OPTHEA

2018
Annual General Meeting

CEO Presentation – 2018 AGM, November 29 2018
Megan Baldwin PhD, CEO & Managing Director

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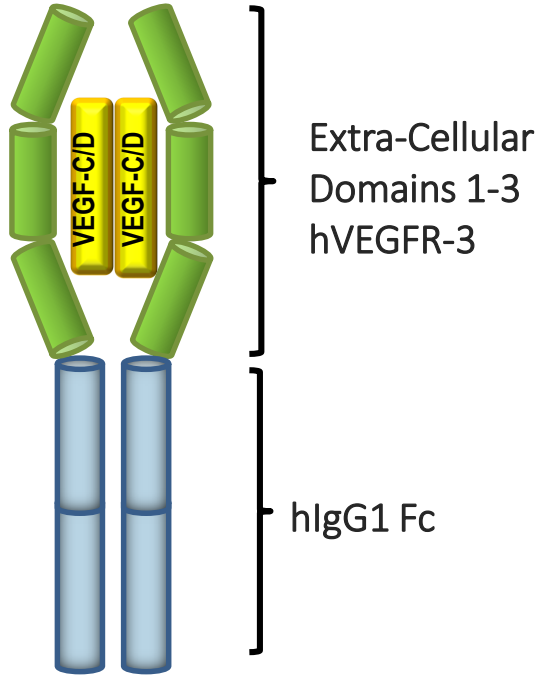
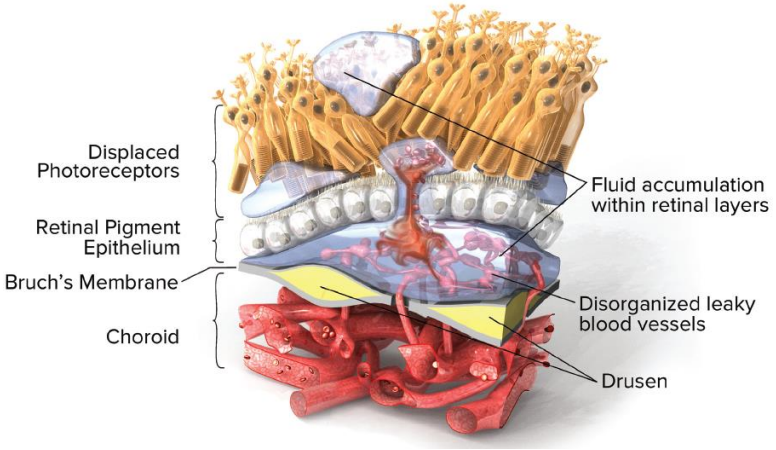
Opthea is Developing OPT-302 as a Novel Combination Therapy for wet AMD & DME

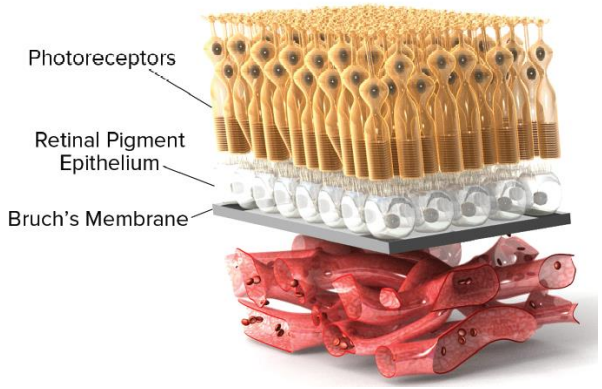
- OPT-302 blocks VEGF-C and VEGF-D
- Blocks vessel growth and leakage, two of the key disease hallmarks
- Wet AMD: Leading cause of blindness in over 55's
- DME: Leading cause of vision loss in diabetics
- Both increasing in prevalence



Wet AMD



Normal Retina



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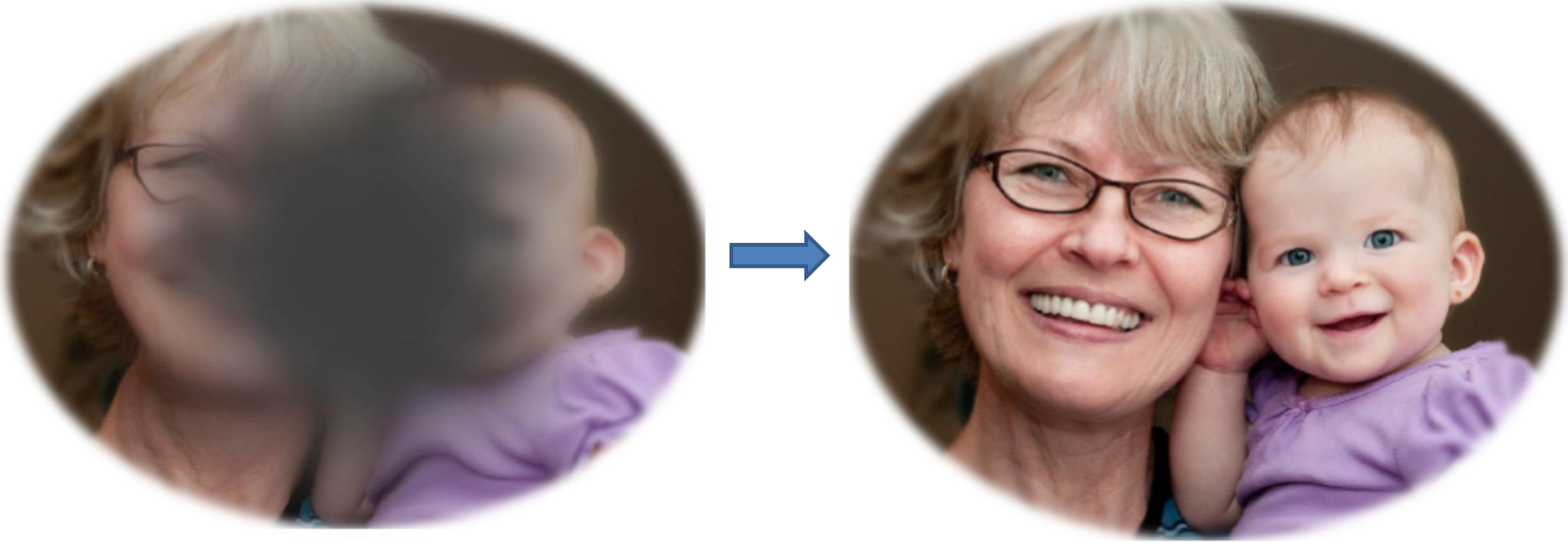
Our Goal: To Improve Vision in Diabetic & Elderly Patients



