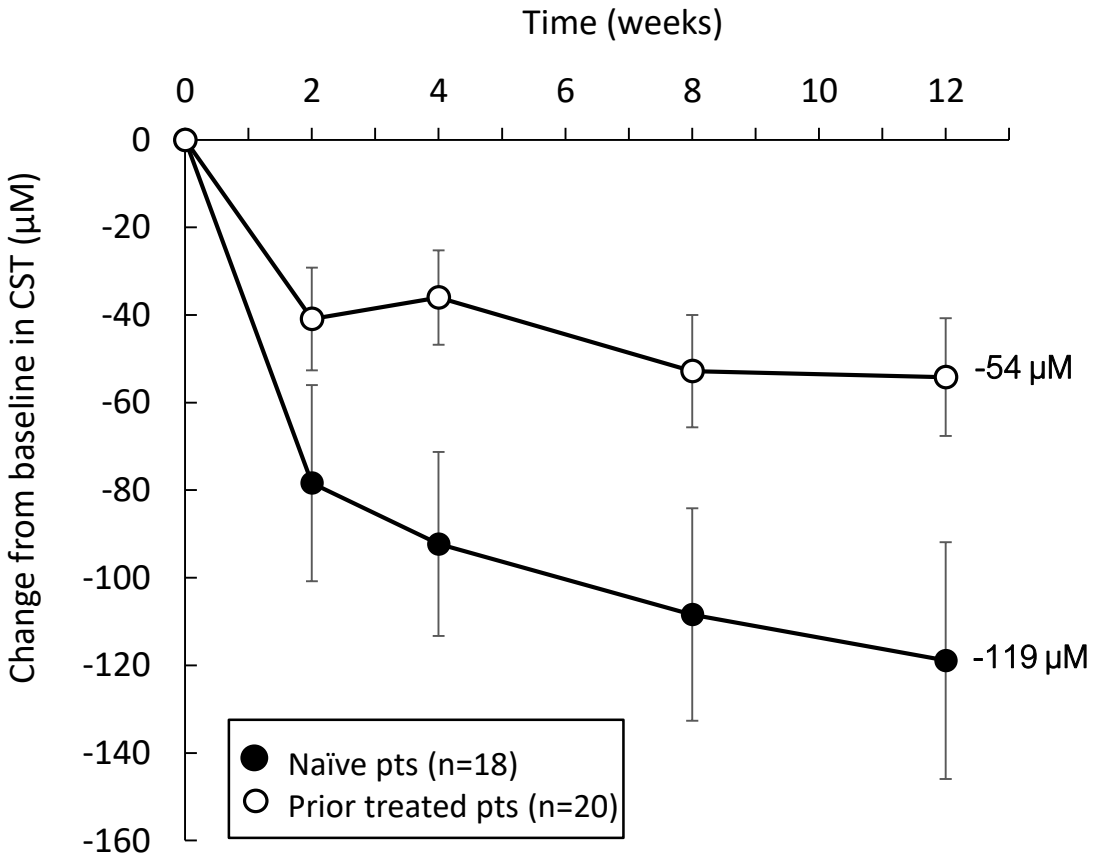
Treatment Naïve Patients:
n = 18; OPT-302 (0.3, 2.0 mg) + ranibizumab (0.5 mg)
Mean Baseline VA = 56.5 Letters

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; Mean number prior anti-VEGF-A injections = 17

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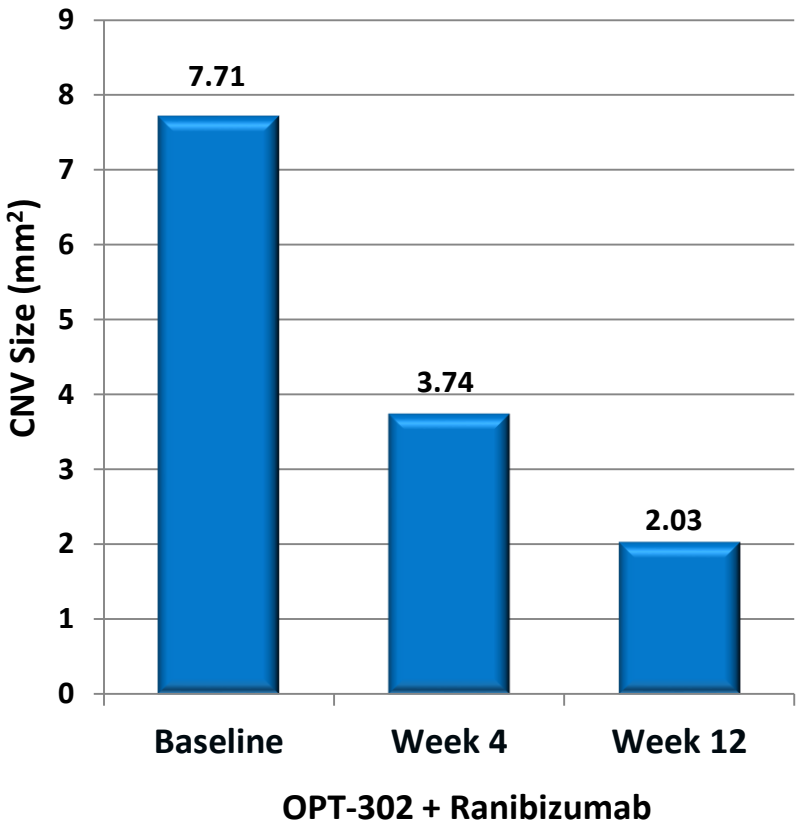
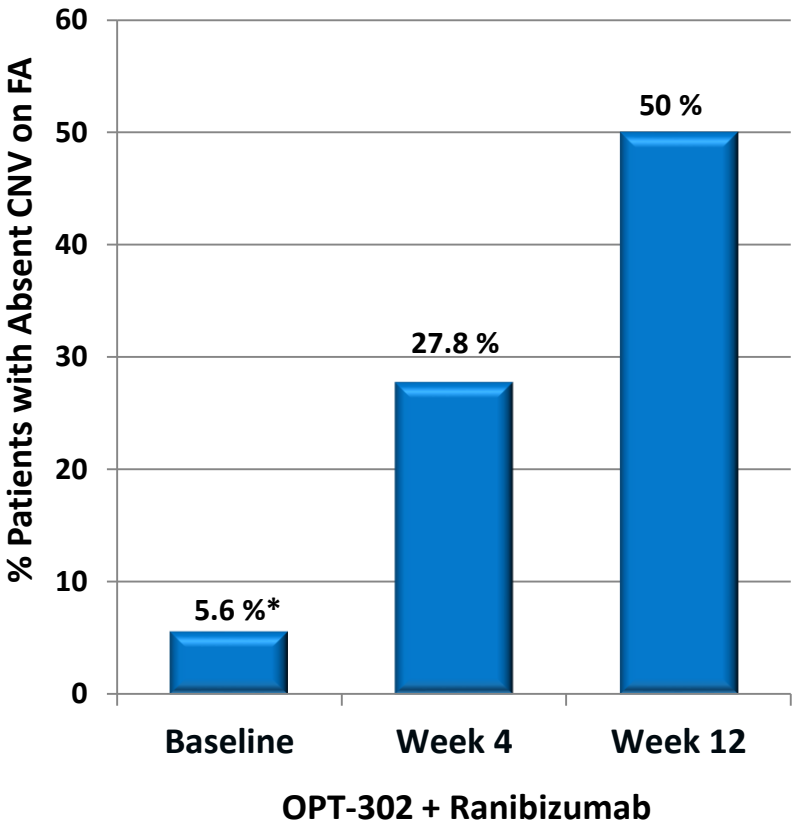
Reductions in CNV in Treatment-Naïve Patients with OPT-302 + Ranibizumab Therapy

