Update on KSI-301 (tarcocimab tedromer) and Antibody Biopolymer Conjugate Development Programs

Diana Do, M.D.
Professor of Ophthalmology
Vice Chair of Clinical Affairs
Byers Eye Institute
Stanford University School of Medicine

Angiogenesis, Exudation, and Degeneration 2023
11 February 2023

Disclosures

- Presenter's Financial Disclosures:
  - Apellis (C), Biogen (C), Boehringer Ingelheim (C, R), Genentech (C), Iveric (C), Kodiak (C, S), Kriya (C, R), Regeneron (C, R) , Santen (C, R)
- This presentation will discuss IRB/IEC approved research of an investigational medicine.

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

Key Points

BEACON study met primary endpoint

Mean change in BCVA with **tarcocimab Q8W was non-inferior to aflibercept Q4W** in RVO

Similar efficacy, meaningfully fewer doses

Tarcocimab is the **first anti-VEGF therapy to show comparable visual acuity outcomes** to monthly aflibercept **while doubling the treatment interval** for all RVO patients

- Matched phase: **strong efficacy** with comparable vision and anatomic improvement as early as Week 1
- Maintenance phase: similar gains from Week 8 to Week 24 with **half the doses**

Data from four additional pivotal studies in 2023

Primary endpoint data from four Phase 3 studies of tarcocimab expected later this year: two studies in DME (GLEAM and GLIMMER), as well as an additional wAMD study (DAYLIGHT) and an NPDR study (GLOW)

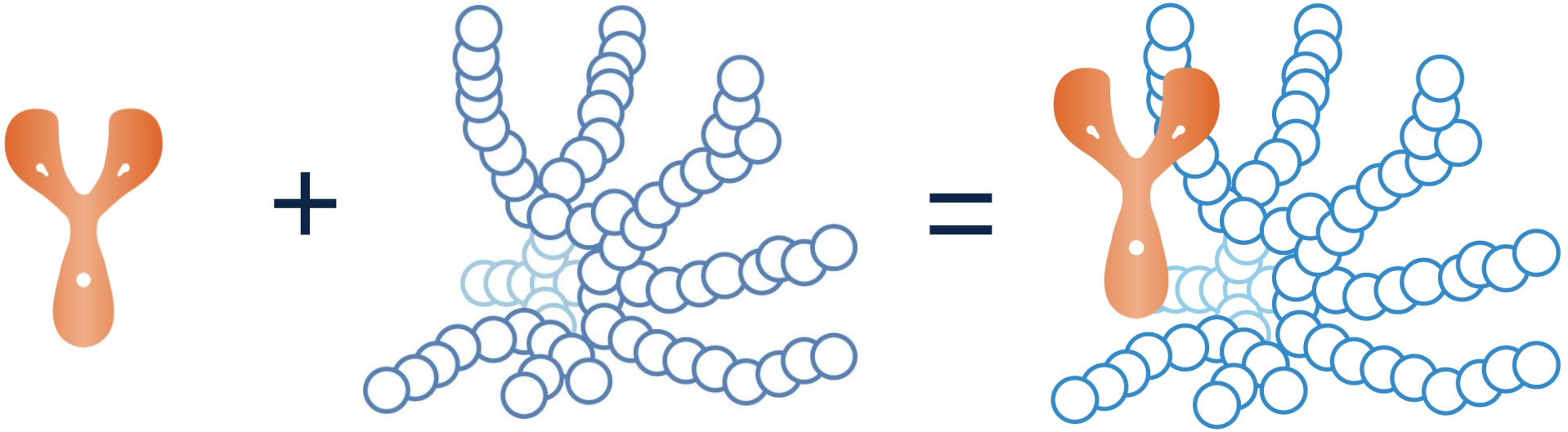
KSI-501 - new category of retinal medicine inhibiting VEGF and IL-6 entering clinic

Dual inhibition of VEGF and IL-6 may offer provide additional clinical benefits in DME, wAMD, uveitic macular edema, and other retinal diseases with an inflammatory component

IND for KSI-501 has cleared and dose escalation study expected to begin shortly

KSI-301 (tarcocimab tedromer): Antibody Biopolymer Conjugates (ABCs)

A novel class of biologics engineered for increased durability and efficacy



ANTIBODY

IgG1 Anti-VEGF Antibody
Immunologically inert

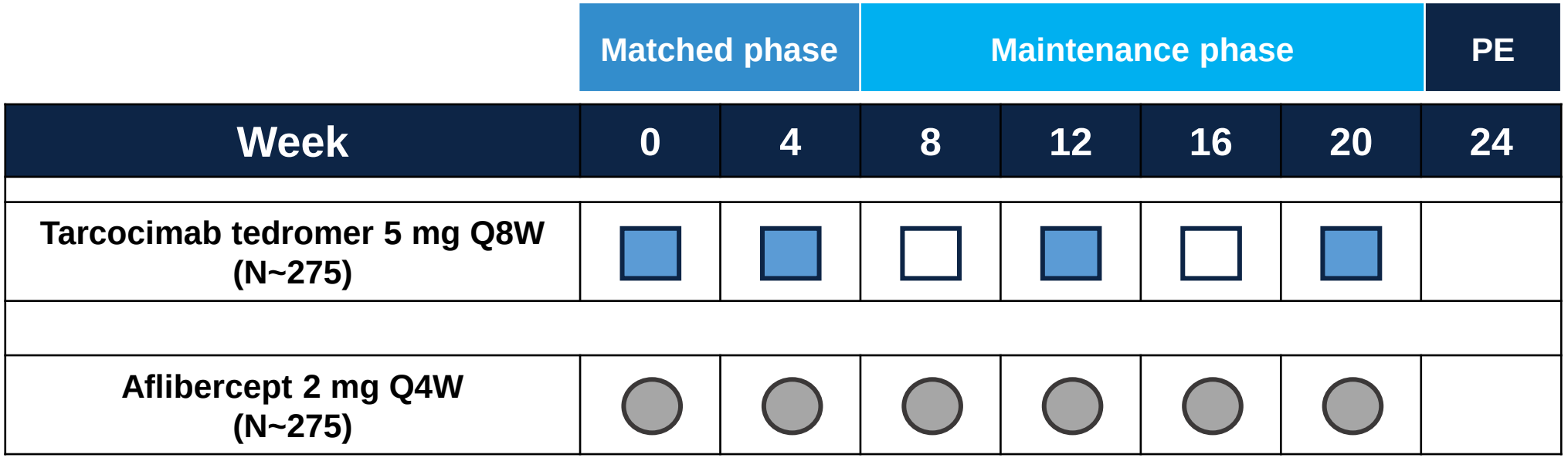
BIOPOLYMER

Branched, Optically Clear,
High Molecular Weight
Phosphorylcholine Polymer

CONJUGATE

KSI-301 (tarcocimab tedromer) is an anti-VEGF ABC that blocks all VEGF-A isoforms

BEACON: non-inferiority study of tarcocimab tedromer every 2 months after only two loading doses vs aflibercept every month in treatment-naïve RVO patients



- Tarcocimab injection
- Aflibercept injection
- Sham injection

Primary Endpoint:
Mean change in BCVA at Week 24

Hierarchical testing for control of type 1 error:

1. Test non-inferiority in BRVO patients
2. Test non-inferiority in all RVO patients (BRVO+CRVO)

Clinicaltrials.gov, study identifier: NCT04592419
RVO: retinal vein occlusion; PE: primary endpoint; BCVA: best-corrected visual acuity

