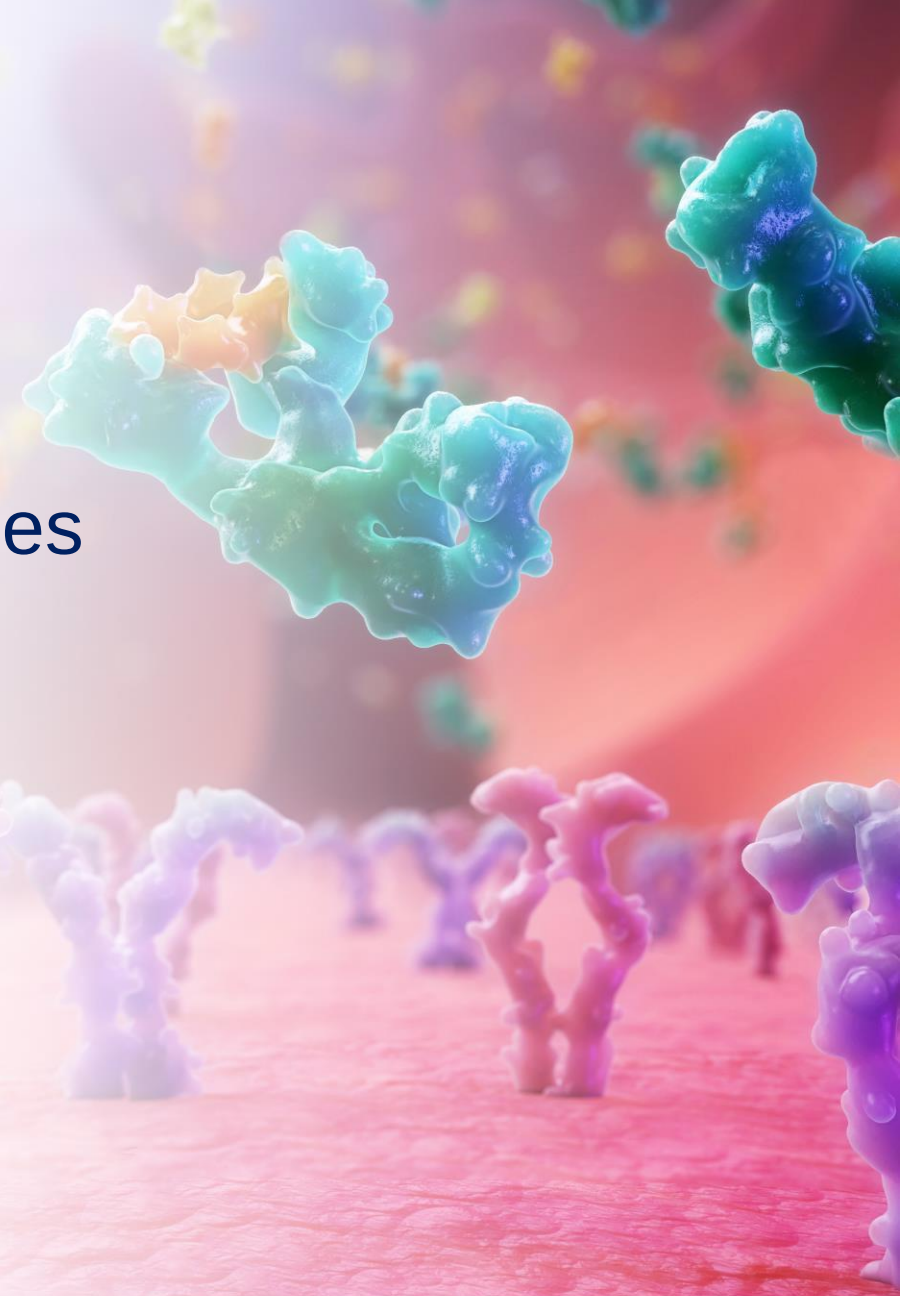
Population Pharmacokinetics and Safety of sozinibercept (OPT-302), an anti-VEGF-C/-D ‘trap’ in Patients with Retinal Vascular Diseases



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ASRS, Seattle, 2023

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Disclosures

Presenter's Financial Disclosures:

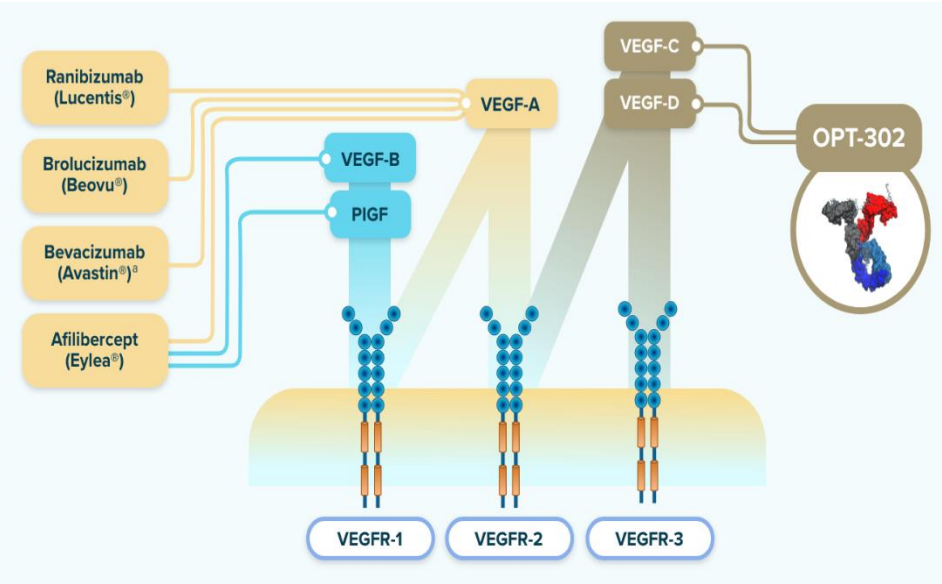
- Adverum (C), Gemini, Genentech, Inc., Iveric Bio, NGM, Opthea (C), Regeneron, Regenxbio

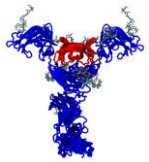
• This presentation will discuss IRB/IEC approved research of an investigational product.

(C): Consultant; (S): Stock/shareholder; (R): Grants/Research Support

Sozinibercept (OPT-302): A novel “Trap” Inhibitor of VEGF-C/-D

When used in combination is complementary/agnostic with anti-VEGF-A molecule used



	Sozinibercept (OPT-302)	LUCENTIS RANIBIZUMAB INJECTION	EYLEA (aflibercept) Injection For Intravitreal Injection
Molecule type	‘Trap’ fusion protein	Antibody fragment	‘Trap’ fusion protein
Structure			
MW	140 kDa	48 kDa	115 kDa
Dose	2 mg	0.5 mg	2 mg
IVT injection volume	0.05 mL	0.05 mL	0.05 mL
VEGF-A inhibition	NO	YES	YES
VEGF-C/-D inhibition	YES	NO	NO

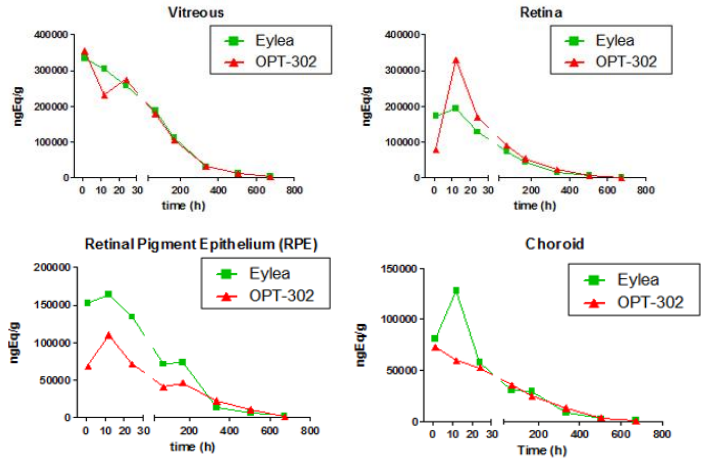
OPT-302 can also be potentially combined with Bevacizumab, Faricimab, Biosimilars, HD Eylea