Reduction in CNV Size on FA



% Patients with Absent CNV on FA



CNV: Choroidal Neovascularisation

Treatment Naïve Patients:

*n = 18; OPT-302 (0.3, 2.0 mg) + ranibizumab (0.5 mg); * Absent on FA, present on OCT*

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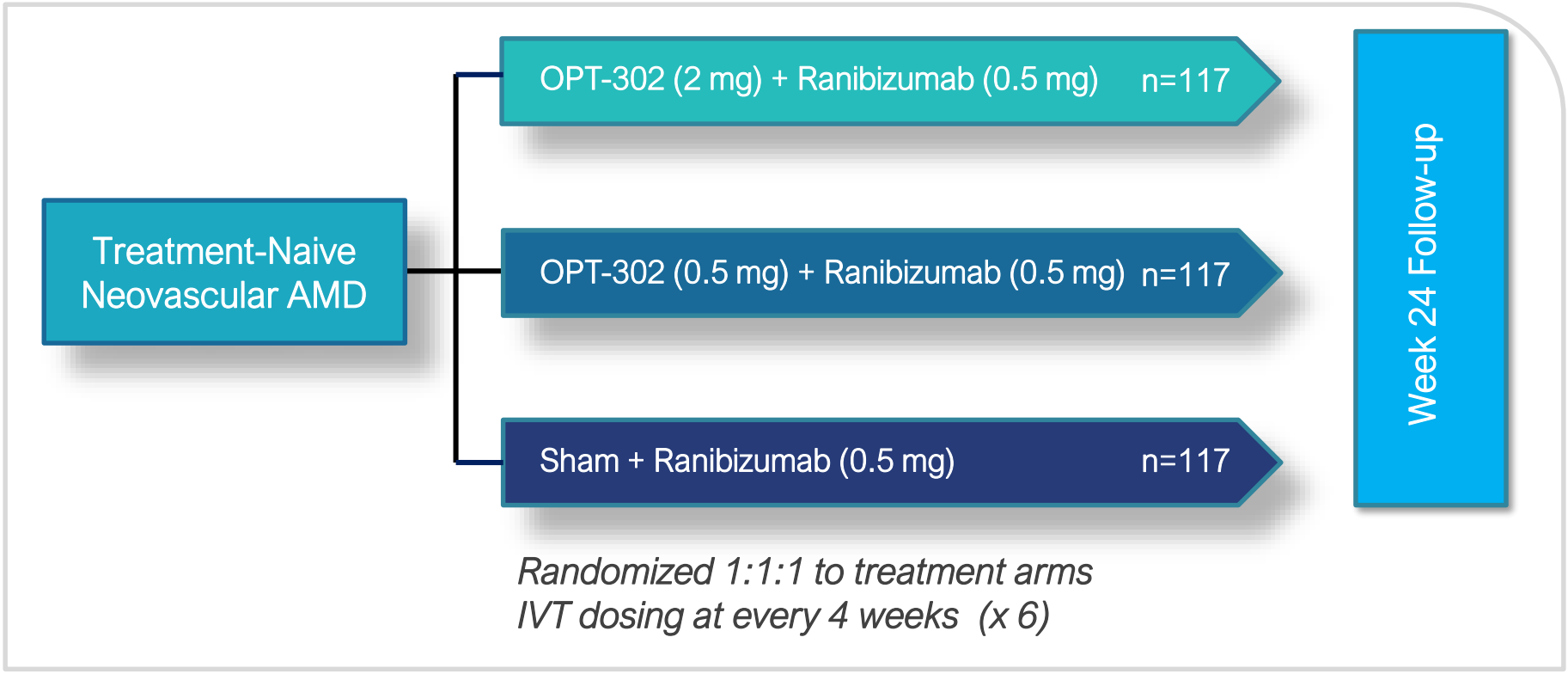
OPT-302 +/- Ranibizumab Phase 2b Trial in Treatment-Naïve nAMD (n=351)