Patient Eligibility Criteria

Key Ophthalmic Inclusion Criteria

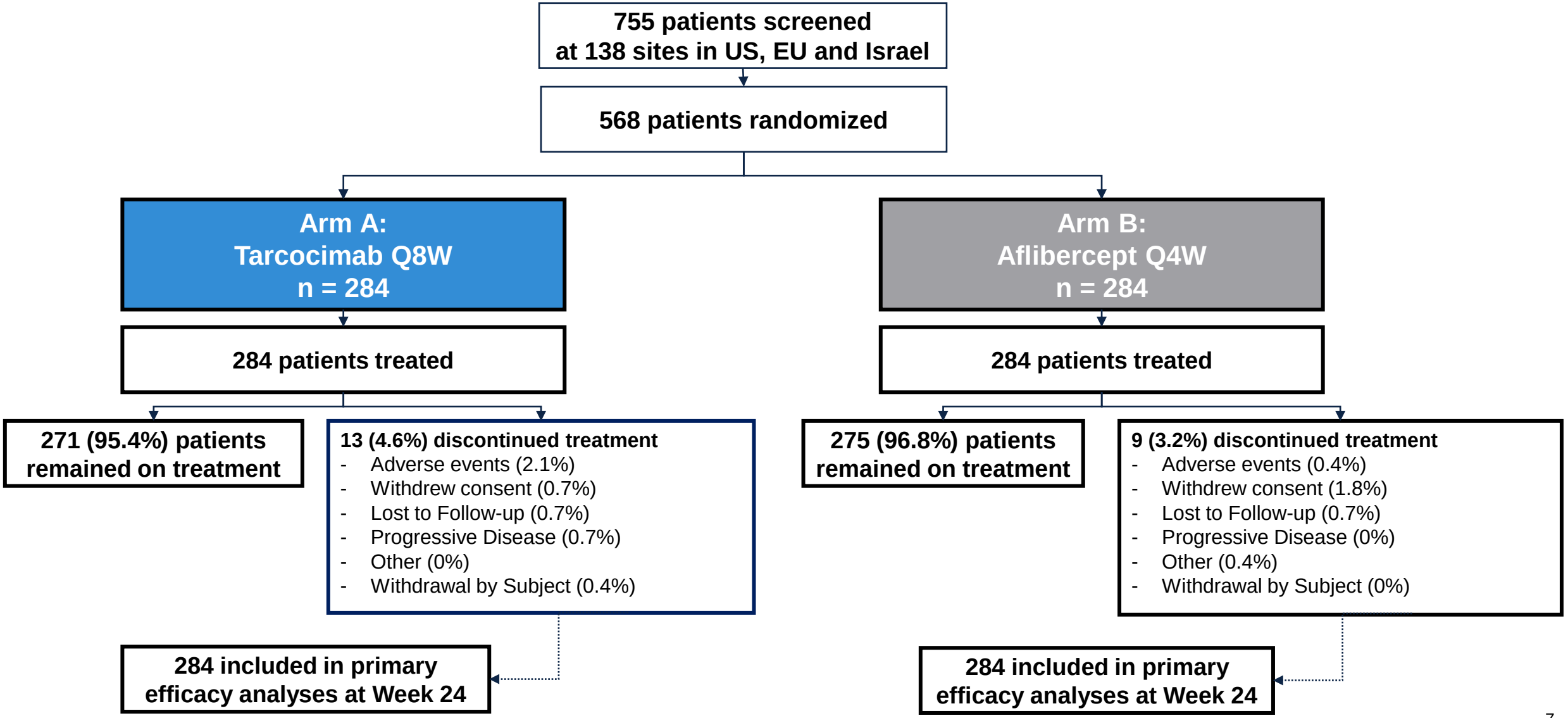
- Treatment-naïve macular edema secondary to RVO (BRVO or CRVO) of **≤ 6 months duration**
- **BCVA of 80 to 25 ETDRS letters** (≈20/25 to 20/320 Snellen)
- **CST of ≥320 microns** on SD-OCT

Key Ophthalmic Exclusion Criteria

- Macular edema in the Study Eye considered to be secondary to a cause other than RVO
- Active iris or angle neovascularization, neovascular glaucoma, neovascularization of the optic disc, retinal neovascularization or vitreous hemorrhage in the Study Eye
- Significant media opacities, including cataract, in the Study Eye that might interfere with visual acuity, assessment of safety, optical coherence tomography or fundus photography
- Prior vitrectomy in the Study Eye
- Active retinal disease other than the condition under investigation in the Study Eye
- Any history or evidence of a concurrent ocular condition that in the opinion of the Investigator could require either medical or surgical intervention or affect macular edema or alter visual acuity during the study (e.g. vitreomacular traction)

ME: macular edema; RVO: retinal vein occlusion; BRVO: branch retinal vein occlusion; CRVO: central retinal vein occlusion; BCVA: best-corrected visual acuity; ETDRS: early treatment diabetic retinopathy study; CST: central subfield thickness; SD-OCT: spectral domain optical coherence tomography.

Patient Disposition – discontinuations were low and balanced between groups; over 95% of patients remained on treatment



Baseline Ocular Characteristics – tarcocimab treated patients started at a slightly higher baseline BCVA

Parameter	Tarcocimab Q8W (n=284)		Aflibercept Q4W (n=284)	
RVO Type, n (%) BRVO CRVO	220 (77.5%) 64 (22.5%)		218 (76.8%) 66 (23.2%)	
	BRVO n=220	**All Patients** n=284	**BRVO** n=218	**All Patients** n=284
BCVA, ETDRS Letters, mean (SD)	**62.6 (12.24)**	**61.0 (13.19)**	**61.4 (13.33)**	**59.8 (14.18)**
≥20/40 Snellen equivalent, n (%)	81 (36.8%)	92 (32.4%)	75 (34.4%)	90 (31.7%)
≤20/200 Snellen equivalent, n (%)	12 (5.5%)	22 (7.7%)	17 (7.8%)	31 (10.9%)
BCVA Category, n (%)				
≤ 49 ETDRS Letters	27 (12.3%)	45 (15.8%)	30 (13.8%)	47 (16.5%)
50 – 69 ETDRS Letters	120 (54.5%)	155 (54.6%)	118 (54.1%)	155 (54.6%)
70 – 80 ETDRS Letters	73 (33.2%)	84 (29.6%)	70 (32.1%)	82 (28.9%)
Disease Duration, n (%)				
< 3 months	201 (91.4%)	262 (92.3%)	195 (89.4%)	256 (90.1%)
≥3 months	19 (8.6%)	22 (7.7%)	23 (10.6%)	28 (9.9%)
OCT Central Subfield Thickness (CST), µm, mean (SD)	526.0 (160.20)	568.4 (187.07)	543.5 (162.91)	587.5 (197.63)
Intraocular Pressure, mmHg, mean (SD)	15.3 (3.22)	15.1 (3.24)	15.3 (3.24)	15.2 (3.20)

n = number of participants treated; the denominator for percentages is the number of participants treated within each treatment arm. Snellen equivalent of 20/40 is 69 ETDRS letters and of 20/200 is 38 ETDRS letters.
RVO: retinal vein occlusion; BRVO: branch retinal vein occlusion; CRVO: central retinal vein occlusion; BCVA: best-corrected visual acuity; ETDRS: early treatment diabetic retinopathy study; OCT: optical coherence tomography