- In combination with any VEGF-A inhibitor, Sozinibercept (OPT-302) **completely blocks** VEGFR-2 and VEGFR-3 signaling, inhibiting the most important pathways driving angiogenesis and vascular leakage

*Dugel et al 2019, Ophthalmology Retina; †Lashkari et al , 2013 ARVO Annual Meeting, 4999-A0128; Bevacizumab used “off-label”; *Faricimab also targets Angiopoietin 2*

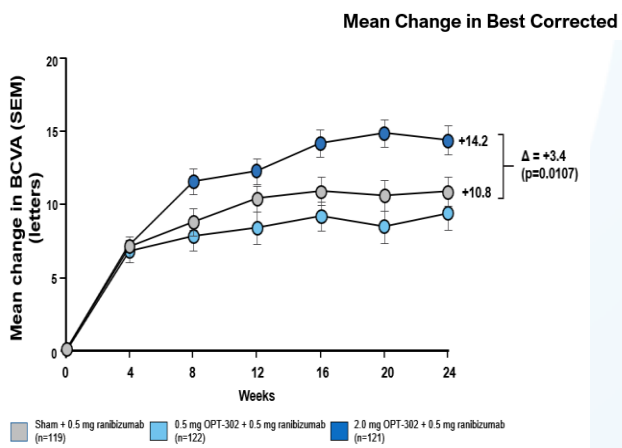
Sozinibercept (OPT-302) combination therapy for retinal vascular diseases

Similar ocular biodistribution & PK of intravitreal Sozinibercept to Aflibercept

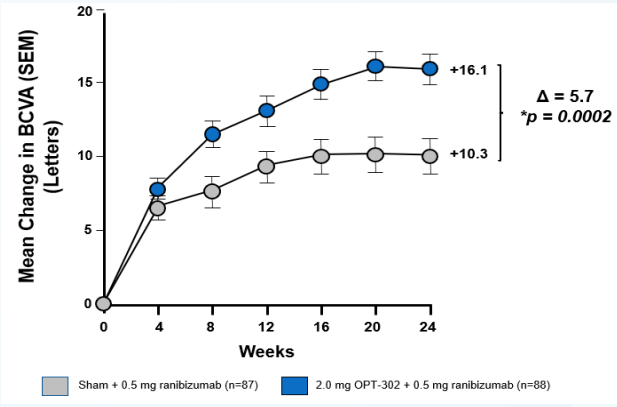


[^{125}I]OPT-302, or [^{125}I]aflibercept IVT injection of 500 µg/eye) (rabbit)

Superiority in BCVA gains with Sozinibercept (2 mg) combination therapy vs anti-VEGF-A monotherapy in Phase 2b study of treatment naïve patients (n=366) with nAMD