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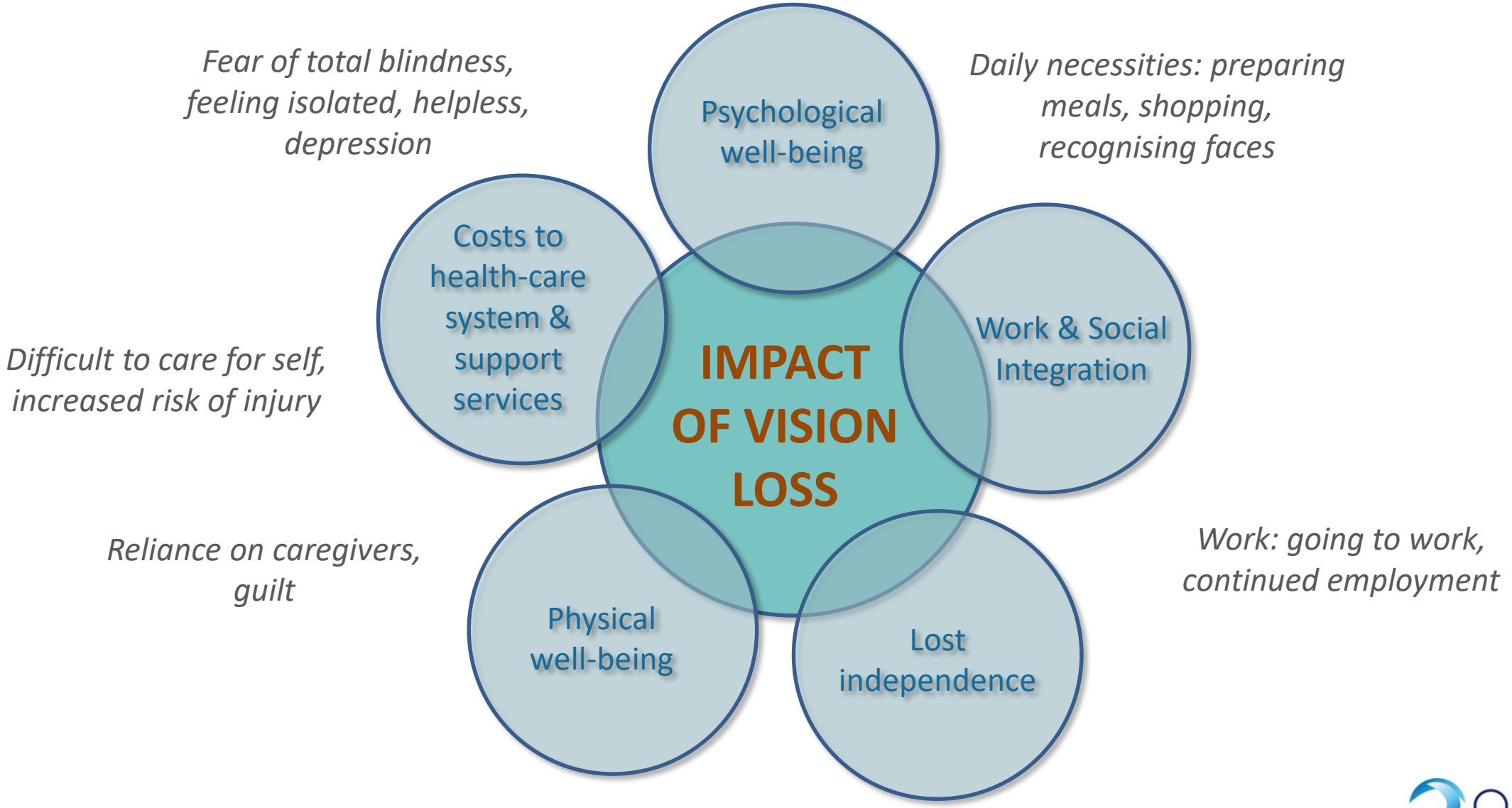
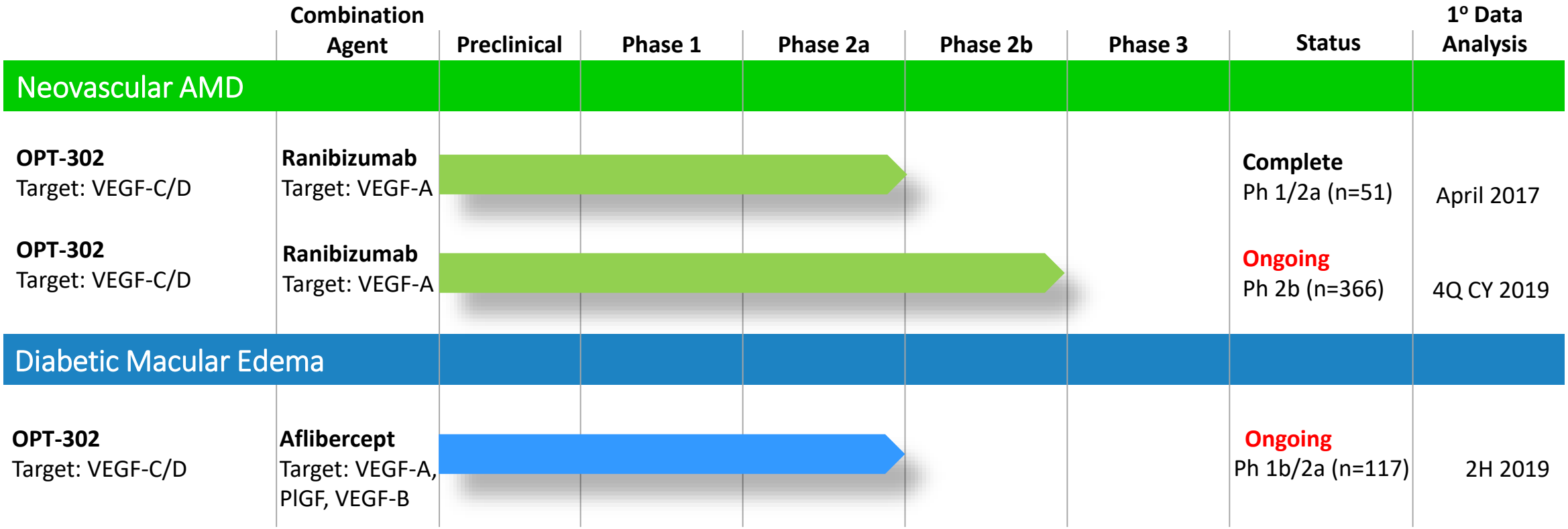
Large Socio-Economic Impact of Vision Loss



OPT-302 Clinical Program

Two ongoing randomised controlled clinical trials in nAMD & DME



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Corporate & Operational Achievements

Phase 2b Wet AMD Trial

- Progressed regulatory submissions with FDA (USA) & Competent Authorities (EU, Israel)
- Initiated and dosed first patient in US (Dec ‘17)
- Dosed first patient in EU & Israel (Mar ‘18)
- DSMB (independent safety monitoring committee) unanimously recommended trial continues without modification (July ’18)
- Completed target recruitment of 351 pts in <12 months and ahead of schedule (Nov ‘18)
- Enrolled last patient, 366 pts randomised (Nov ‘18)
- Brought forward top-line data reporting date to 4Q CY 2019

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Corporate & Operational Achievements

Phase 1b/2a DME Trial

- Commenced DME Phase 1b trial at US sites (Dec ’17)
- Met primary safety objective in Phase 1b DME study
  - OPT-302 well tolerated when administered in combination with aflibercept (Eylea®) (Jul ’18)
- Dosed first patient in Phase 2a DME trial (Jul ’18)
- Dosed first Australian patient in Phase 2a DME (Sep ‘18)
- Reported positive 3-month data from Phase 1b DME study (9 pts) (Oct ‘18)
- Presented Phase 1b data to international clinical & investor forums (Nov ’18)
- Progressed recruitment into Phase 2a (ongoing)

Corporate & Operational Achievements

Corporate

- Strengthened cash position to >$37m:
  - Received A$12m R&D tax credit (Aust & O/S eligible expenditure)
  - >99.4% options exercised generating >$13.3m proceeds
- Company well-funded through clinical milestones in wAMD & DME
- Continued to raise company profile with local and international investors & global pharmaceutical companies
  - Opthea KOL forum NYC moderated by Citigroup (Nov ‘18)
- Data presented at international conferences by management, clinical advisory board & investigators
  - OIS@American Academy Ophthalmology Conference (Oct ‘18)
  - Retina Society, EURetina

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Financial Position (Unaudited)

Key Financial Details	ASX: OPT
Ticker Symbol	ASX:OPT
Share Price (Nov 27 2018)	~A$0.58
Total Ordinary Shares on Issue	249,413,639
Market Capitalisation (Nov 27 2018)	~A$145m (~USD104m)
Trading Range (last 12 months)	A$0.42 – 0.80
Cash Balance (Oct 31 2018)	~A$37m
Forecast Net Operating Cash Burn (CY 2018)	~$18m
Top 20 Shareholders Own	69%
Institutional Holders	84%

Share Price Performance (December 2016 - November 2018)

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wAMD & DME: Large & Growing Market Opportunities