Results

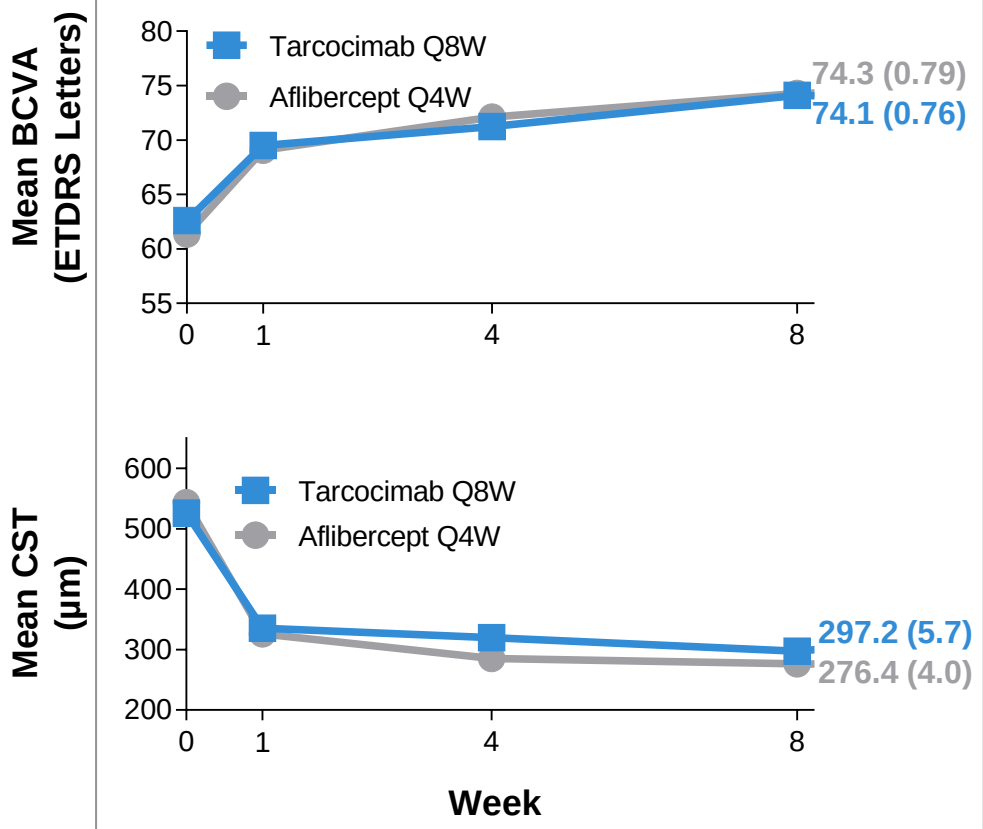
Primary Endpoint Met

Tarcocimab Q8W was non-inferior to aflibercept Q4W in both BRVO and All RVO patients

Tarcocimab achieved comparable vision and anatomical outcomes in BRVO patients, demonstrating non-inferiority to aflibercept Q4W

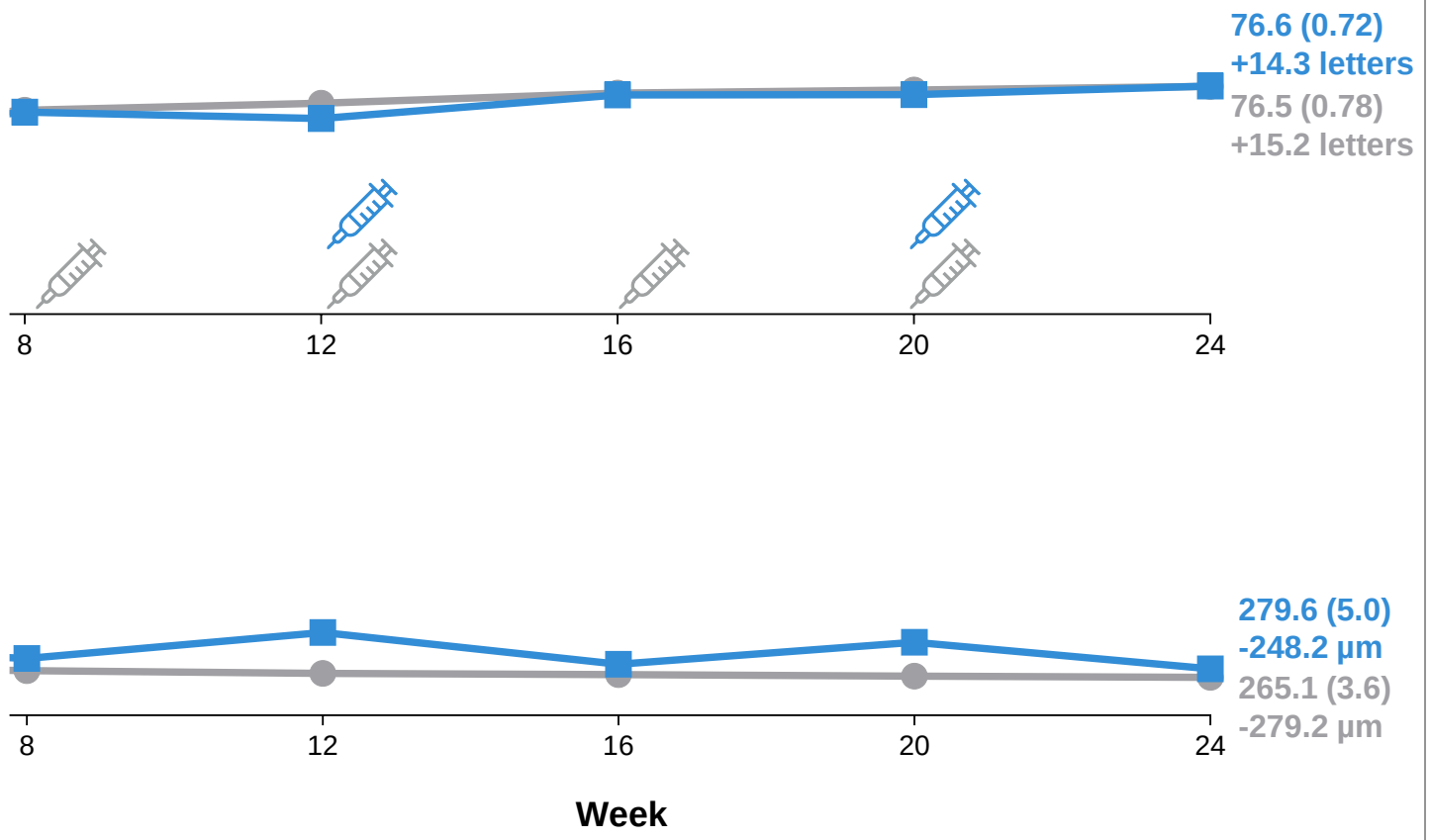
Matched Phase

Strong immediate improvements are seen as early as Week 1



Maintenance Phase

Similar visual and anatomical gains are achieved by tarcocimab from Week 8 to Week 24, with half the doses