- Currently enrolling
- Primary data analysis early 2020

ClinTrials Identifier NCT 03345082

OPT-302 Mechanism of Action Supports Investigation in DME

VEGF-C and its interaction with VEGFR-2 and VEGFR-3 plays a functional role in pathogenesis of DME:

- OPT-302 has shown evidence of activity to resolve retinal fluid [1]
- VEGFR-2 expression is greater in diabetic retina than non-diabetics [2,3,4]
- VEGF-C is elevated in diabetic retinopathy [4]
- Vitreous levels of VEGF-D are elevated in diabetes [5]
- VEGF-C expression is elevated by glucose & pro-inflammatory cytokines [6,7]
- Inhibition of VEGF-C and VEGF-D in adipose tissue of mice improves metabolic parameters and insulin sensitivity [8,9]
- Advanced glycation end products accumulate faster in diabetics and stimulate VEGF-C expression and secretion from the RPE [6]
- Single nucleotide polymorphisms (SNPs) in diabetic patients indicate that genetic variation in the VEGF-C gene is associated with diabetic retinopathy and diabetic macular edema [10]

VEGF-C/D Signaling Pathway is Implicated in Diabetes

1. Phase 1/2a OPT-302 trial results: www.opthea.com; 2. Sun et al., 2014; 3. Witmer et al., 2002; 4. Zhao et al., 2007; 5. Kovacs et al., 2015; 6. Puddu et al., 2012; 7. Nagineni et al., 2011; 8. Karaman et al., 2014; 9. Karaman et al., 2016; 10. Kaidonis et al., 2015

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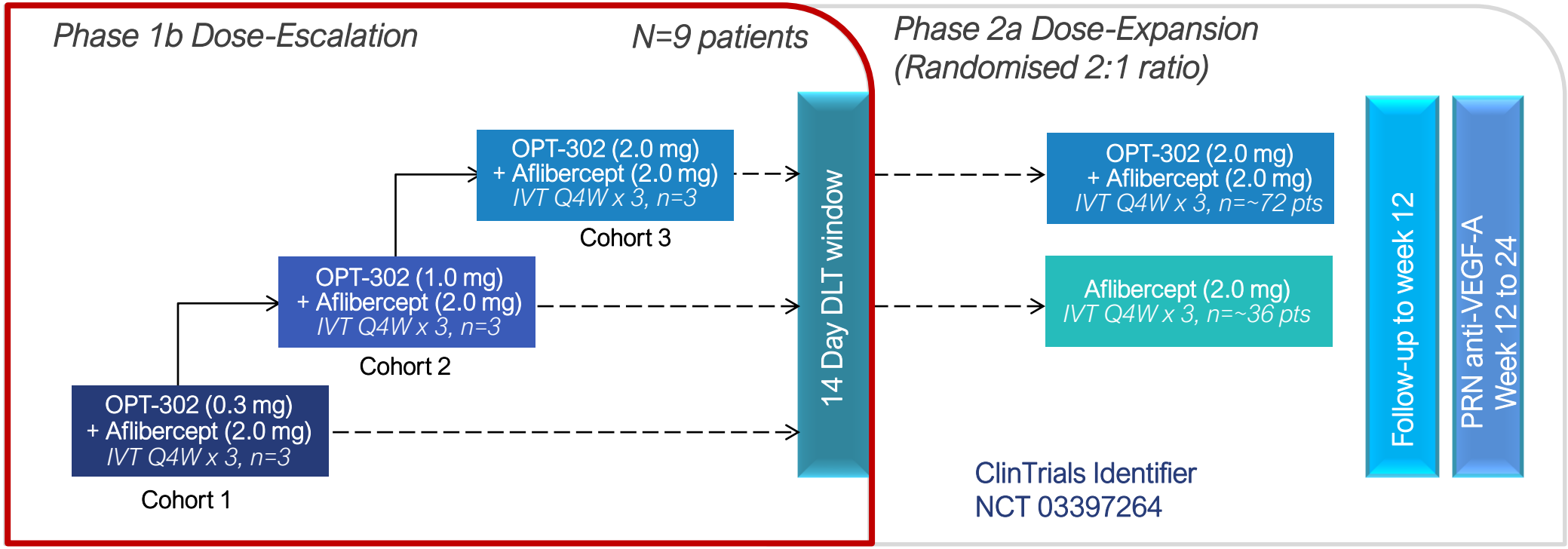
Phase 1b Dose Escalation study of OPT-302 + Aflibercept in DME



Key Inclusion Criteria

- Age ≥ 18 years; centre-involving DME
- CST ≥ 335 µm*
- BCVA 73 – 24 ETDRS letters (20/40 – 20/320 Snellen
- Prior exposure to anti-VEGF-A therapy with sub-optimal therapeutic response
  - ≥ 3 intravitreal injections
  - Last injection ≤ 6 wks prior to study day 1
  - Prior bevacizumab only allowed if switched to IVT aflibercept or ranibizumab prior to study

CST as measured by Spectralis (Heidelberg) at screening, ≥ 320 µm for Cirrus.