VEGF-A Inhibitors

Novartis
Genentech

Regeneron
Bayer

Roche
Genentech

2017: ~$9.3BN USD
40% Market Share

Off-Label Use
60% Market Share

Market Opportunity

>$10BN Worldwide

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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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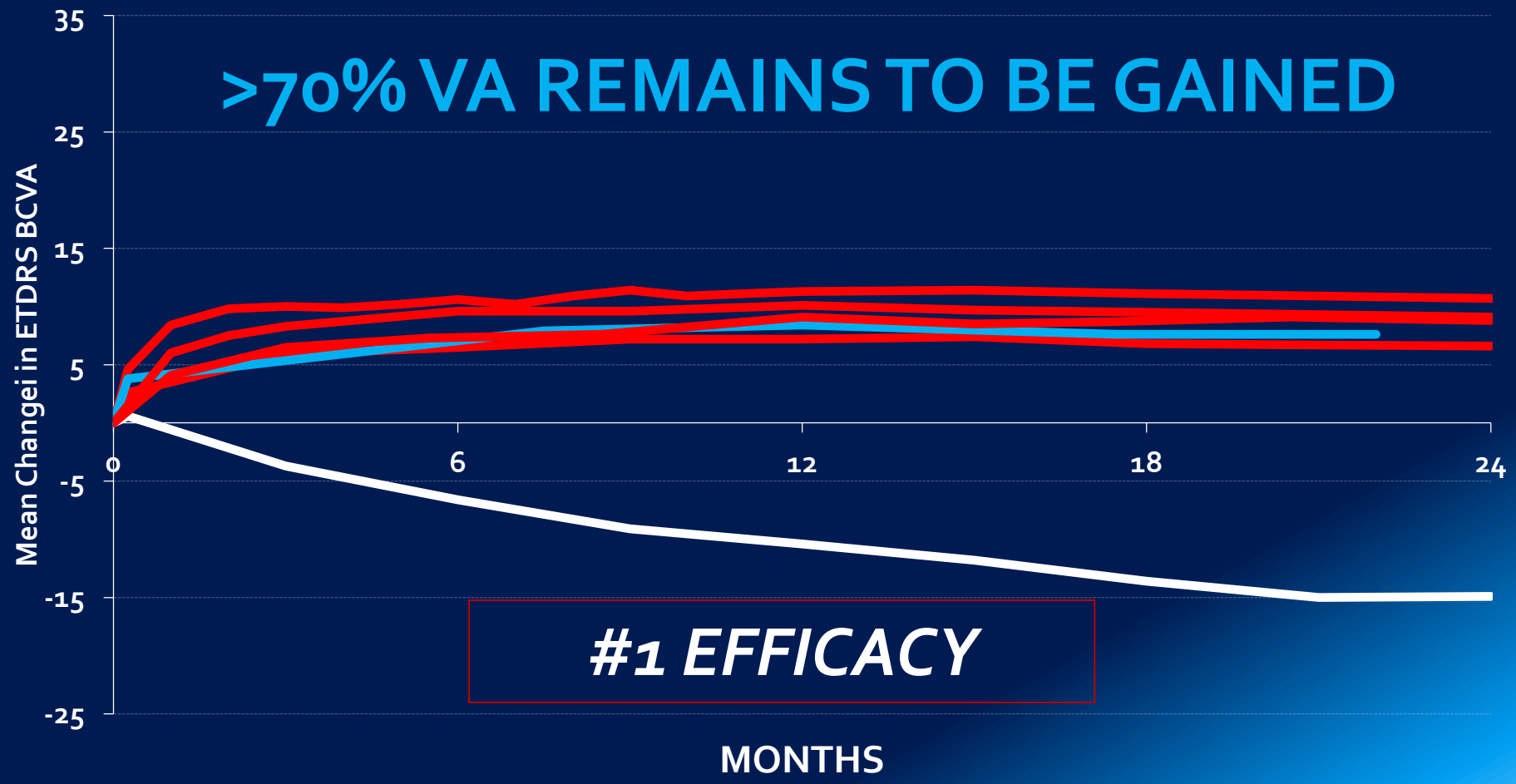
Presented at Opthea's KOL Forum NYC: Dr. Arshad Khanani

NEOVASCULAR AMD – SHORTCOMINGS OF VEGF-A BLOCKADE

20/20

20/100



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

Very Few Novel Combination Therapies in Development

DURABILITY (fewer injections) & BIOSIMILARS Targeting Anti-VEGF-A

Phase III

- **Abicipar pegol**
  Anti-VEGF-A
  Molecular Partners
  Allergan
- **Ranibizumab biosimilar***
  Anti-VEGF-A
  Formycon
- **Brolucizumab (RTH-258)**
  Anti-VEGF-A
  Novartis
- **Squalamine**
  Anti-VEGF
  Ohr Pharmaceutical

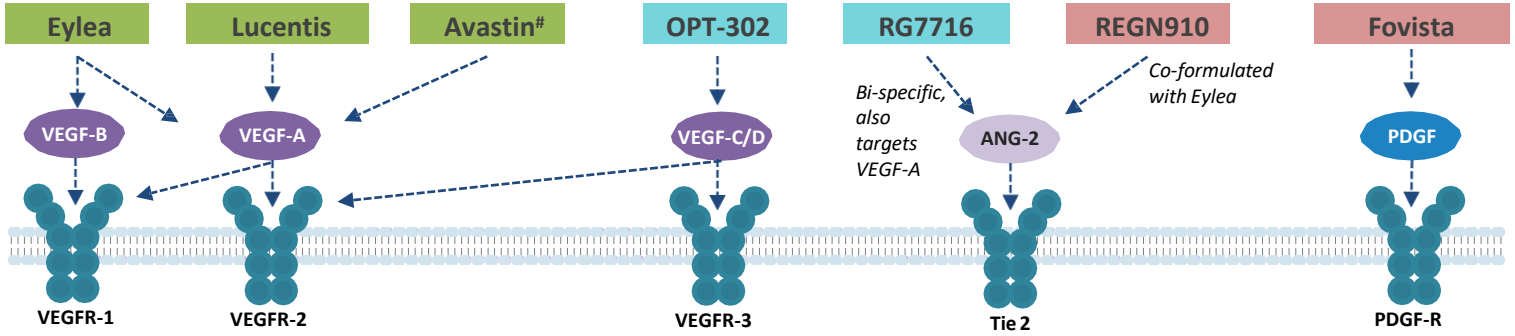
Phase II

- **PAN-90806**
  Anti-VEGF-A
  PanOptica
- **SB11 (Lucentis biosimilar)**
  Anti-VEGF-A
  Samsung Bioepis
- **Ranibizumab biosimilar**
  Anti-VEGF-A
  Pfenex
- **X-82**
  Anti-VEGF/PDGF
  Tyrogenex

Phase I

- **Sevacizumab**
  Anti-VEGF-A
  Apexigen
- **RGX-314**
  Gene therapy
  Regenxbio
- **Ranibizumab biosimilar***
  Anti-VEGF-A
  Lupin Ltd.

Mechanism Comparison Of IVT Administered Wet AMD Agents



= In Clinical Development
= Failed to meet primary endpoint or not advancing to Phase 3
= Approved therapies

Opthea is the Only Company Working on VEGF-C/D

 # Avastin is used off-label for the treatment of wet AMD

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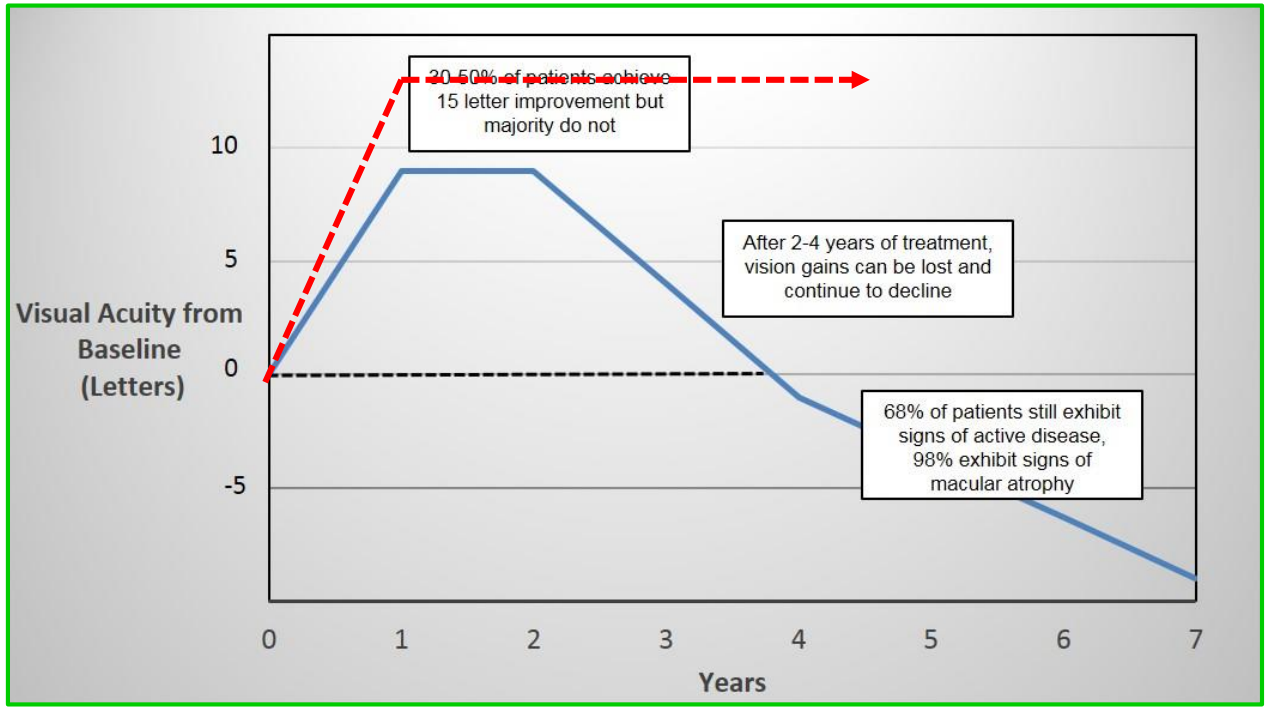
The Opportunity for OPT-302



- To increase the **number** of patients who experience a significant gain in vision
- To increase the **magnitude** of the vision gain
- To **prolong response** to therapy and prevent visual decline
- Potential to **reduce** dosing frequency