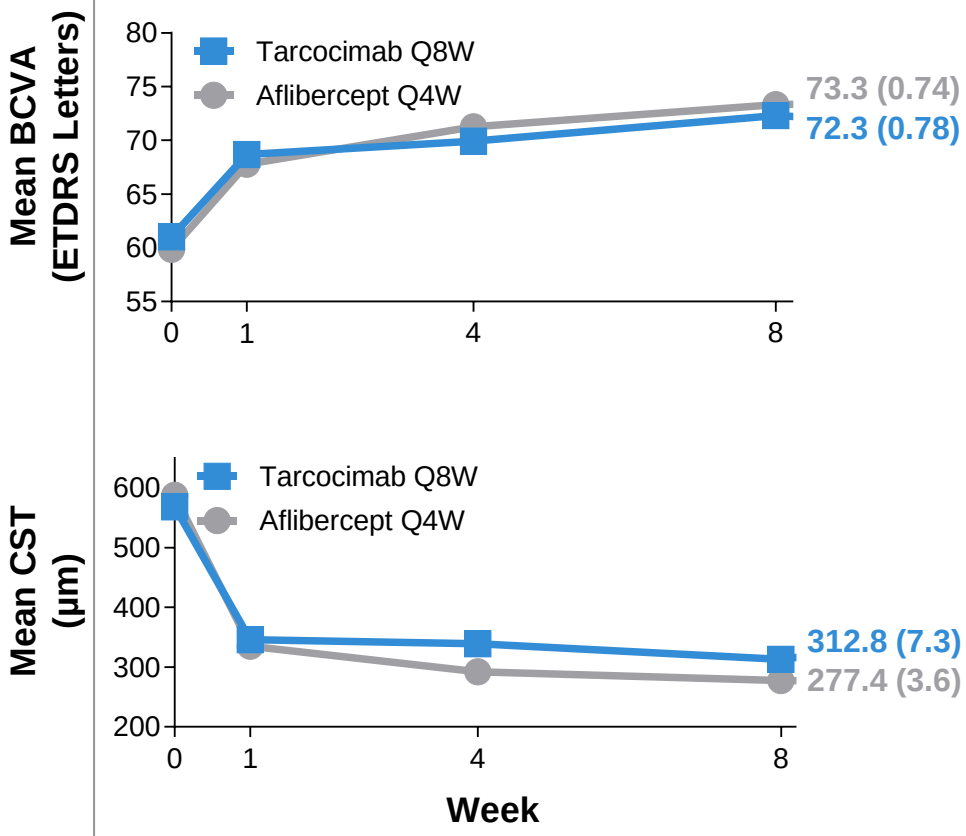


Observed data, graphed as Mean ± Standard Error of the Mean; Week 8 and 24 datapoints are Mean (Standard Error of the Mean). Standard errors are not visible on the graphs.
LS mean BCVA change from baseline at Week 24 (MMRM) was +14.2 letters for Tarcocimab vs. +15.6 letters for aflibercept, with a p-value for non-inferiority of 0.0004.
Tarcocimab Q8W n=220, Aflibercept Q4W n=218 at baseline; BCVA: best-corrected visual acuity; ETDRS: early treatment diabetic retinopathy study; OCT: optical coherence tomography; CST: central subfield thickness.

Similarly, tarcocimab demonstrated non-inferiority to aflibercept Q4W in <u>all RVO patients</u>, achieving comparable vision and anatomical outcomes

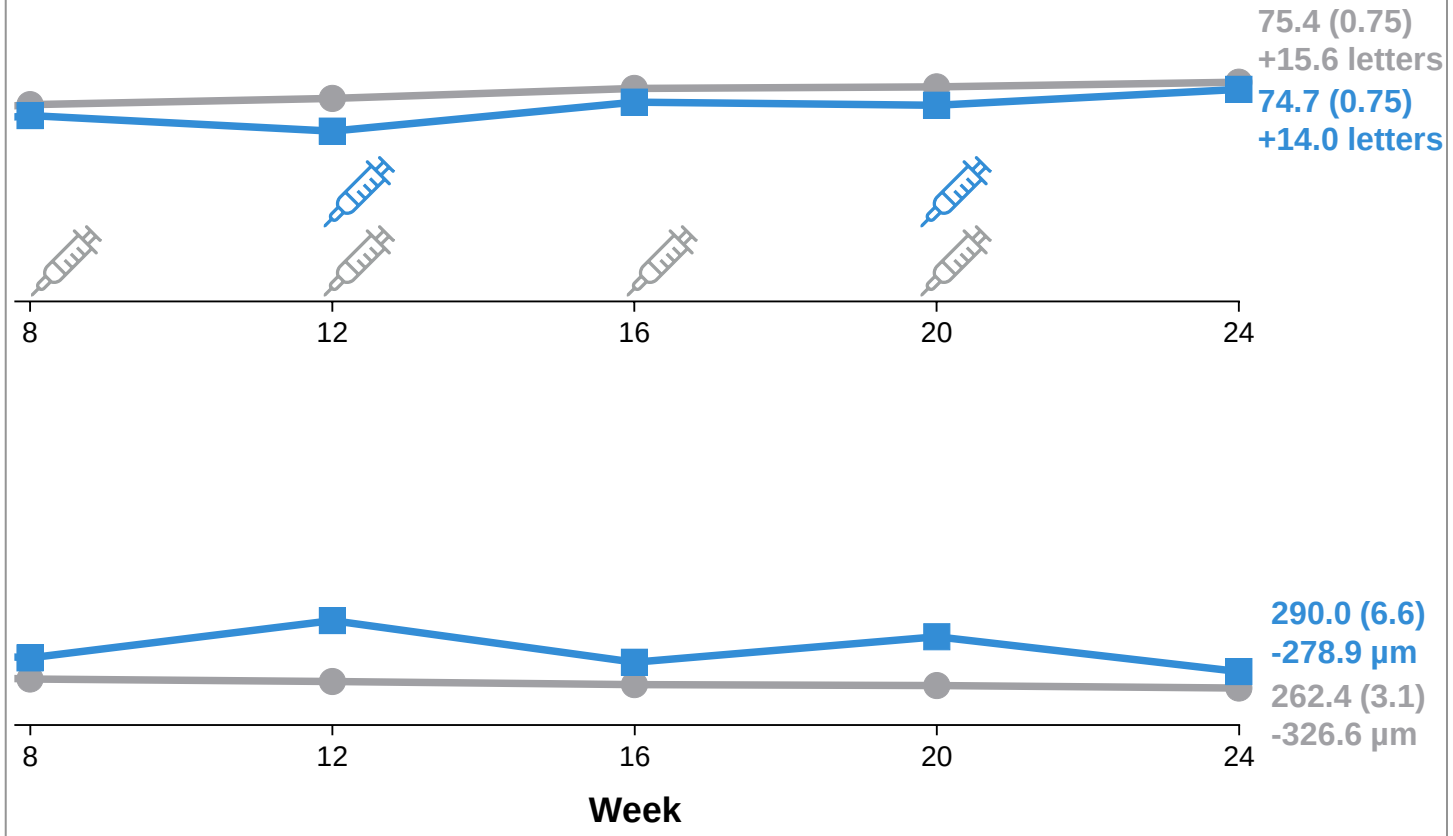
Matched Phase

Strong immediate improvements are seen as early as Week 1



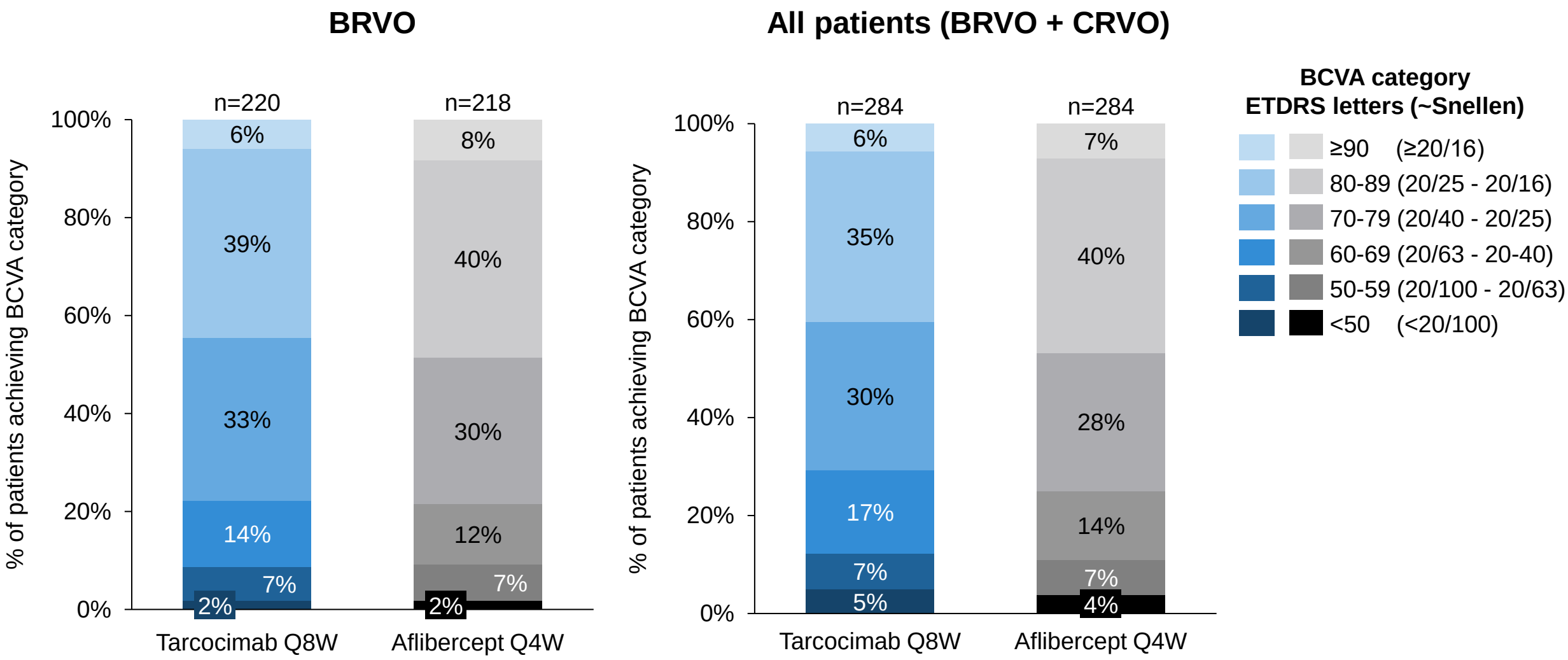
Maintenance Phase

Similar visual and anatomical gains are achieved by tarcocimab from Week 8 to Week 24, with half the doses