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 use of dexamethasone or fluocinolone implant in study eye

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Baseline Ocular Characteristics – Prior Treated

Characteristic	OPT-302 (0.3 mg) + Aflibercept (2.0 mg) (n=3)	OPT-302 (1 mg) + Aflibercept (2.0 mg) (n=3)	OPT-302 (2 mg) + Aflibercept (2.0 mg) (n=3)	Total Number of Subjects (N=9)
Vision				
Mean BCVA, ETDRS letters (SD)	64.3 (9)	64.6 (5)	66.7 (3.1)	65 (5.5)
Better than 55 letters vision, n (%)	3 (100%)	3 (100%)	3 (100%)	9 (100%)
Worse than 55 letters vision, n (%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Anatomic				
Mean CST, µm (SD)	460 (103)	410 (26)	432 (24)	434 (58)
CST ≤ 450 µm, n (%)	1 (33%)	3 (100%)	2 (67%)	6 (67%)
CST ≥ 450 µm, n (%)	2 (67%)	0 (0%)	1 (33%)	3 (33%)
Mean duration of diabetes at screening, years (SD)	14 (7.9)	17.3 (13)	10.9 (12.6)	14.1 (10.3)
Mean prior intravitreal injections of anti-VEGF-A therapy, number (SD)	5 (2.6)	7.3 (2.5)	6.7 (2.3)	6.3 (2.4)
Mean time from prior Tx to day 1, days	42 (0)	33.7 (7.2)	31 (4.4)	35.6 (6.5)
Mean HbA1c*, % (SD)	7.5 (2.4)	7.1 (0.3)	7.4 (1.4)	7.3 (1.4)

**HbA1c = glycated hemoglobin*

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OPT-302 + Aflibercept Safety Results

- OPT-302 (0.3, 1 or 2 mg) + aflibercept (2 mg) administered by IVT injection (Baseline, Week 4, Week 8)
- OPT-302 intravitreal doses up to 2 mg in combination with aflibercept (2 mg)
  - No dose limiting toxicities (Maximum Tolerated Dose not reached)
  - No study drug related adverse events
- Ocular AEs in the study eye primarily related to IVT injection procedure (Mild/moderate, resolved)
- No clinically significant changes in IOP, ECG's, or vitals.
- OPT-302 was generally safe and well tolerated + aflibercept

OPT-302 has a favorable safety profile when administered with aflibercept (DME) expanding upon similar results when given as monotherapy or in combination with ranibizumab (wet AMD)

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OPT-302 + Aflibercept – Safety Summary of selected AEs

Selected Adverse Events: Ocular or Systemic	OPT-302 (0.3 mg) + Aflibercept (2.0 mg) (n=3)	OPT-302 (1 mg) + Aflibercept (2.0 mg) (n=3)	OPT-302 (2 mg) + Aflibercept (2.0 mg) (n=3)	Total Number of Subjects (N=9)
Intraocular inflammation	0	0	0	0
Endophthalmitis	0	0	0	0
Retinal detachment	0	0	0	0
Vitreous hemorrhage	0	0	0	0
Hypertension	1*	0	0	1*
APTC events#				
Nonfatal myocardial infarction	0	0	0	0
Nonfatal stroke	0	0	0	0
Vascular or cardiac death or death of unknown cause	0	0	0	0
Combined APTC events	0	0	0	0
Any other death	0	0	0	0
IOP, mmHg: Baseline, week 12; (change from baseline)	13.0; 15.7 (2.7)	17.3; 15.3 (-2.0)	16.7; 17.0 (0.3)	15.7; 16.0 (0.3)

- No safety signals or unexpected findings

#APTC = Antiplatelet Trialists' Collaboration
**Determined by treating investigator as unrelated to study drug(s)*

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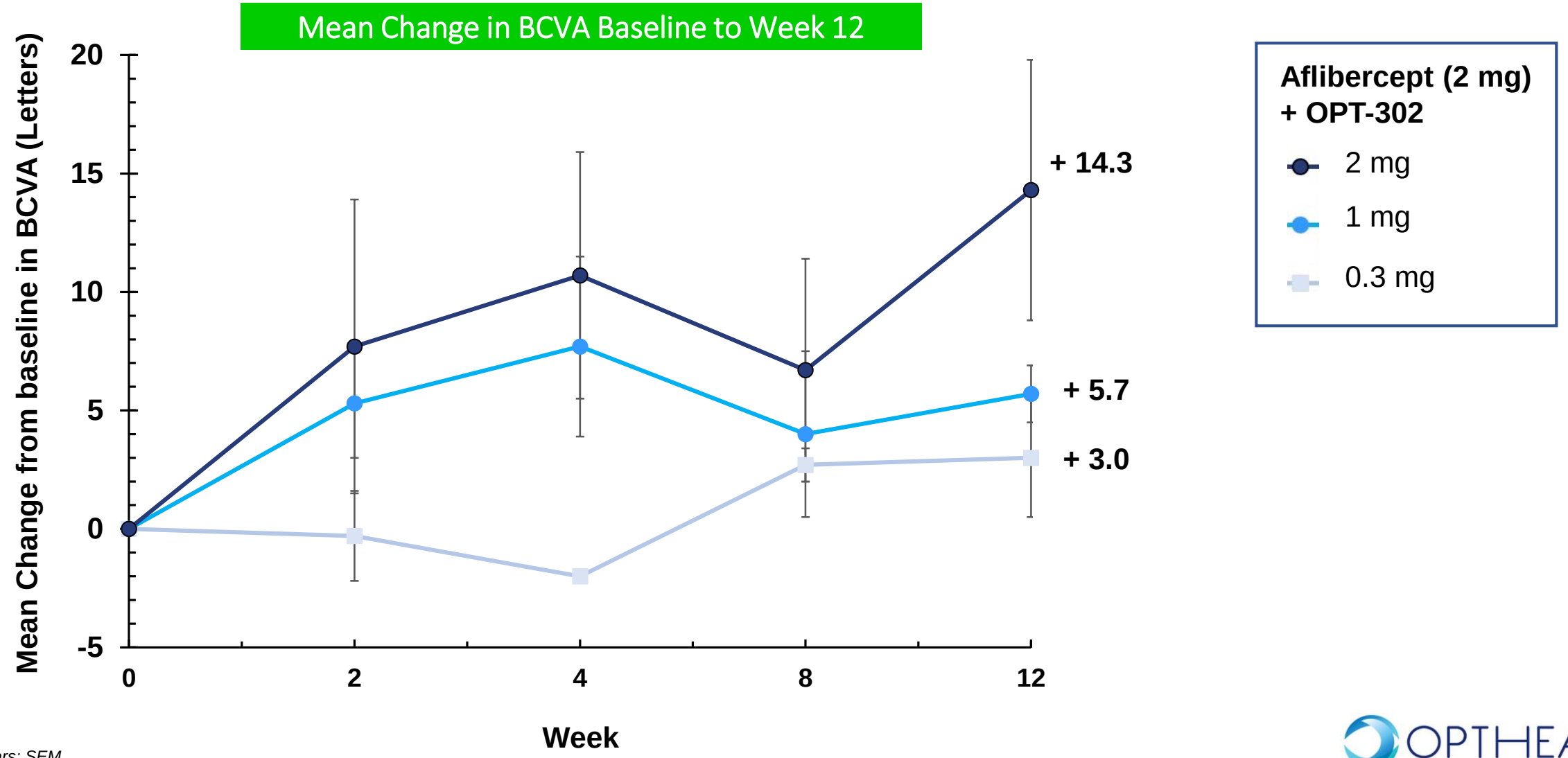
Dose Response in BCVA changes from Baseline to Week 12