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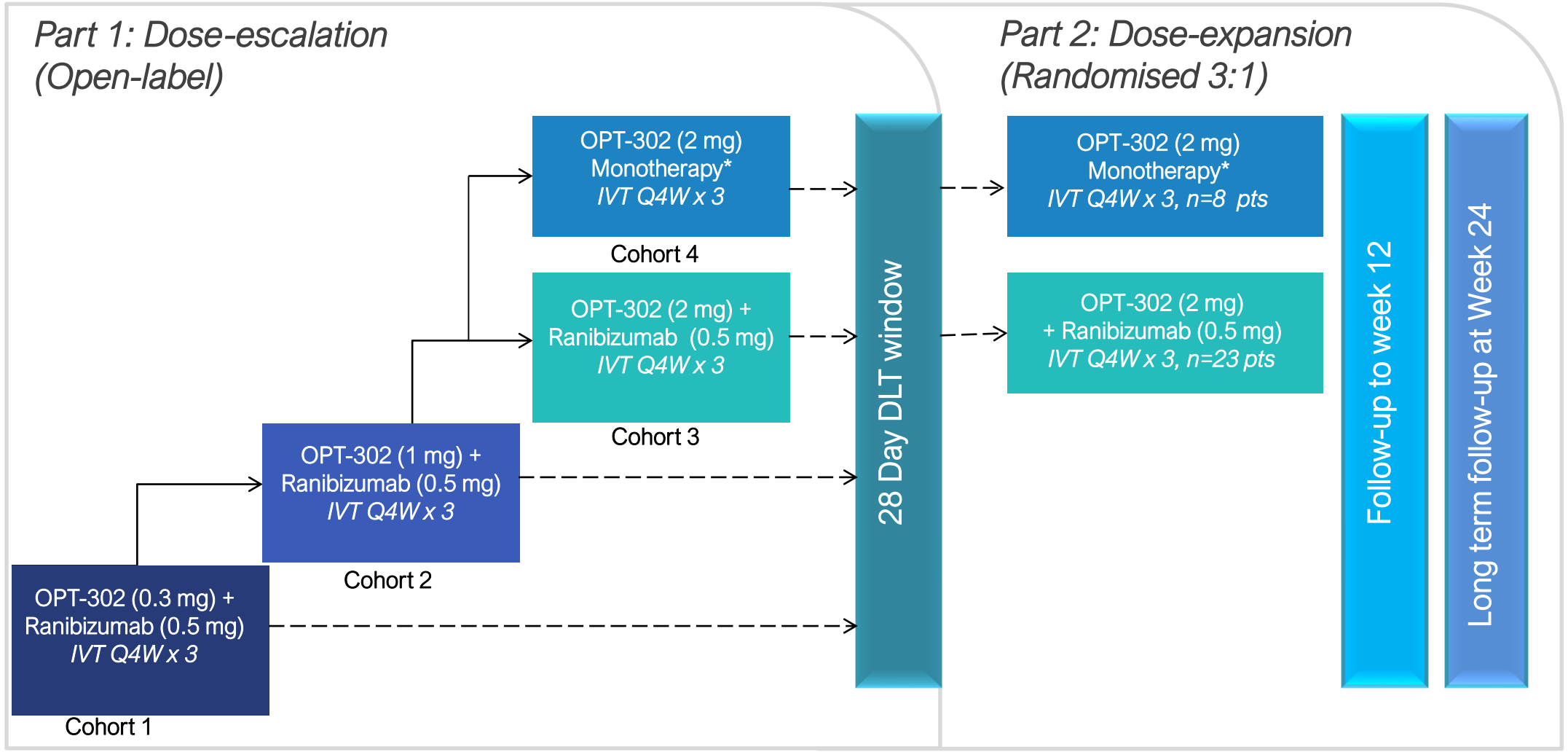
OPT-302 Phase 1/2a First-in-Human Study in Neovascular AMD (n=51)



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

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

ClinTrials Identifier NCT 02543229

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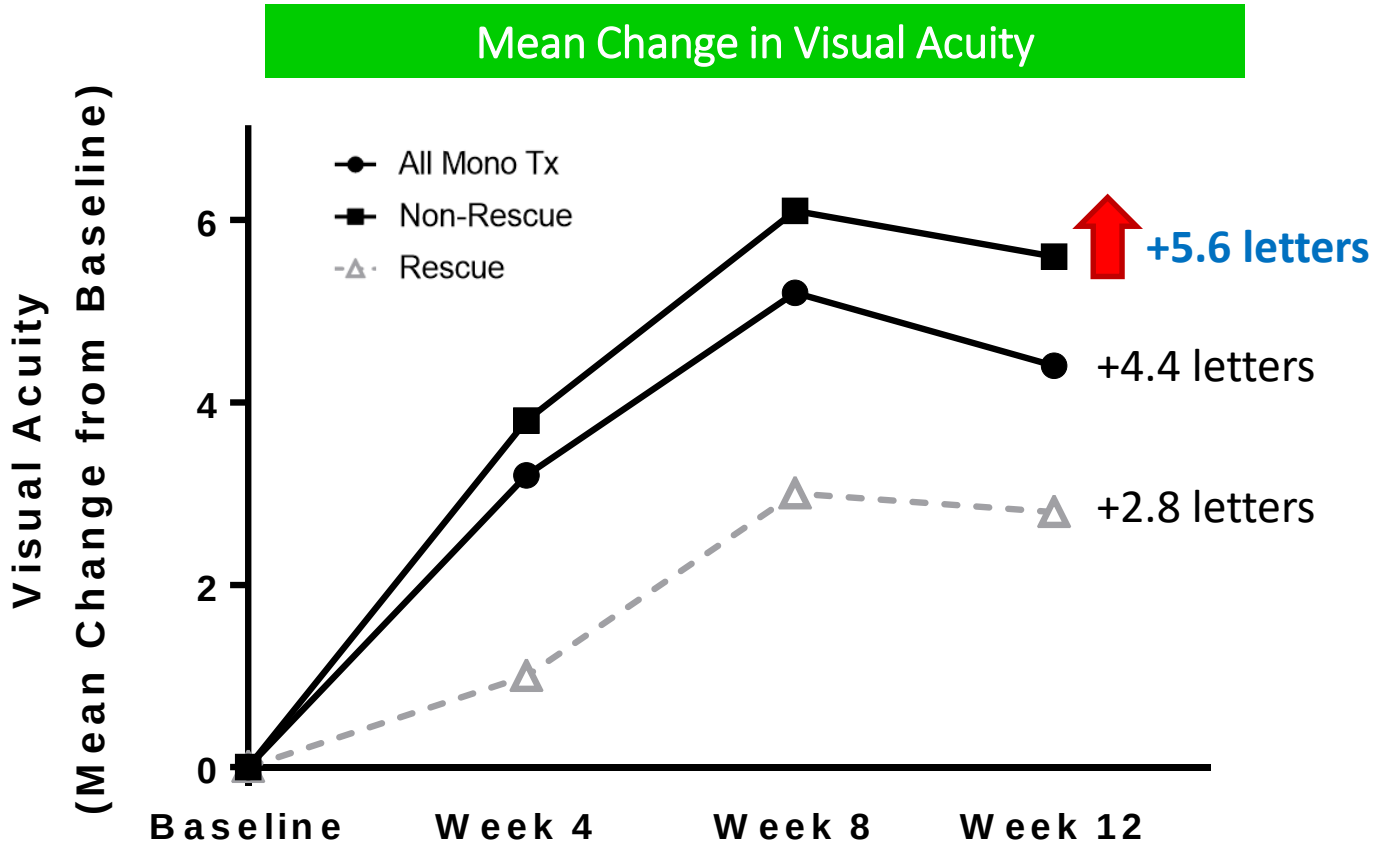
Evidence of biological activity in patients treated with intravitreal OPT-302 (2 mg) monotherapy