Observed data, graphed as Mean ± Standard Error of the Mean; Week 8 and 24 datapoints are Mean (Standard Error of the Mean). Standard errors are not visible on the graphs.
LS mean BCVA change from baseline at Week 24 (MMRM) was +13.0 letters for Tarcocimab vs. +15.5 letters for aflibercept, with a p-value for non-inferiority of 0.0243.
Tarcocimab Q8W n=284, Aflibercept Q4W n=284 at baseline; BCVA: best corrected visual acuity; ETDRS: early treatment diabetic retinopathy study; OCT: optical coherence tomography; CST: central subfield thickness.

Tarcocimab Q8W and aflibercept Q4W had similar distribution of vision outcomes both among BRVO and all RVO patients at Week 24

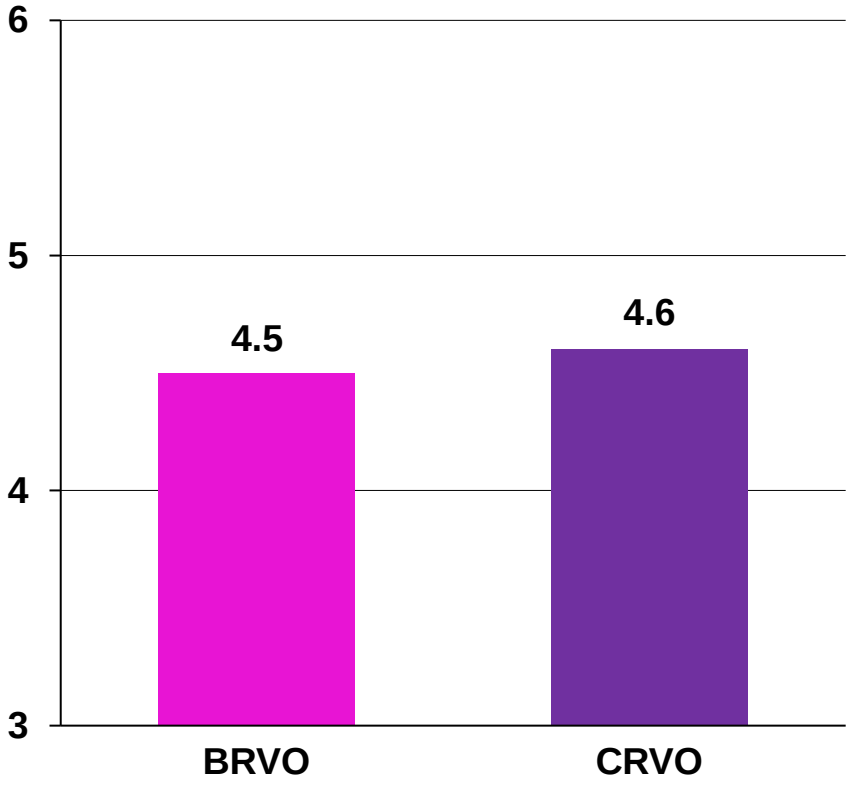


* Observed data. For patients with missing data at Week 24, the last value observed was used. BCVA: best corrected visual acuity; ETDRS: early treatment diabetic retinopathy study

Tarcocimab is the first anti-VEGF therapy to demonstrate non-inferior vision outcomes with fewer doses than the average used in clinical practice

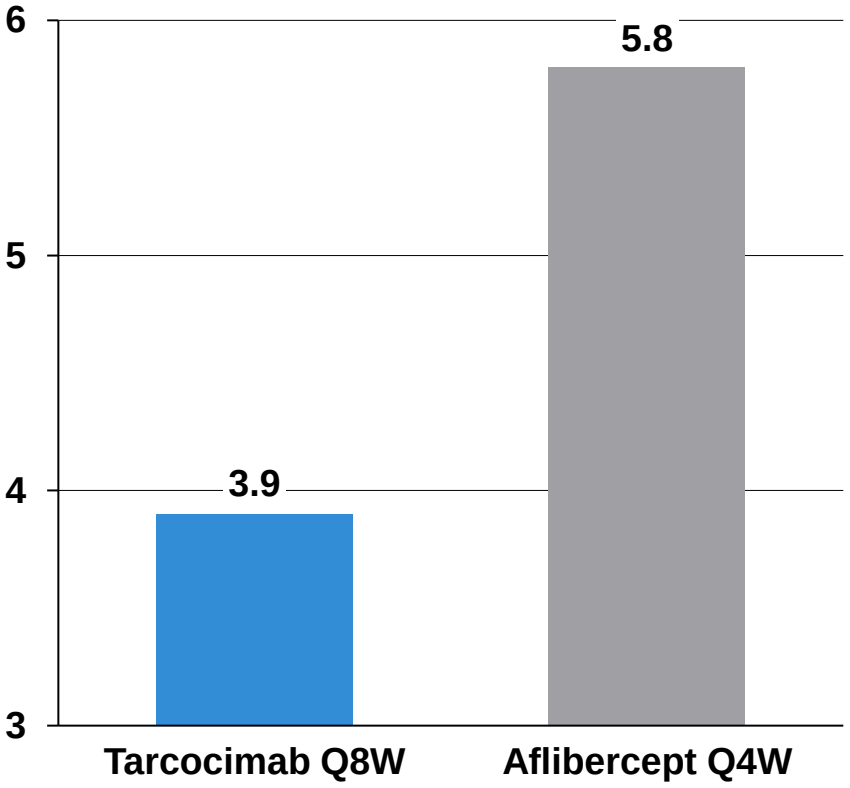
Real World Evidence[1]

Mean number of anti-VEGF injections in the first 6 months of RVO treatment



BEACON

Mean number of injections through Week 24



1. Ciulla T, et al. Br J Ophthalmol 2021;105:1696–1704. doi:10.1136/bjophthalmol-2020-317337. Represents 8,876 BRVO eyes, 6,737 CRVO eyes from Vestrum database. Mean 4.5/4.6 anti-VEGF injections over first 6 months (aflibercept, ranibizumab, or bevacizumab).