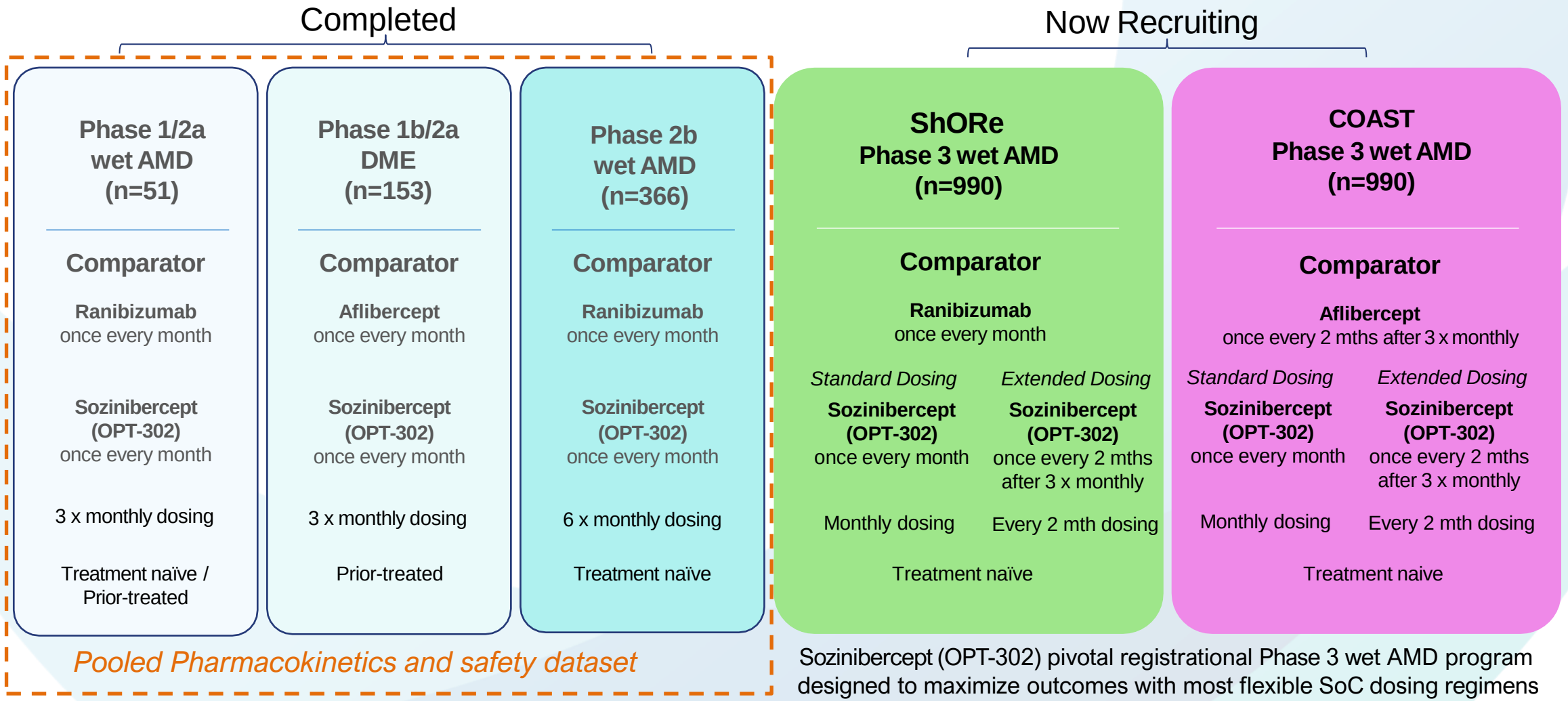
Additional +3.4 letter gain (p=0.0107) over ranibizumab in total population



Additional +5.7 letter gain in high responder subgroup (minimally classic & occult lesions)

- Currently two ongoing global pivotal registrational Phase 3 studies in wet AMD
- Analysis of OPT-302 serum pharmacokinetics (PK) of completed studies is important for interpreting safety and efficacy results and informing dosing for phase III trials
- A population PK model and pooled data analysis from clinical studies in patients with wet AMD and DME were used to describe PK parameters and safety following intravitreal (IVT) OPT-302 administration

Sozinibercept (OPT-302) Combination Therapy Clinical Program



Sozinibercept (OPT-302) pivotal registrational Phase 3 wet AMD program designed to maximize outcomes with most flexible SoC dosing regimens