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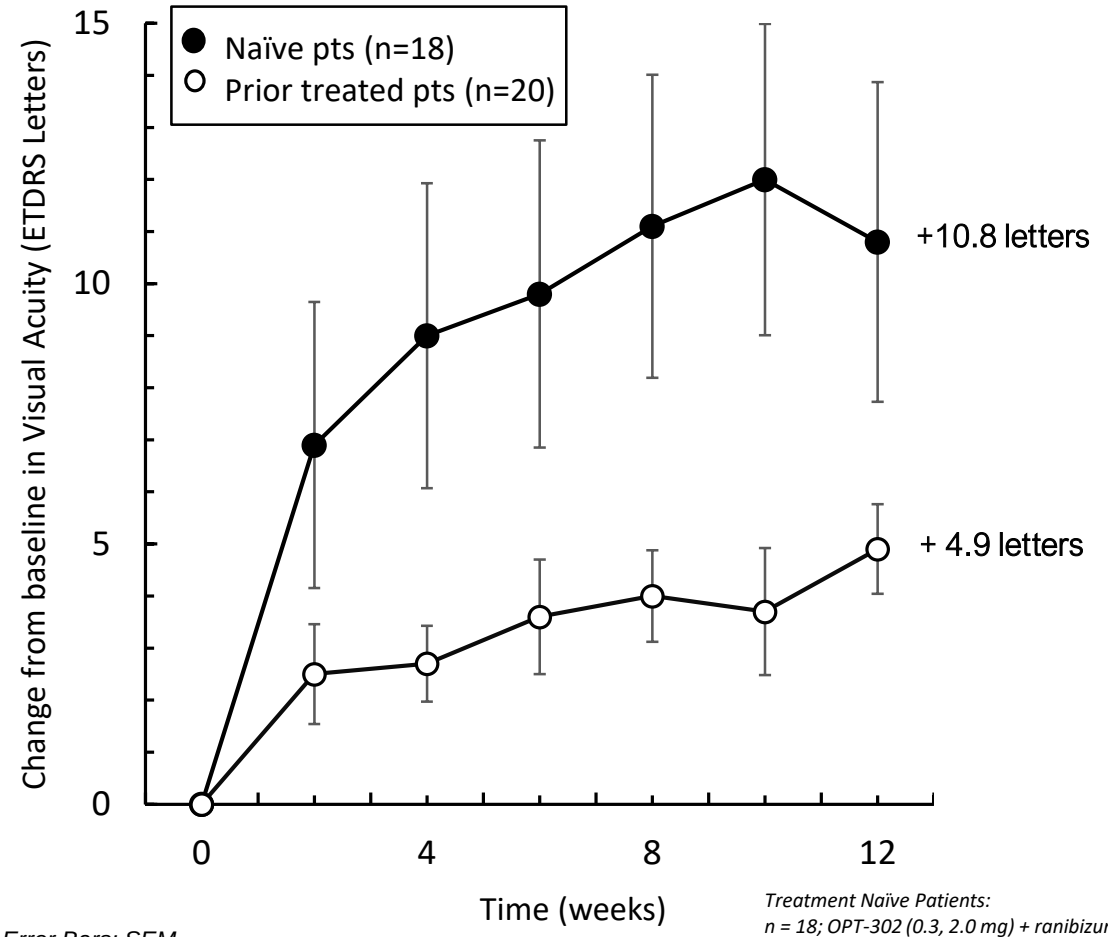
Gains in Visual Acuity and Reduced Retinal Thickness in Patients with OPT-302 + Ranibizumab Therapy

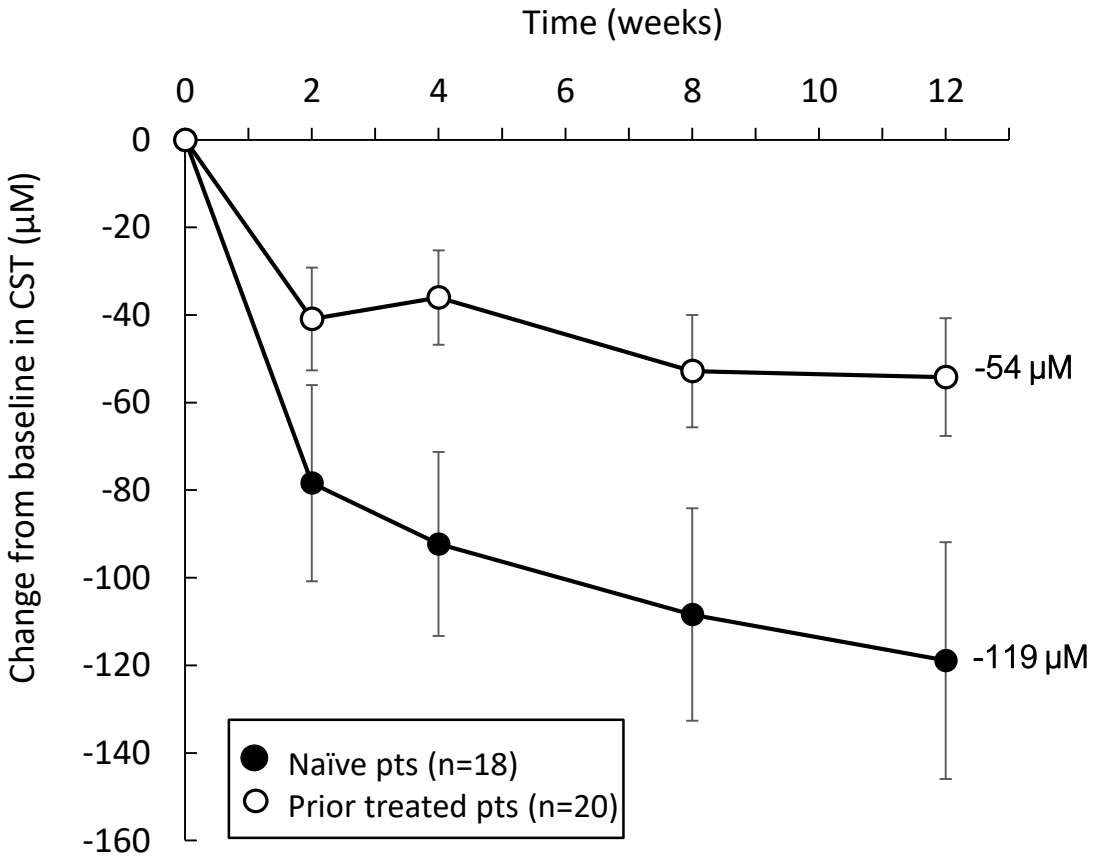
Change in mean BCVA



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

Error Bars: SEM

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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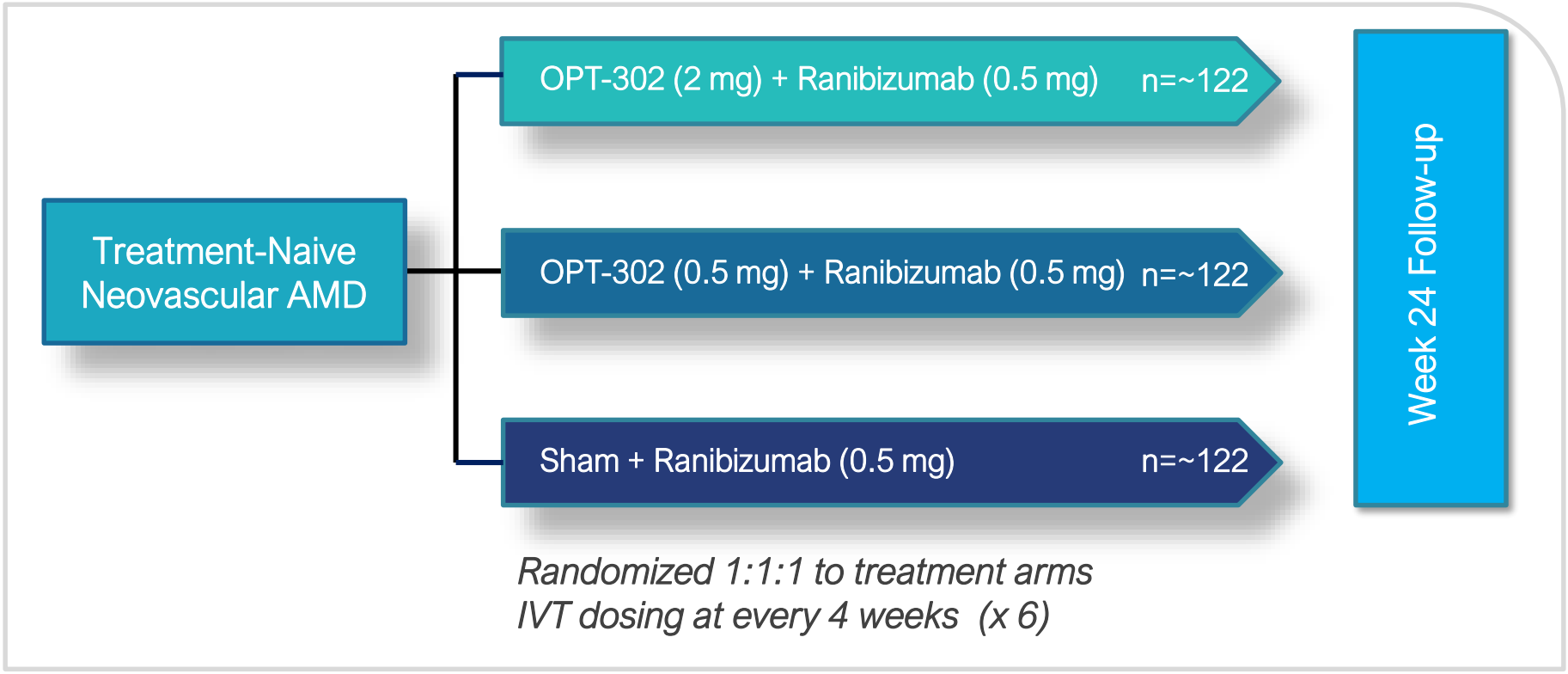
OPT-302 +/- Ranibizumab Phase 2b Trial in Treatment-Naïve nAMD (n=366)