Safety: tarcocimab Q8W was well-tolerated, with low rates of adverse events

Intraocular Inflammation in Study Eye up to Week 24	Tarcocimab Q8W (n=284)	Aflibercept Q4W (n=284)
Subjects Reporting at Least 1 Intraocular Inflammation AE	4 (1.4%)	1 (0.4%)
Uveitis	2 (0.7%)	0
Keratic precipitates	1 (0.4%)	0
Vitritis	1 (0.4%)	1 (0.4%)

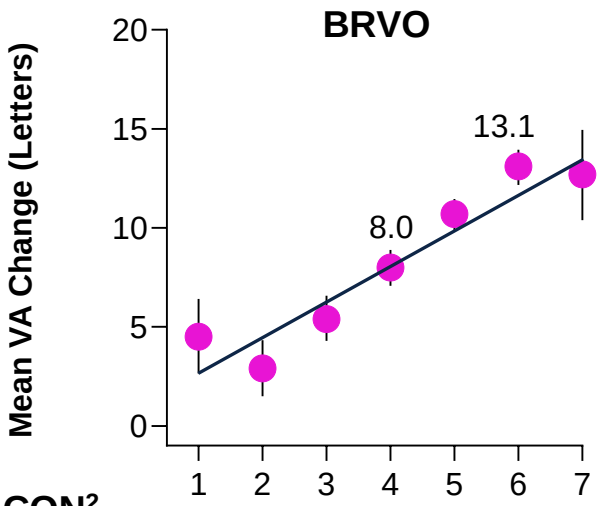
Endophthalmitis (Procedure-Related) in Study Eye up to Week 24	Tarcocimab Q8W (n=284)	Aflibercept Q4W (n=284)
Endophthalmitis (Procedure-Related)	0	0

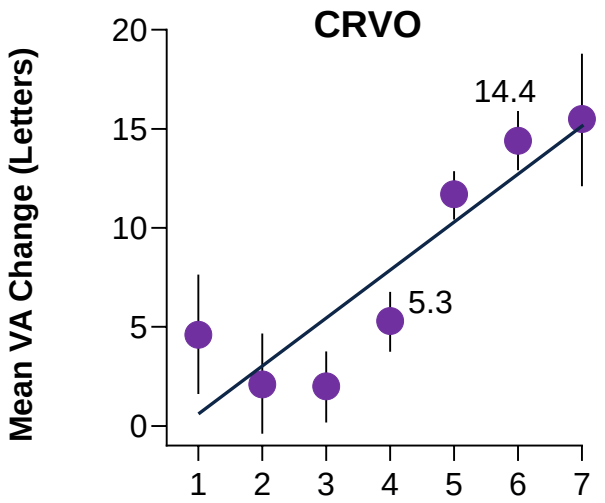
- **Rates of intraocular inflammation were low and comparable between treatment groups, and there were no cases of endophthalmitis**
- **No cases of intraocular inflammation with vasculitis or vascular occlusion were observed**

Results presented for the Week 24 Safety Population. Events are investigator reported. Adverse events are events with start date ≥first study drug date and ≤last study drug date + 28 days.

BEACON Phase 3 study in RVO: Reducing treatment burden from 6 to 4 injections while maintaining vision outcomes is highly meaningful for patients

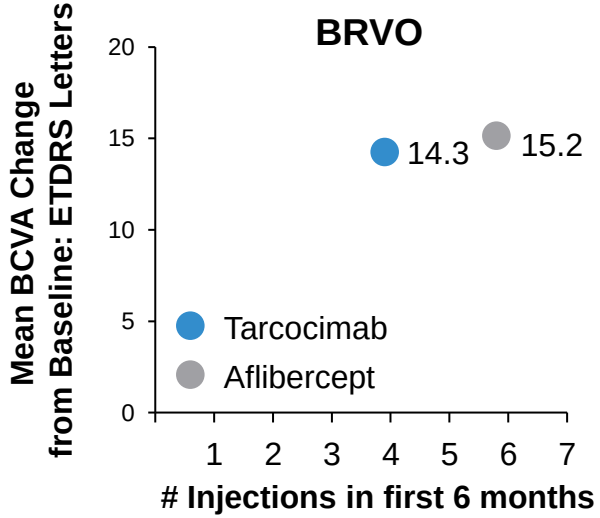
Real World Evidence[1]

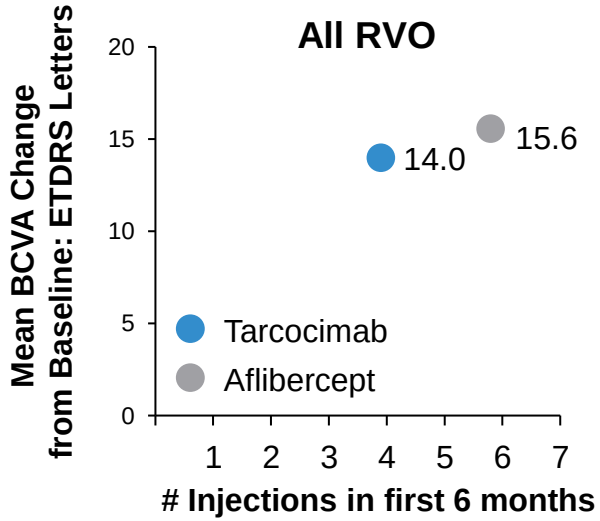




Real world evidence showed that **reducing doses from 6 to 4 results in reduction of visual acuity gains of 39% and 63%** in BRVO and CRVO patients, respectively

BEACON[2]

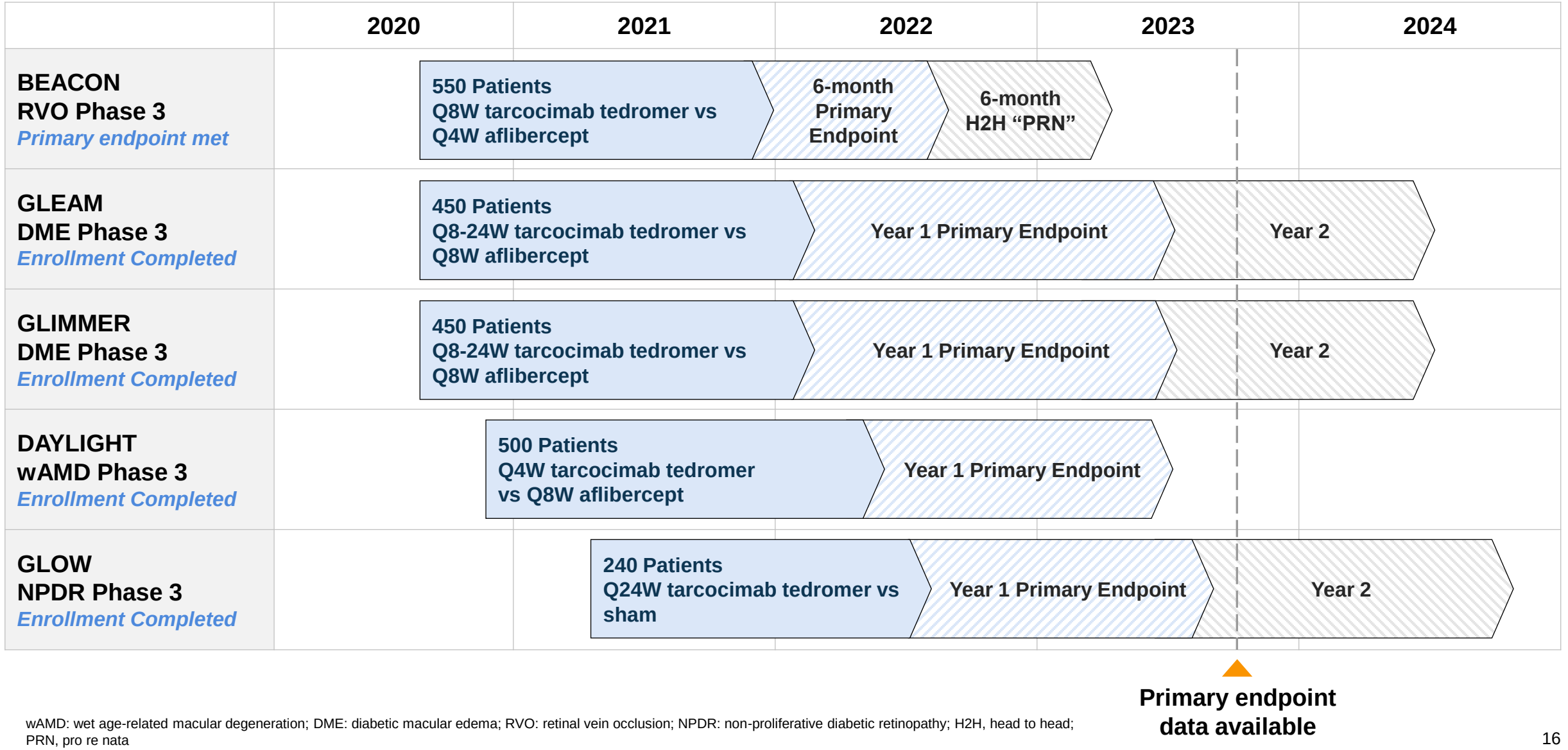




Tarcocimab is the first anti-VEGF therapy to demonstrate comparable vision gains while doubling the treatment interval from monthly to every-other-month dosing