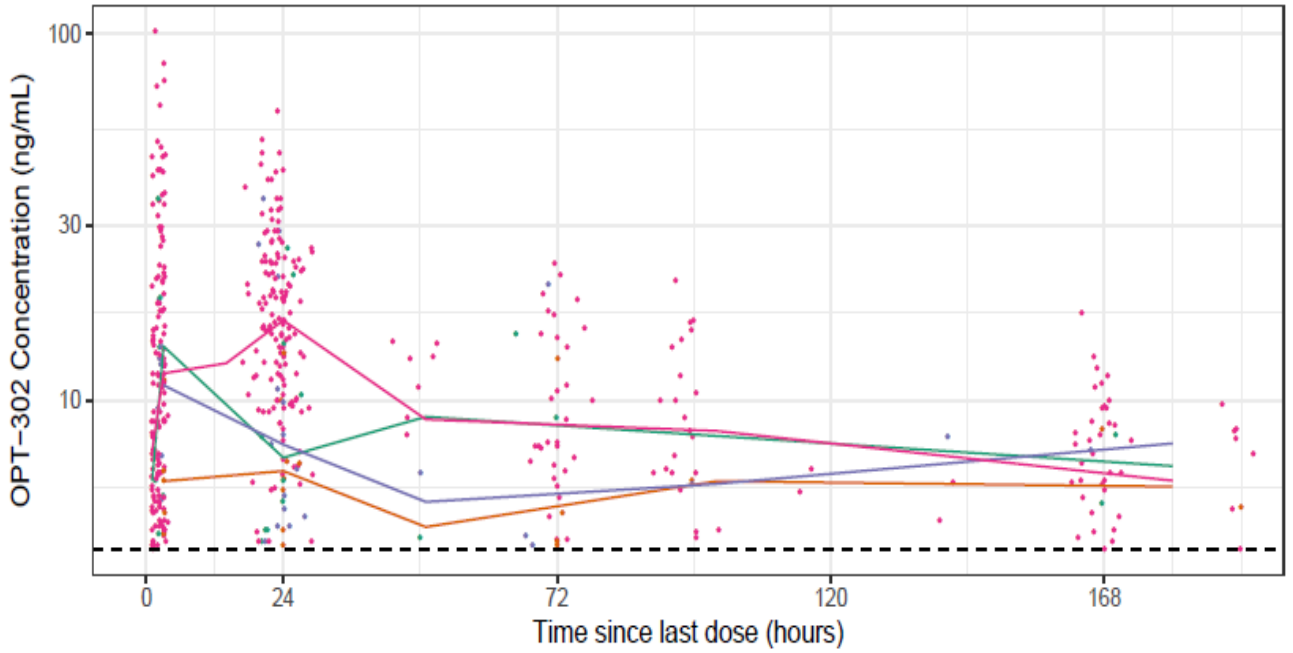
Exposure and demographics of pooled PK / safety dataset

Pooled data from a total of 1,853 intravitreal injections of sozinibercept (OPT-302: 0.3, 0.5, 1 or 2 mg)

- includes 1,130 IVT injections of 2.0 mg OPT-302
- PK samples in human serum were mostly collected at pre-dose, then ≥ 1 to 168 hours post-dose
- The PK bioanalytical method used a ELISA assay for determination of total OPT-302 serum concentrations (VEGF-C and -D bound and free OPT-302), the lower limit of quantitation of the assay was 3.91 ng/mL

	Age (years)	Weight (kg)	BMI (kg^2/m^2)	CrCL (mL/min)	eGFR (ml/min/1.73m^2)	Sex	Race	Pr Tx	Disease
N	394	394	394	394	394	Male: 176 (44.7%)	White: 375 (95.2%)	No: 265 (67.3%)	nAMD: 291 (73.9%)
Mean	73.8	78.4	28.6	81.1	77.8	Female: 218 (55.3%)	Black: 10 (2.5%)	Yes: 129 (32.7%)	DME: 103 (26.1%)
SD	11.3	18.4	5.58	40.4	26		Asian: 1 (0.3%)		
CV%	15.3	23.5	19.5	49.9	33.4		Other: 8 (2%)		
Median	76	75	27.9	72.6	76.8				
Min	39	47	18.8	17.7	18.5				
Max	95	178	61.6	318	178				

Sozinibercept (OPT-302) systemic PK profile & noncompartmental parameters



The solid lines show the median, with the filled circles representing the observed data, dashed black line = LLOQ (3.9 ng/mL). Plots truncated at 180 hours post-dose. Data below the LLOQ (3.9 ng/mL) excluded. Y-axis on log-scale.

Pooled systemic serum PK data:

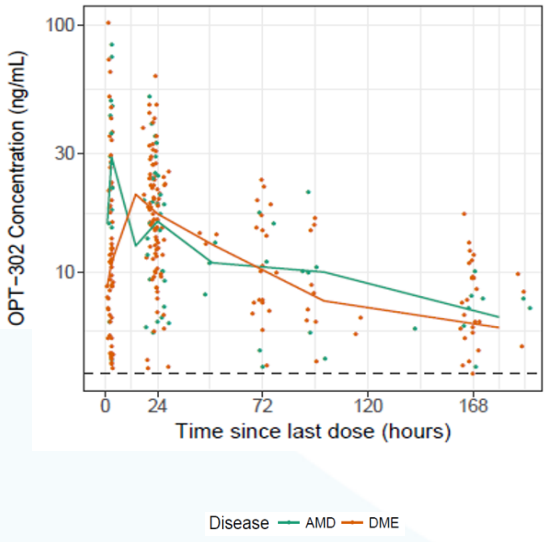
- C_{max} ~20 ng/mL [4 - 83]
- T_{max} ~30 hrs [1.8 - 96]
- $T_{1/2}$ ~7 days [2 -12]