ClinTrials Identifier NCT 03345082

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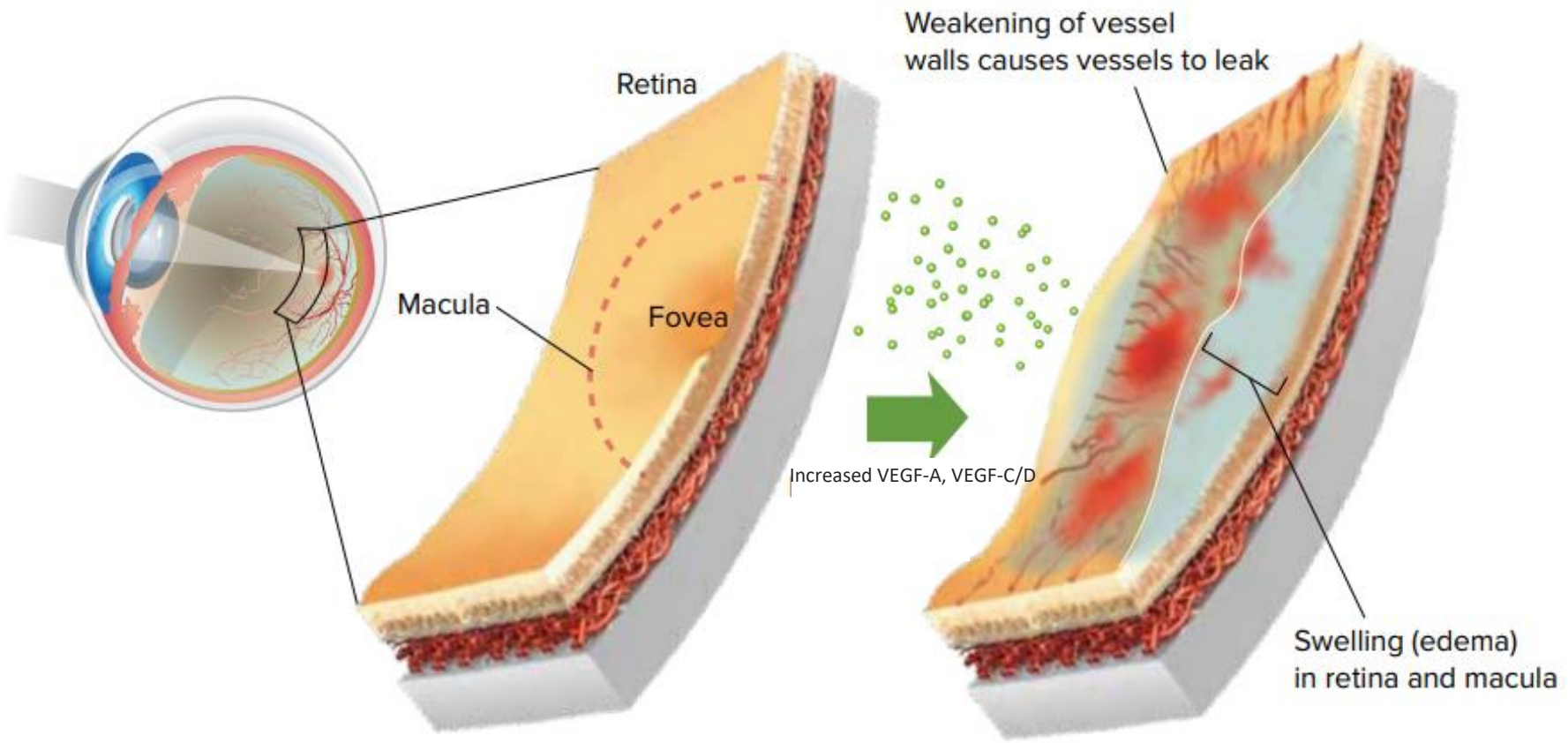
Development of DME



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An Unmet Medical Need for DME

- **DME is the leading cause of vision loss in working-age adults in the US & Europe**
  - An estimated 2M people are affected by DME worldwide
  - Increasing prevalence due to growing global health epidemic of diabetes, high proportion of patients not diagnosed
  - For those that are treated with anti-VEGF-A therapy, many do not achieve 20/40 or better vision

- **Approved therapies for wet AMD & DME target VEGF-A, but not VEGF-C or VEGF-D**
  - VEGF-C and VEGF-D activate the same, as well as independent, pathways to VEGF-A
  - VEGF-C and VEGF-D may mediate resistance to VEGF-A inhibitors (Lucentis, Eylea, Avastin)

Despite receiving a VEGF-A inhibitor (Lucentis, Eylea or Avastin):

>35% — Fail to achieve significant vision gains #

1/3 — Continue to have macular thickening / swelling ^

Our objective with OPT-302 is to address the unmet medical need for patients who experience persistent DME despite treatment with a VEGF-A inhibitor

** 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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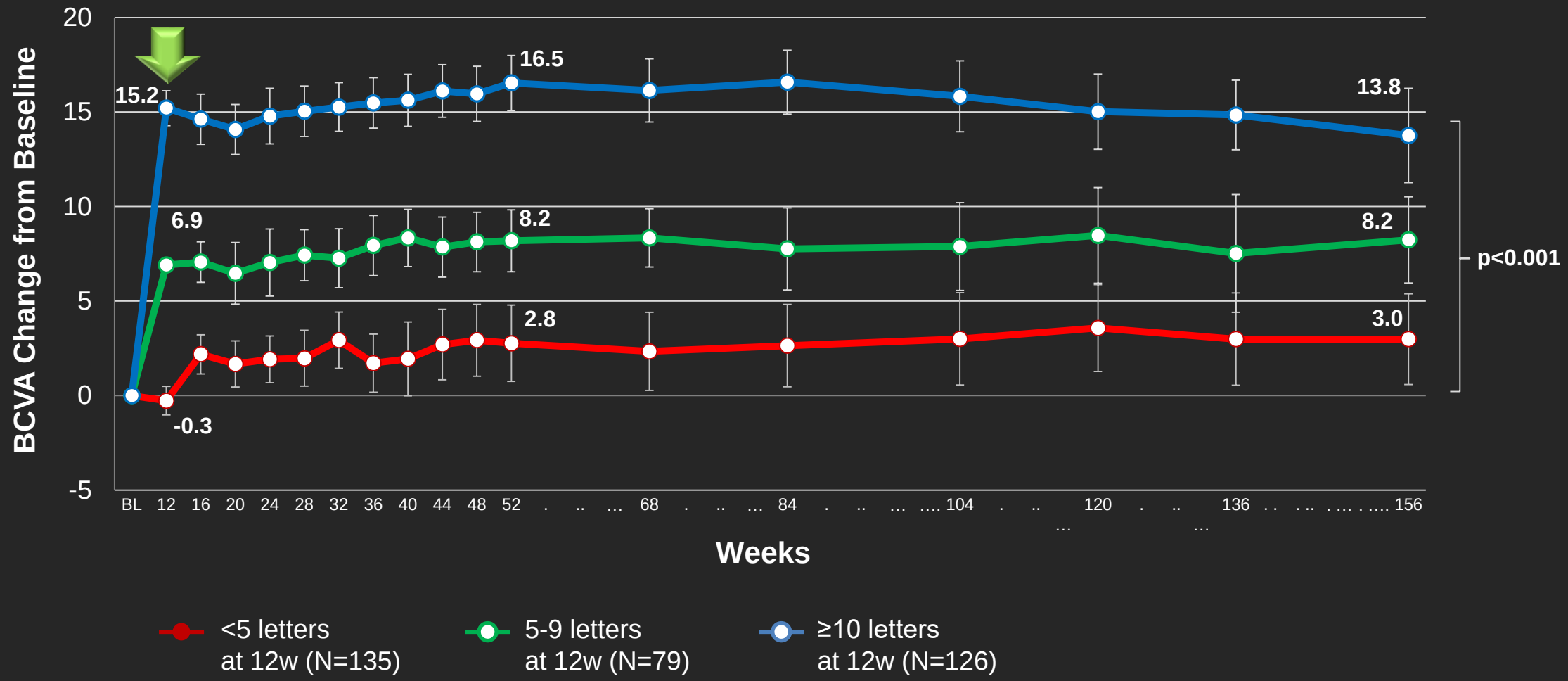
We Know Very Quickly Whether or Not Patients Will Respond to Anti-VEGF-A



Am J Ophthalmol. 2016 Dec;172:72-79. Early and Long-Term Responses to Anti-Vascular Endothelial Growth Factor Therapy in Diabetic Macular Edema: Analysis of Protocol I Data. Gonzalez VH, Campbell J, Holekamp NM, Kiss S, Loewenstein A, Augustin AJ, Ma J, Ho AC, Patel V, Whitcup SM, Dugel PU.