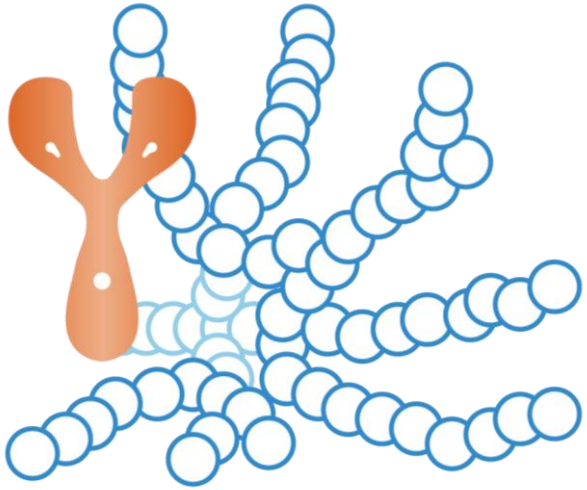
1. Ciulla T, et al. Br J Ophthalmol 2021;105:1696–1704. doi:10.1136/bjophthalmol-2020-317337. Represents 8,876 BRVO eyes, 6,737 CRVO eyes from Vestrum database. Mean 4.5/4.6 anti-VEGF injections over first 6 months (aflibercept, ranibizumab, or bevacizumab). 2. Observed means from BEACON study

Four additional Phase 3 studies of tarcocimab are expected to read out in 2023: DME (two studies), wet AMD and NPDR



wAMD: wet age-related macular degeneration; DME: diabetic macular edema; RVO: retinal vein occlusion; NPDR: non-proliferative diabetic retinopathy; H2H, head to head; PRN, pro re nata

A pipeline of ABCs for retinal diseases: leveraging bispecifics and small molecules on the biopolymer conjugate platform to further address major causes of vision loss



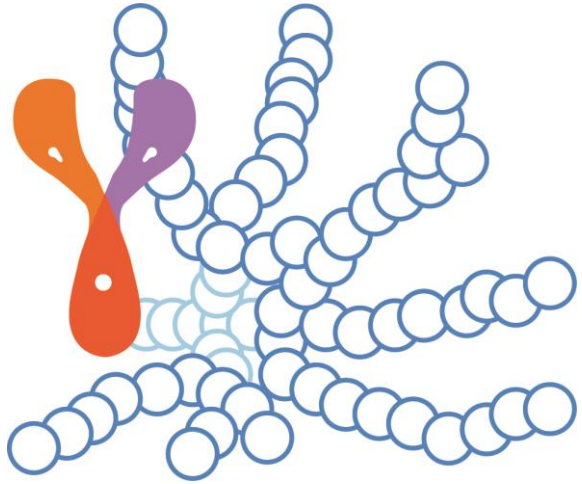
MONOSPECIFIC

1 Molecule, **1 Target**

Antibody conjugated to phosphorylcholine biopolymer

Tarcocimab tedromer (KSI-301)

Inhibits VEGF – In Phase 3 clinical development



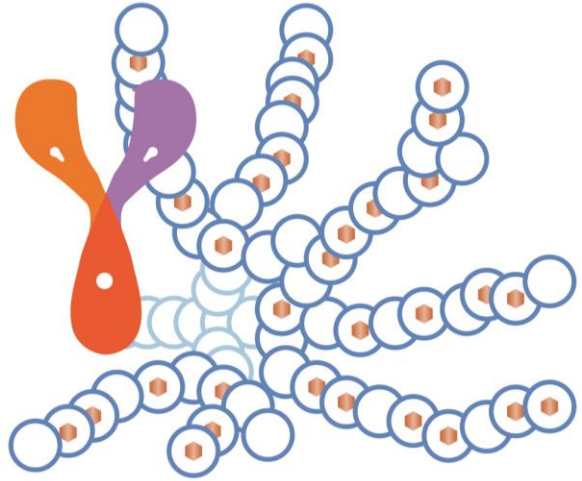
BISPECIFIC

1 Molecule, **2 Targets**

Dual inhibitor trap antibody fusion conjugated to phosphorylcholine biopolymer

KSI-501

Inhibits IL-6 (anti-IL-6 mAb) and VEGF (VEGF trap) for retinal vascular and inflammatory diseases – IND cleared Phase 1 study to commence early 2023



TRIPLET

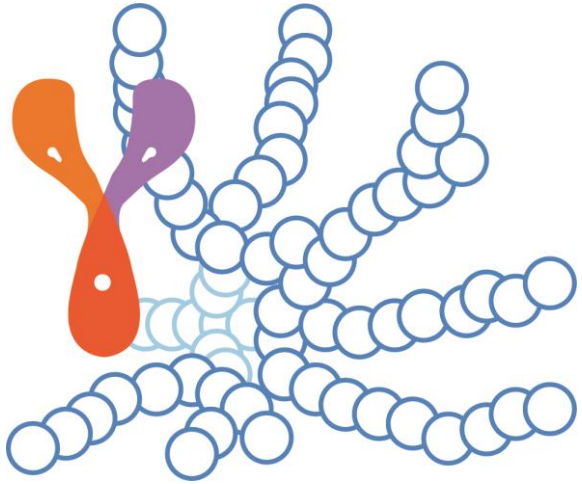
1 Molecule, **3 Targets**

Dual inhibitor trap antibody fusion conjugated to phosphorylcholine biopolymer embedded with 100's of copies of small-molecule drug

KSI-601

For high-prevalence multifactorial diseases, such as dry AMD

KSI-501 is a new category of retinal medicine: first-in-class bispecific ABC that inhibits two powerful pathophysiologic mechanisms in retinal disease – VEGF and IL-6



KSI-501

Trap-antibody fusion for bispecific inhibition of IL-6 and VEGF

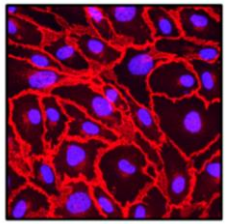
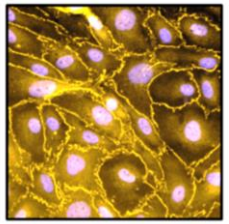
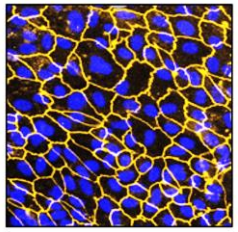
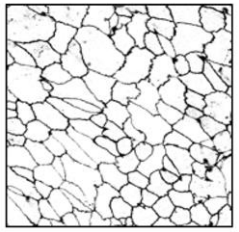
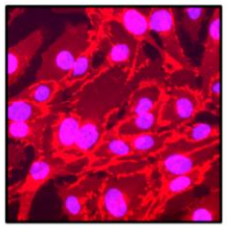
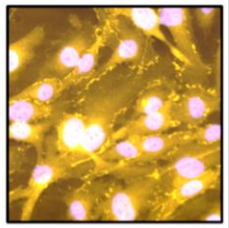
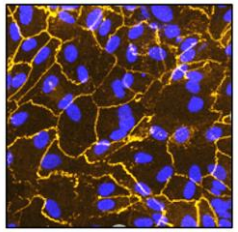
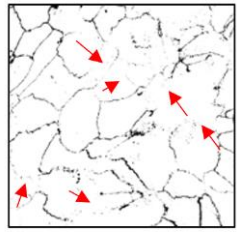
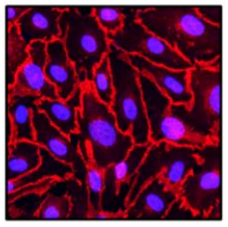
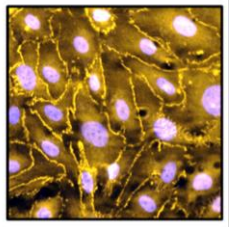
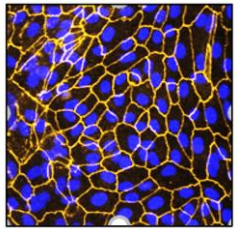
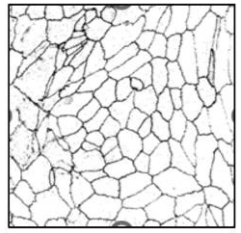
conjugated to phosphorylcholine biopolymer