The majority of the PK data for OPT-302 was collected following an IVT dose of 2 mg, where serum (C_{max}) occurs ~30 hours after administration.
Quantifiable concentrations remained in some subjects at 168 hours post- dose.
The interpretation of linear kinetics across dose range studied is challenging given the limited data from low dose groups ≤ 1 mg due to BLQ. .

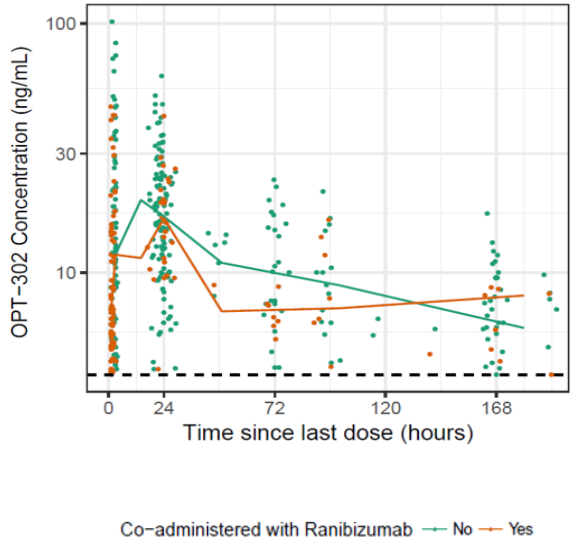
Sozinibercept (OPT-302) PK profiles by:

(A) ranibizumab co-therapy (nAMD); or (B) disease indication, nAMD vs DME; or (c) age group; or (d) renal impairment classification

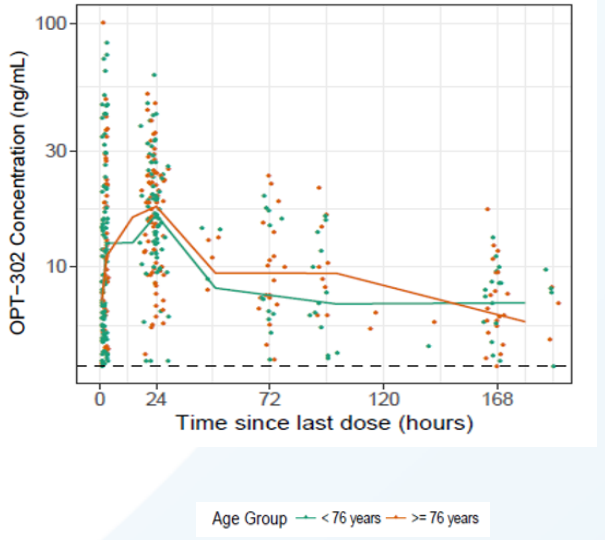
(A) ± ranibizumab co-therapy (nAMD)