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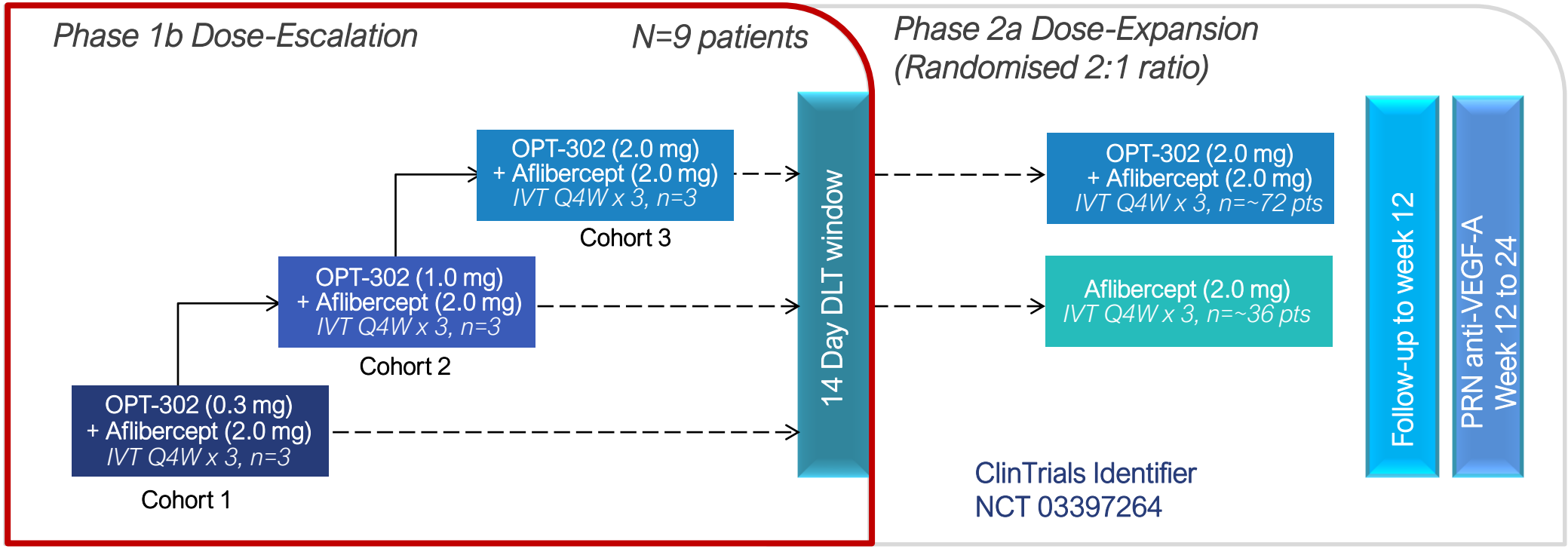
Phase 1b Dose Escalation study of OPT-302 + Aflibercept in DME



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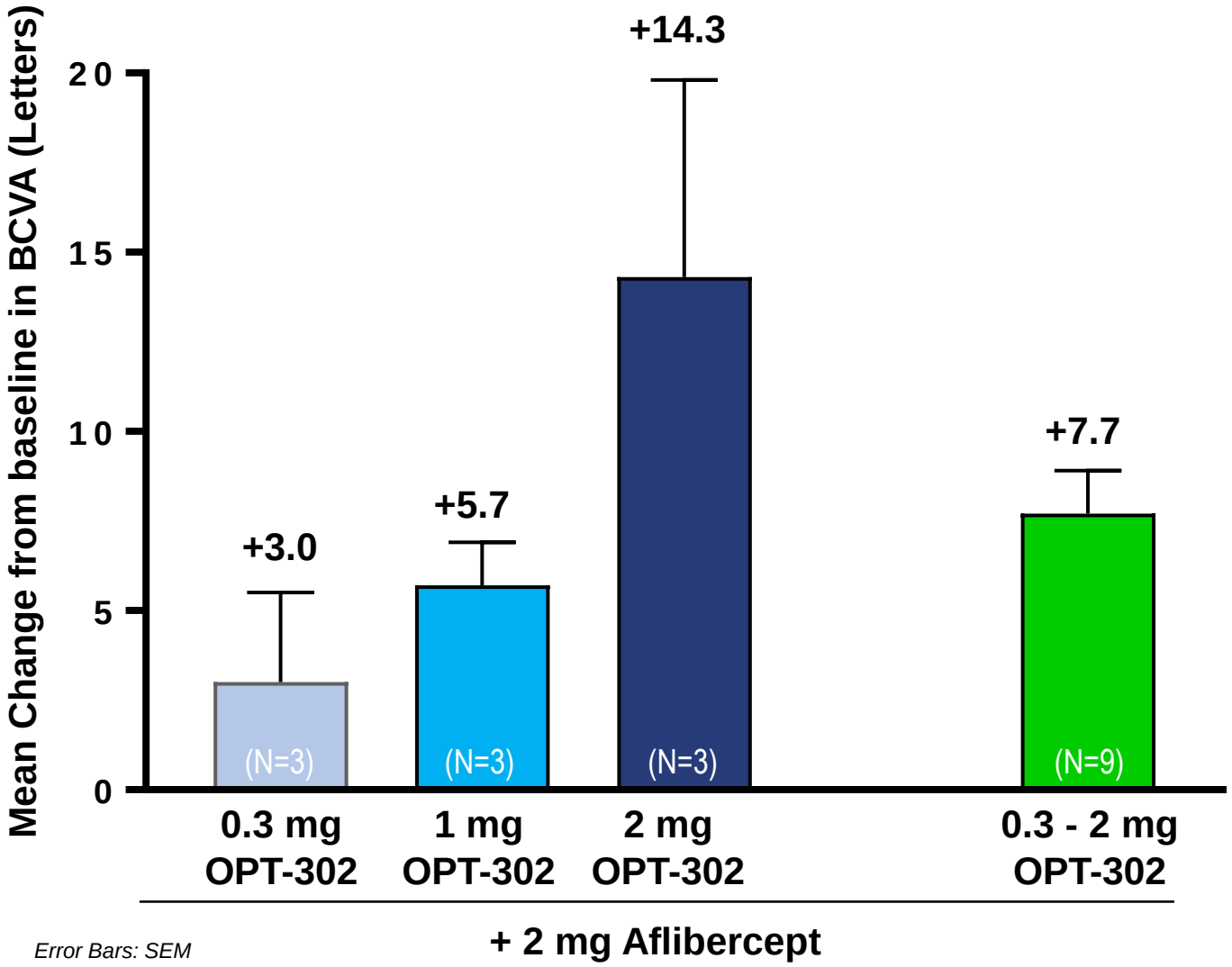
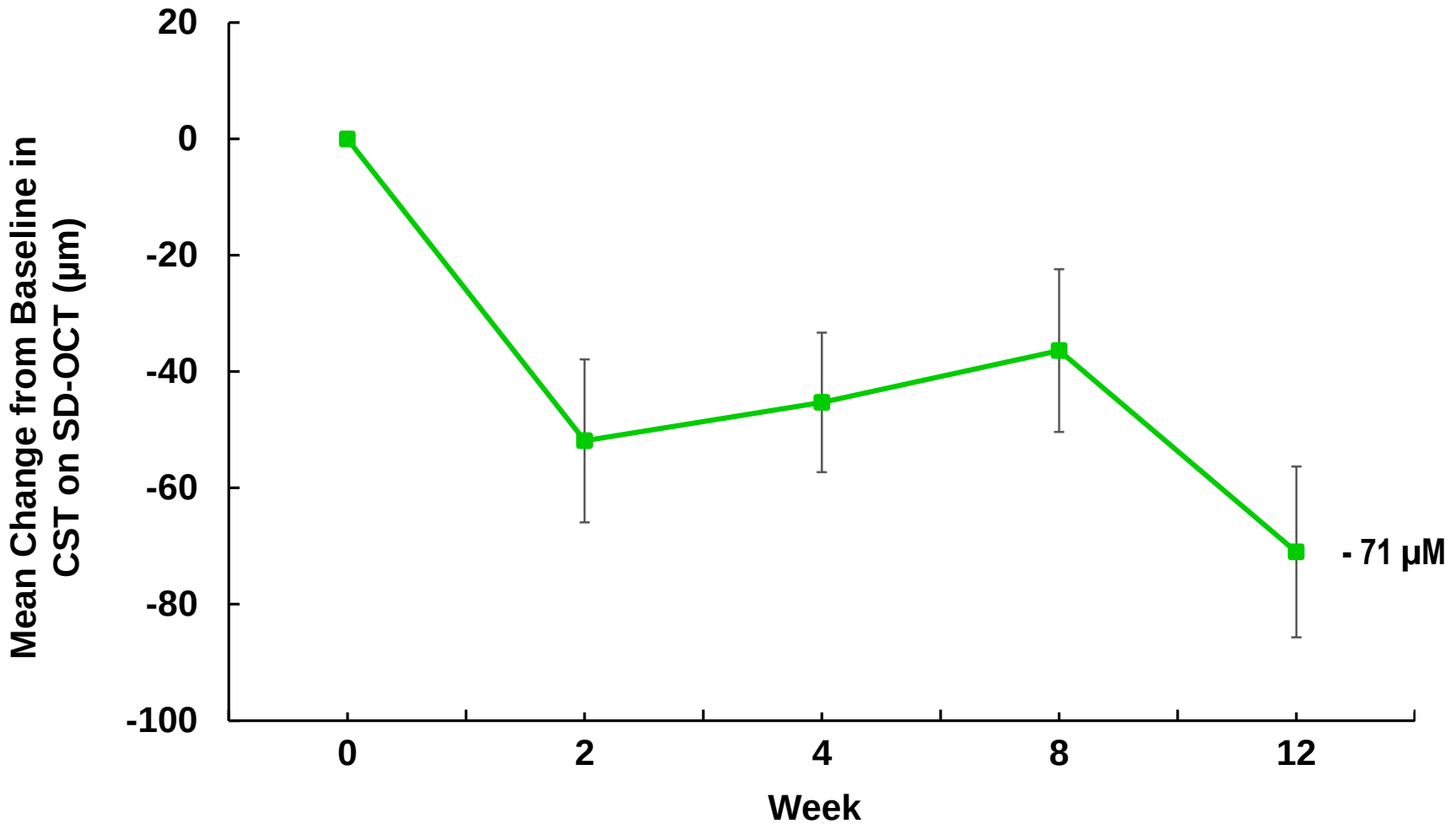
OPT-302 + Aflibercept: Gains in BCVA at Week 12
Dose Response Relationship