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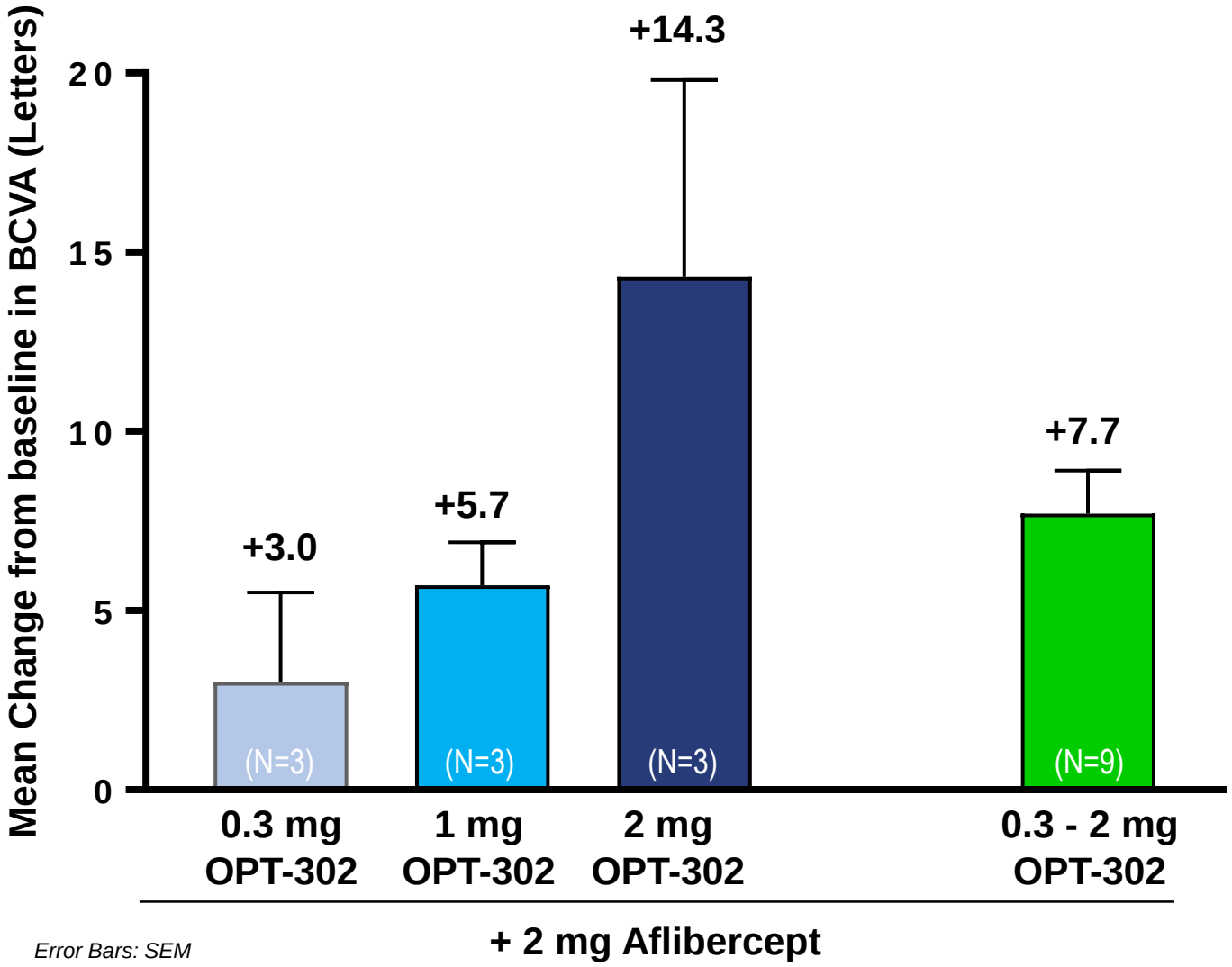
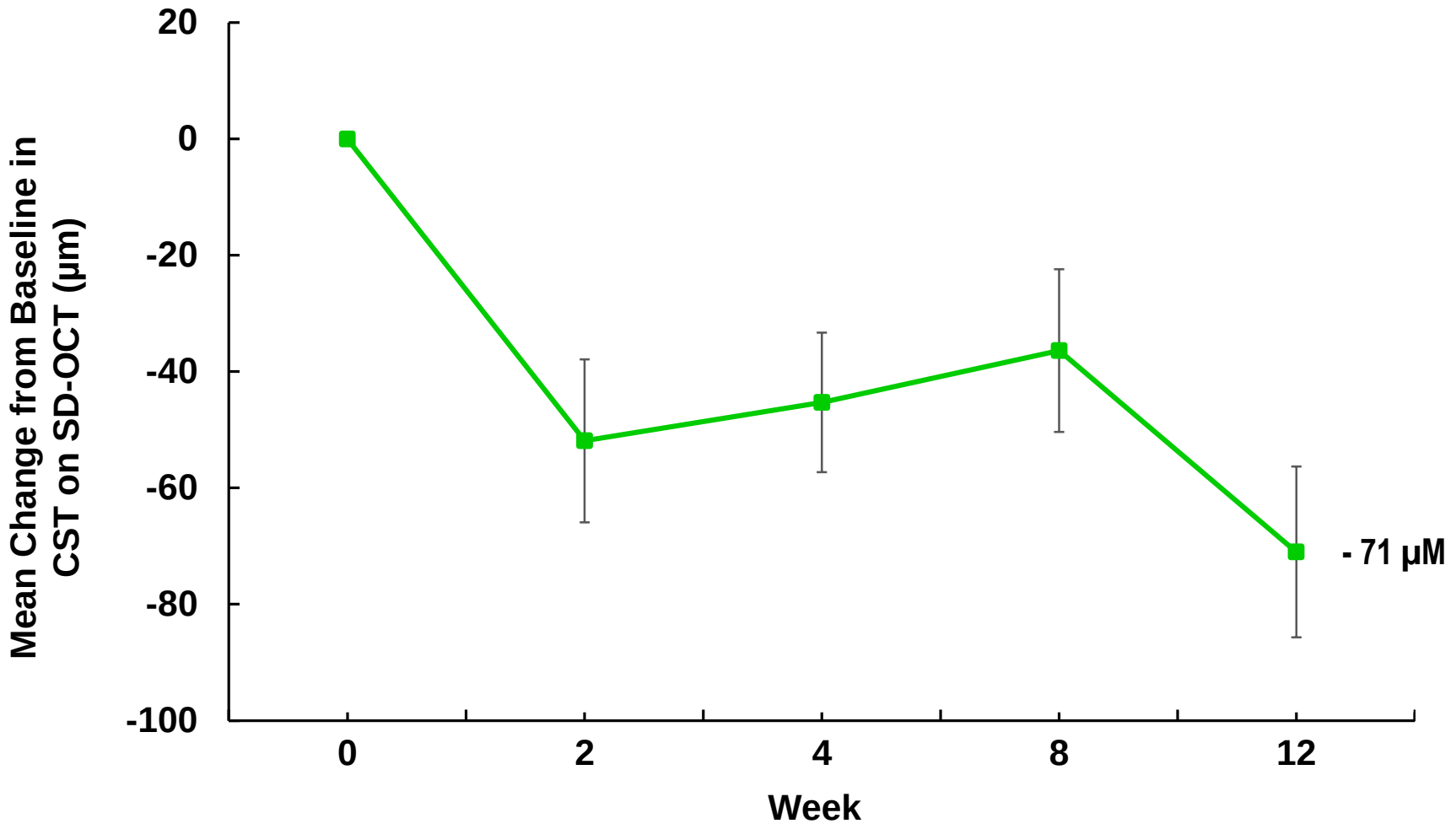
OPT-302 + Aflibercept: Gains in BCVA at Week 12
Dose Response Relationship