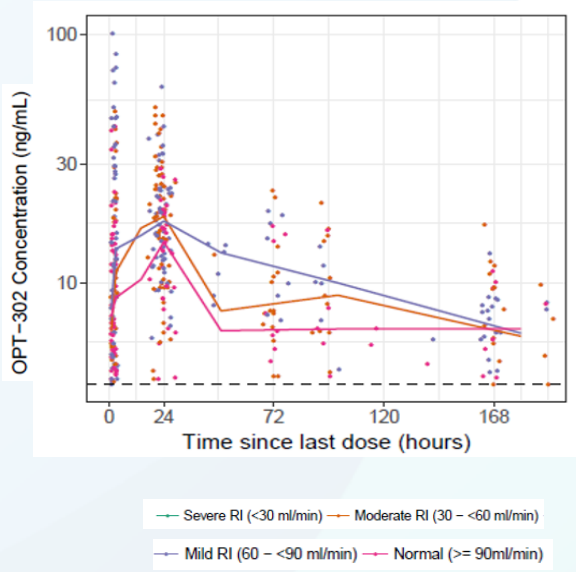
(B) nAMD vs DME



(C) age group

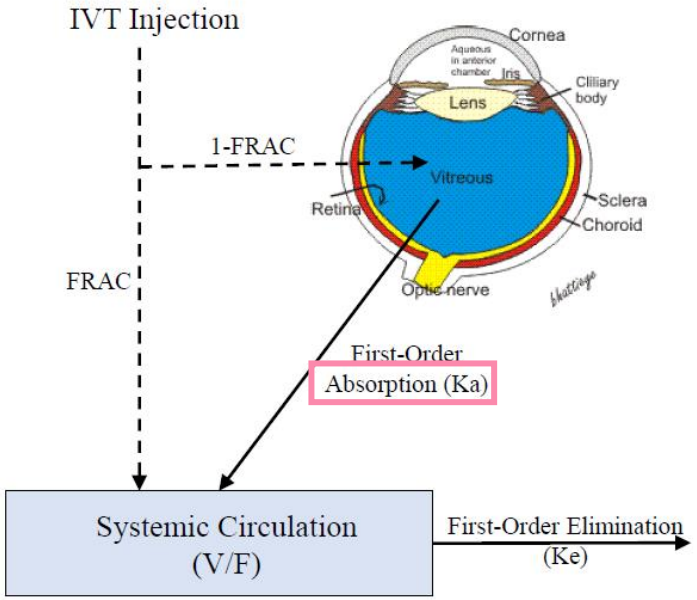


(D) renal impairment



No evidence of altered sozinibercept (OPT-302) PK by co-variates, as the profiles are comparable irrespective of (A) ranibizumab co-administration or (B) disease indication or (C) Age or (D) renal impairment classification

Vitreous Parameter Estimates from sozinibercept (OPT-302) Population PK Model



Parameter	Estimate (%RSE)	95% CI
Elimination $t_{1/2}$ (days)	0.145 (12.8)	0.113 – 0.189
Volume of Distribution (V/F, L)	3.52 (15.9)	2.65 – 4.96
Absorption $t_{1/2}$ (days)	4.64 (10.5)	3.62 – 5.78
Fraction absorbed directly into systemic circulation (%)‡	6.94 (12.8)	3.10 - 12.1
Between subject variability on elimination $t_{1/2}$ (%CV)	26.4 (36.6)	0.26 – 44.3
Between subject variability on V/F (%CV)	50.3 (13.5)	36.4 – 67.0
Between subject variability on FRAC (variance)‡	0.342 (47.7)	3.42E-05 – 1.57
Between occasion variability on absorption $t_{1/2}$ (%CV)	40.7 (19.3)	24.5 – 56.1
Residual unexplained variability (proportional, %CV)	43.5 (10.7)	31.6 – 53.4
Residual unexplained variability (additive SD, ng/mL)	1.63 (13.9)	1.10 - 2.27

†$V/F = 3.2 \cdot (1\text{-}0.391)^{SEX}$, where SEX = 0 for males and 1 for females. ‡$FRAC = \exp(-2.596+\eta)/(1+\exp(-2.596+\eta))$, where η followed a normal distribution with a mean of zero and a variance of 0.342. 95% CI from bootstrap analysis of 1000 samples.

The PK model retained the single distribution compartment and linear elimination. Absorption from the vitreous space was described by a first-order process.
During selected dosing occasions, a small fraction, (≈7%) of the administered OPT-302 bypassed the vitreous compartment into the systemic circulation.
This phenomena has previously been described for IVT ranibizumab using a population PK approach.
The absorption of OPT-302 was the rate-limiting step, with the PK of OPT-302 via IVT administration described by 'flip-flop' kinetics.
The model assumes no clearance of OPT-302 in the vitreous compartment. The M3 method was used during estimation given the BLQ data.