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

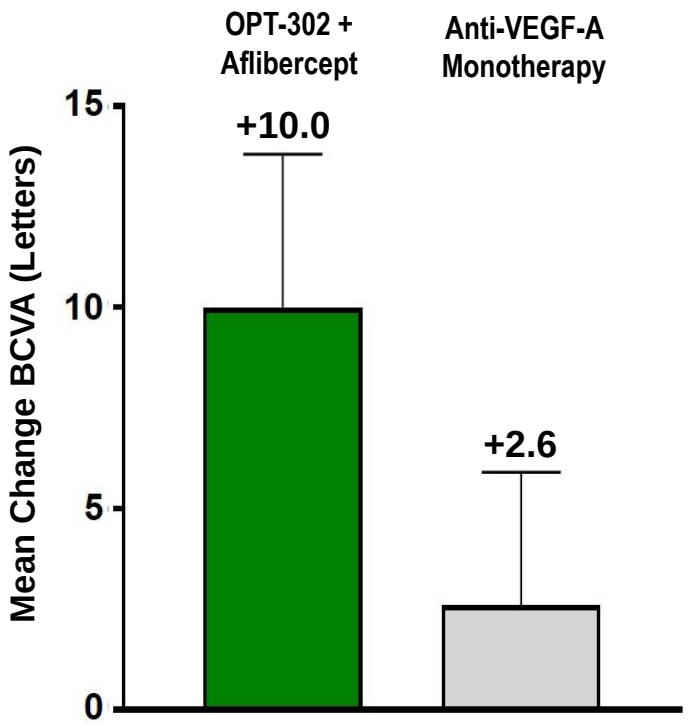
OPT-302 (0.3-2 mg) + Aflibercept (2 mg): Mean changes in CST from Baseline to Week 12



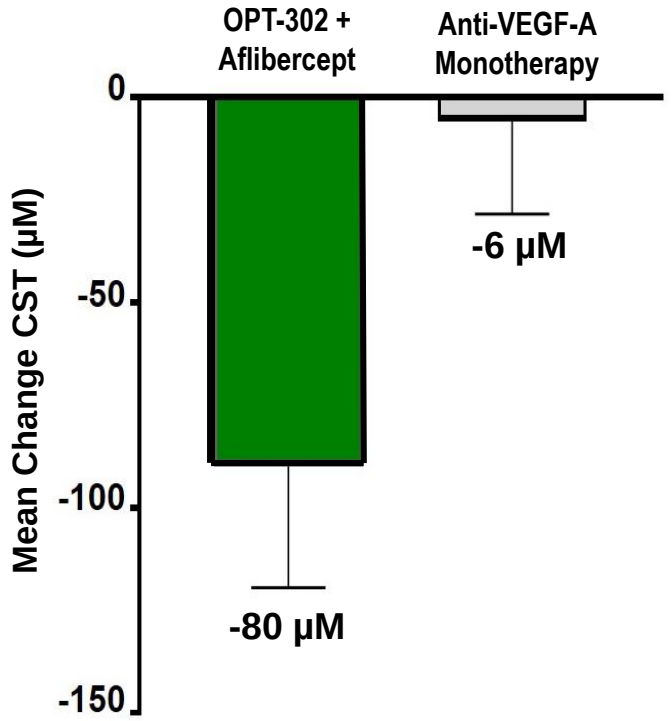
Error Bars: SEM; Mean Baseline CST = 434 µm

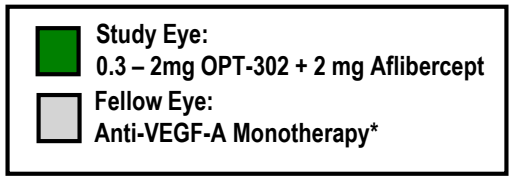
DME Patients with Bilateral Disease* Study Eye vs Fellow Eye (N=5)

Mean Change in BCVA Baseline to Week 12



Mean Change in CST (uM) Baseline to Week 12





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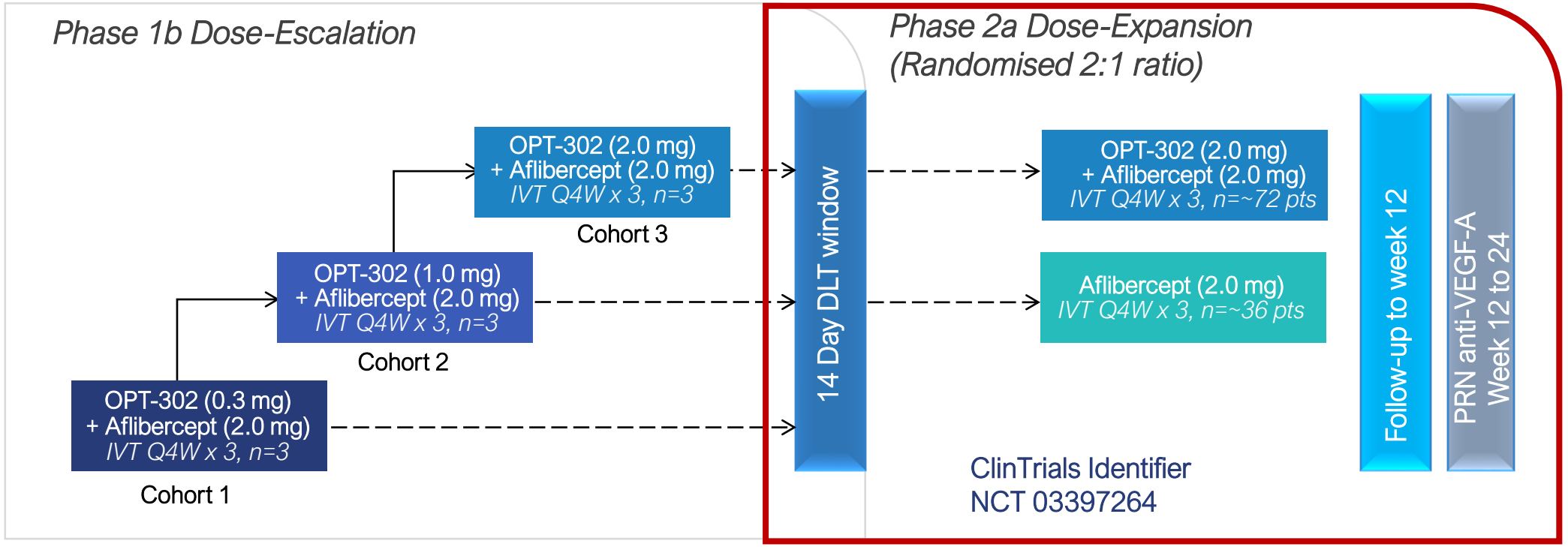
Phase 2a Randomised Dose Expansion study of OPT-302 + Aflibercept in Persistent DME



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

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Opthea Program Highlights & Upcoming Milestones

- OPT-302 targets validated pathway & may address mechanisms of incomplete response to existing standard of care treaments
- Large unmet medical need & market opportunity – will 'add-on' to existing therapy rather than 'replace'
- Clinical data to date demonstrates:
  - Favourable safety profile in combination with ranibizumab in wAMD and in combination with aflibercept in DME
  - Clear evidence of clinical activity of OPT-302 in both wet AMD and DME across multiple endpoints, including visual acuity gains and reductions in retinal thickness
- Two Phase 2 primary data readouts in 2019:
  - ~108 patient randomised controlled Phase 2a trial in DME (2H CY 2019)
  - 366 patient randomised controlled Phase 2b trial in wAMD (4Q CY 2019)

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