Dose of OPT-302 + Aflibercept (2 mg)	% of pts with BCVA gain ≥ 5 letters	Mean # prior anti-VEGF-A injections
0.3 mg	1/3 (33%)	5
1 mg	2/3 (67%)	7.3
2 mg	3/3 (100%)	6.7
0.3 to 2 mg	6/9 (67%)	6.3

Error Bars: SEM

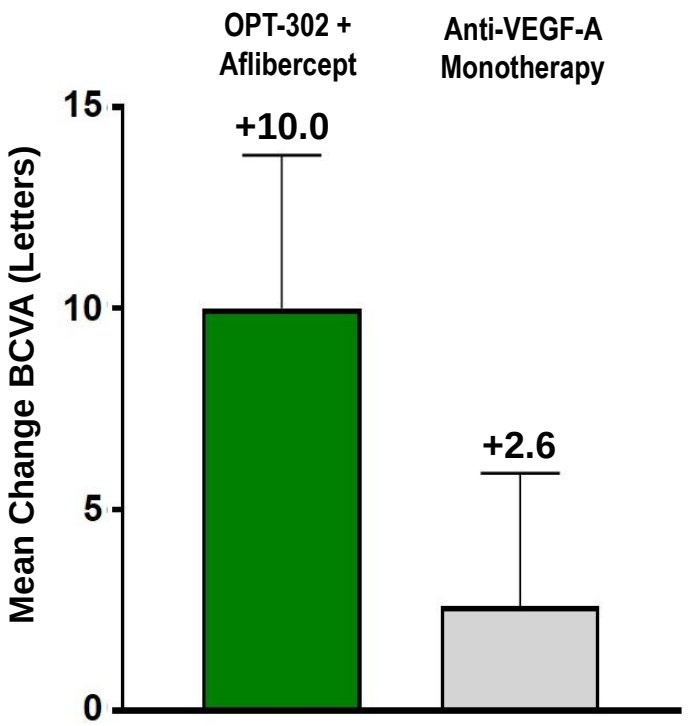
OPT-302 (0.3-2 mg) + Aflibercept (2 mg): Mean changes in CST from Baseline to Week 12