- **IL-6 is a pro-inflammatory cytokine implicated in the pathophysiology of multiple retinal diseases and is associated with poor anti-VEGF treatment response**
  - Associated with higher incidence of proliferative DR
  - Associated with disease progression in AMD, DR and RVO
  - Implicated in anti-VEGF treatment resistance
  - Upregulates VEGF
  - Stimulates defective angiogenesis, independent of VEGF
- **IND for KSI-501 has cleared**
- **Phase 1 SAD/MAD dose escalation study in DME patients to commence in early 2023**

KSI-501 inhibits angiogenesis and also normalizes inner and outer blood retinal barriers

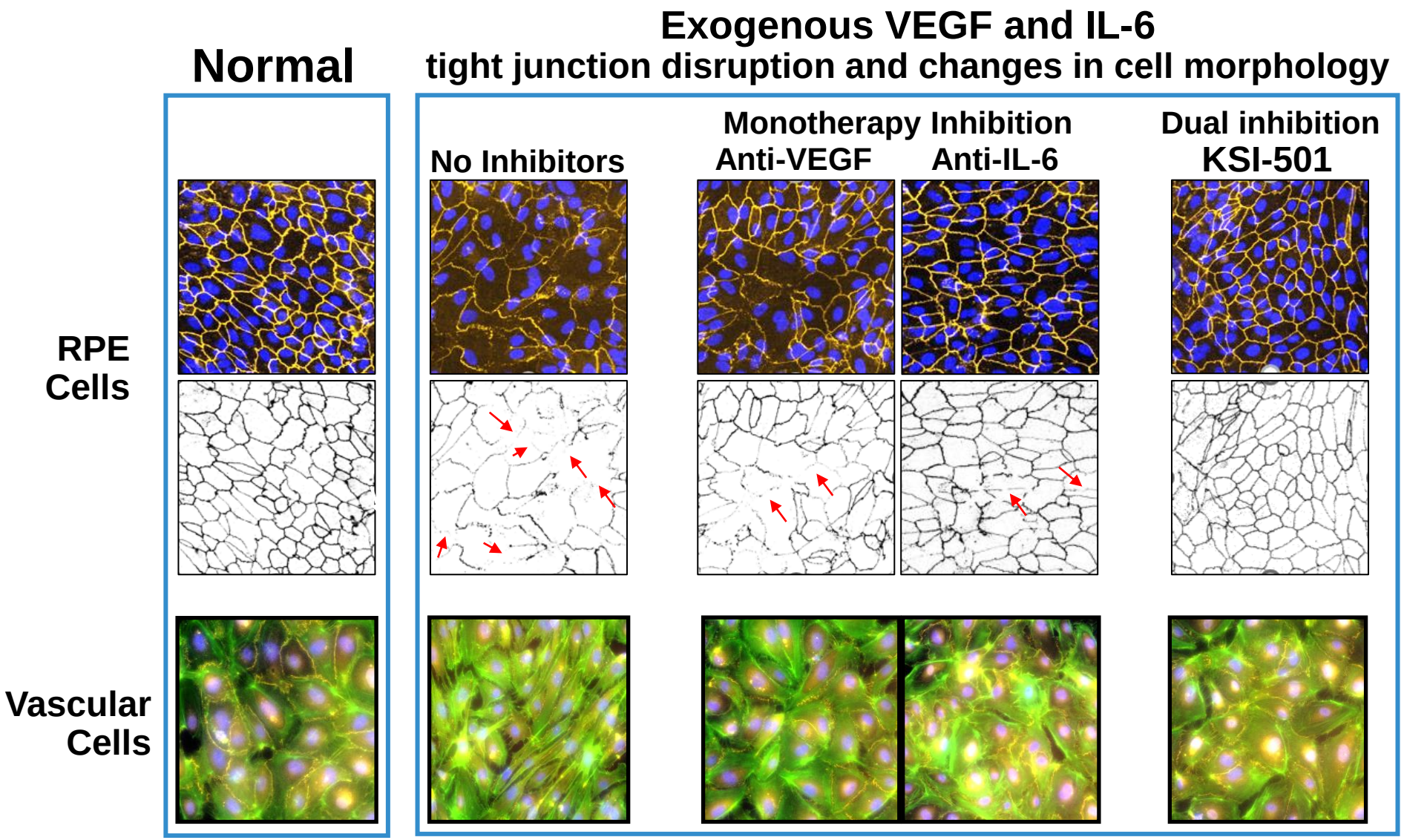
Inner blood-retinal barrier: leakage from vascular endothelium disruption leads to macular edema and hemorrhage[1]

Outer blood-retinal barrier: RPE integrity prevents choroidal vascularization from invading the retina[2]

	Vascular Cells		RPE Cells		
	VE-cadherin	ZO-1	ZO-1		
Normal environment					**Tight junctions containing VE-cadherin and ZO-1 proteins regulate cell permeability in both inner and outer blood-retinal barrier**
With exogenous VEGF and IL-6					**VEGF and IL-6 drive tight junction disruption and changes in cell morphology**
With VEGF and IL-6 + KSI-501					**KSI-501 normalizes VEGF and IL-6 mediated junctional protein loss**

1.Opendenakker et al. (2019). Cell Mol Life Sci 76: 3157-3166. 2. Cunha-Vaz et al. (2011) Eur J Opthamol 21 (Suppl. 6): S3-S9.

Dual inhibition of VEGF and IL-6 by KSI-501 confers superior normalization compared to either anti-VEGF or anti-IL-6 monotherapy alone



In additional studies, KSI-501 has been shown to inhibit endothelial cell proliferation and tube formation to a greater extent than anti-VEGF or anti-IL-6 monotherapy

RPE cells: nuclei in blue, ZO1 (tight junction protein) in yellow. Vascular cells: nuclei in purple, ZO1 (tight junction protein) in yellow, actin in green.

Key Points

BEACON study met primary endpoint	Mean change in BCVA with **tarcocimab Q8W was non-inferior to aflibercept Q4W** in RVO
Similar efficacy, meaningfully fewer doses	Tarcocimab is the **first anti-VEGF therapy to show comparable visual acuity outcomes** to monthly aflibercept **while doubling the treatment interval** for all RVO patients • Matched phase: **strong efficacy** with comparable vision and anatomic improvement as early as Week 1 • Maintenance phase: similar gains from Week 8 to Week 24 with **half the doses**
Data from four additional pivotal studies in 2023	Primary endpoint data from four Phase 3 studies of tarcocimab expected later this year: two studies in DME (GLEAM and GLIMMER), as well as an additional wAMD study (DAYLIGHT) and an NPDR study (GLOW)
KSI-501 - new category of retinal medicine inhibiting VEGF and IL-6 entering clinic	Dual inhibition of VEGF and IL-6 may provide additional clinical benefits in DME, wAMD, uveitic macular edema, and other retinal diseases with an inflammatory component IND for KSI-501 has cleared and dose escalation study expected to begin shortly