Pooled safety for completed sozinibercept (OPT-302) Trials

Combination therapy well-tolerated and comparable to standard of care monotherapy

N Participants (%)	OPT-302 Any dose N=399 (N=1,842 injections)	OPT-302 2.0 mg N=263 (N=1,121 injections)	Sham + anti-VEGF-A control N=169 (N=854 injections)
Ocular TEAEs - Study Eye – related to study product(s)	22 (5.5%)	20 (7.6%)	22 (13.0%)
Ocular TEAEs - Study Eye – Severe	4 (1.0%)	2 (0.1%)	2 (1.2%)
Intraocular inflammation – Study Eye	7[1,2,3] (1.8%)	3[1] (1.1%)	3[1] (1.8%)
Participants with AEs leading to treatment discontinuation	4[2,4-6] (1.0%)	1[4] (0.4%)	2[7,8] (1.2%)
Any APTC event	4[4,5,9,10] (1.0%)	3[5,9,10](1.1%)	2[11,12] (1.2%)
Deaths	2[10,13] (0.5%)	2[10,13] (0.8%)	2[14,15] (1.2%)

[1] Transient anterior chamber cell (trace 1-4 cells); [2] SAE of endophthalmitis, with AE's of hypopyon and anterior chamber cell; [3] SAE of vitritis; [4]Non-fatal myocardial infarction; [5]Cerebrovascular accident; [6]Enteritis; [7]Abdominal pain; [8]Increased IOP; [9] Non-fatal angina pectoris; [10]Fatal congestive heart failure/myocardial infarction; [11]Non-fatal arterial embolism; [12]Embolic stroke; [13]Metatstaic ovarian cancer; [14] Pneumonia; [15] infective endocarditis

Phase 3 trials of Sozinibercept (OPT-302) Combination therapy (*ongoing*)

ShORe

Study of **OPT-302**
in combination
with Ranibizumab

Treatment naïve wet AMD patients

Randomised 1:1:1 (n=990)

- **Ranibizumab (0.5 mg)** q4w **+ OPT-302 (2 mg)** q4w
- **Ranibizumab (0.5 mg)** q4w **+ OPT-302 (2 mg)** q4w x 3; then q8w
- **Ranibizumab (0.5 mg)** q4w **+ Sham** q4w

Key Inclusion Criteria

- *Active CNV ≥50% lesion,*
- *classic / minimally classic / occult*
- *BCVA between 25 & 60 letters (20/63 – 20/320)*

Key Exclusion Criteria

- *Subfoveal fibrosis or >25% of total lesion*
- *Haemorrhage >50% total lesion*
- *Other clinically significant ocular disease*

COAST

Combination
OPT-302 with
Aflibercept STudy

Treatment naïve wet AMD patients

Randomised 1:1:1 (n=990)

- **Aflibercept (2 mg)** q4w x 3; then q8w **+ OPT-302 (2 mg)** q4w
- **Aflibercept (2 mg)** q4w x 3; then q8w **+ OPT-302 (2.0 mg)** q4w x 3; then q8w
- **Aflibercept (2 mg)** q4w x 3; then q8w **+ Sham** q4w

Primary Efficacy Endpoint
Mean change from Baseline in ETDRS BCVA letters at Week 52

Continued dosing through Year 2 safety follow-up
Final Assessment at Week 100

- **Design:** Multi-centre, double-masked, randomised (1:1:1), sham control
- **Regulatory quality:** 90% power, 5% type I error rate

- *Sham administered at visits when OPT-302 is not administered*

Summary: Sozinibercept (OPT-302) pooled PK and safety

- The PK profiles of intravitreal sozinibercept (OPT-302) from completed studies in patients with nAMD and DME indicated:
  - low systemic exposure
  - within one week drug levels were mostly no longer detectable in serum
  - Estimated vitreous absorption half-life was ~4.6 days [95% CI 3.6-5.8] comparable to other IVT biologics
  - The PK profile was unaltered by anti-VEGF-A co-therapy, disease indication (nAMD vs DME), age or renal function
- Pooled safety analysis shows soziniberept (OPT-302) combination therapy has a favourable safety and tolerability profile
  - comparable to standard of care anti-VEGF-A monotherapy
- Promising treatment option for wet AMD currently in two pivotal registrational Phase 3 studies