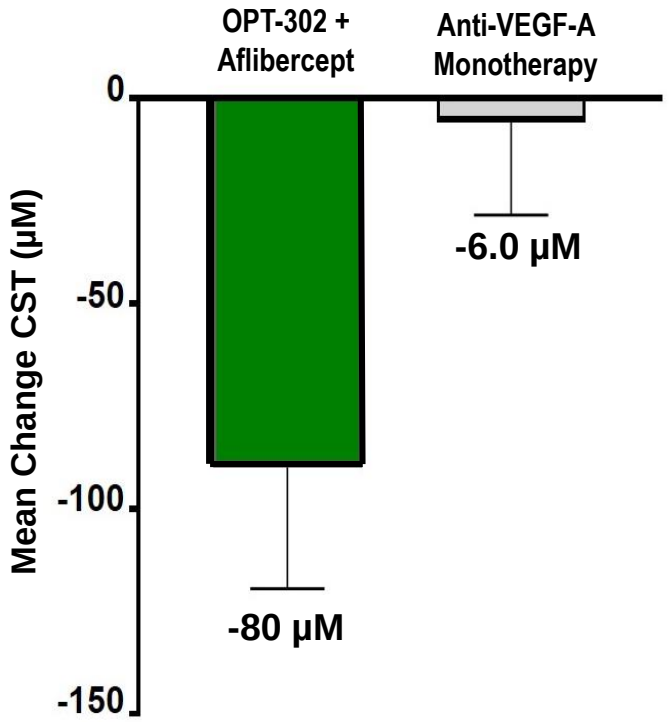
Error Bars: SEM; Mean Baseline CST = 434 µm

DME Patients with Bilateral Disease* Study Eye vs Fellow Eye (N=5)

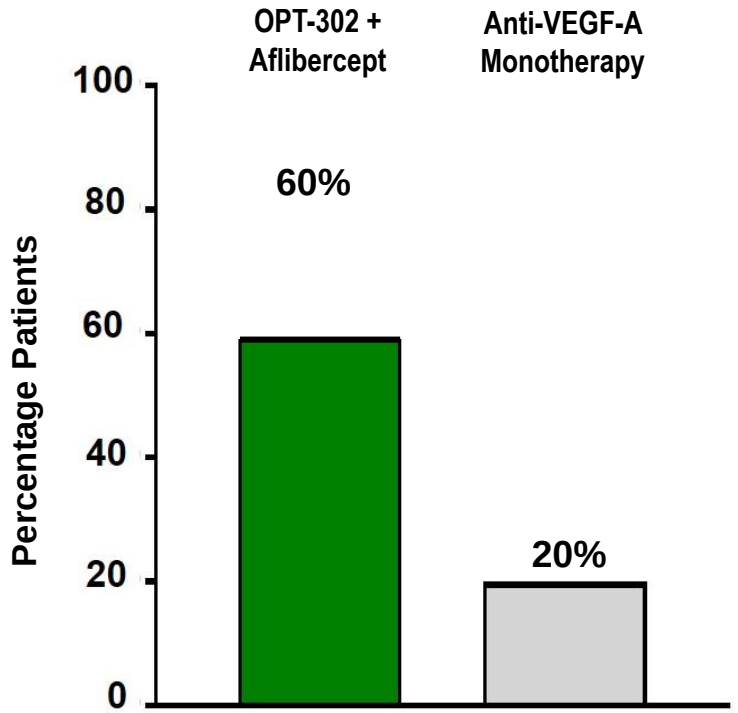
Mean Change in BCVA Baseline to Week 12

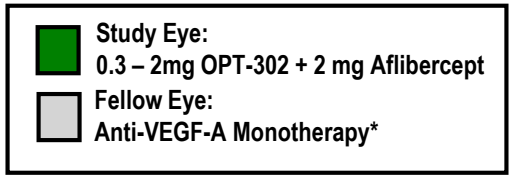


Mean Change in CST (uM) Baseline to Week 12



% Pts with ≥ 50% Reduction in Excess Foveal Thickness





**Patients with bilateral disease and persistent DME in the fellow eye receiving anti-VEGF-A (ranibizumab or aflibercept) monotherapy*
Prior anti-VEGF-A therapy in Fellow Eyes BL to Wk 12: 3x Aflibercept, 3x Ranibizumab, 1x Ranibizumab, 4x Ranibizumab, 3x Aflibercept

Mean baseline BCVA, CST: Study Eyes (63 letters, 445 µM); Fellow Eye (73 letters, 389 µM)
 # Excess foveal thickness was determined by using 300 µm Spectralis scan values and 285 µm Cirrus scan values

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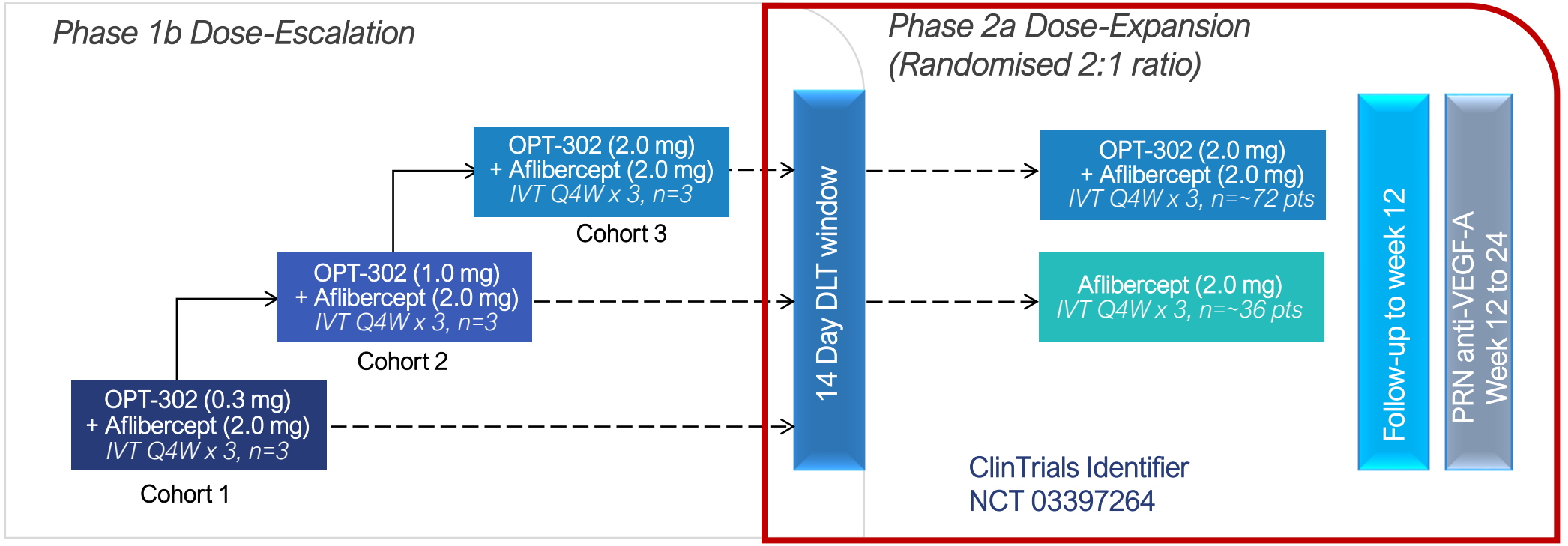
Phase 2a Randomised Dose Expansion study of OPT-302 + Aflibercept in Persistent DME



- Phase 2a currently enrolling patients in US and Australia
- Primary data analysis 2019

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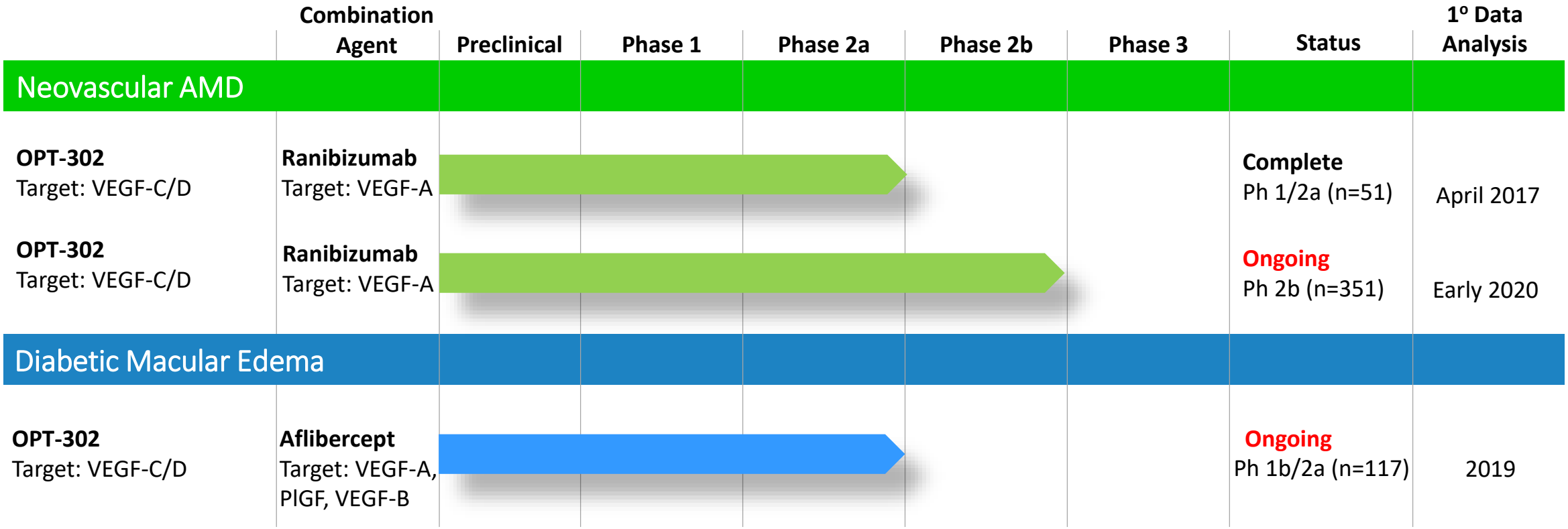
OPT-302 Clinical Program

- Two ongoing randomised controlled clinical trials in nAMD & DME



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Conclusion

- Current treatments target primarily VEGF-A; OPT-302 inhibits VEGF-C/D
- The successful dose escalation of OPT-302 in combination with aflibercept in DME builds upon the similar favourable safety profile in combination with ranibizumab in nAMD
- Evidence of a dose response for OPT-302 combination treatment on gains in BCVA in persistent DME, together with biological responses on anatomic measures in nAMD and DME indicates that Pan-VEGF (A, C and D) inhibition may offer benefits that exceed the inhibition of VEGF-A alone
- Currently recruiting patients in two Phase 2 multi-center international trials:
  - ~108 patient randomised controlled Phase 2a trial in DME
  - 351 patient randomised controlled Phase 2b trial in nAMD
- Primary data readouts 2019 (DME) and early 2020 (nAMD)

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Megan Baldwin, PhD
CEO & Managing Director
T +61 (3) 9826 0399
M +61 447 788 674
E megan.baldwin@opthea.com
www.opthea.com

Suite 0403, Level 4,
650 Chapel Street,
South Yarra 3141 Victoria Australia