KSI-501:
A Novel Bispecific Antibody Biopolymer Conjugate Targeting IL-6 and VEGF

Mark Barakat, M.D.
Retinal Consultants of Arizona

Clinical Trials at the Summit 2023
10 June 2023

Disclosures

- Presenter's Financial Disclosures:
  - Kodiak (C, R)
- This presentation will discuss IRB/IEC approved research of an investigational medicine.

AbbVie Inc[C]
Adverum Biotech[CR]
Alcon[C]
Alimera[C]
Allegro[C]
Allergan[C]
Annexon Biosciences[R]
Apellis[B]
Arctic Vision[C]
Bausch and Lomb[C]
Biogen[C]
Clearside Biomedical[CR]
Coherus Biosciences[C]
EyePoint Pharma[CR]
Gemini Therapeutics[R]
Genentech[BCR]
Graybug[CR]
Gyroscope Therapeutics[R]
Kodiak Sciences[CR]
Novartis[BCR]
NeuBase[E]
Ocular Therapeutix[C]
Oculis[R]
Opthea[CR]
Outlook Therapeutics[C]
Oxular[R]
Oxurion[ER]
Palatin Technologies[C]
Regeneron[B]
RegenxBio[CR]
ReNeuron[R]
RevOpsis Therapeutics[CE]
Ribomic[R]
Roche[C]
Stealth Biotherapeutics[R]
Unity Biotechnology[R]

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

Key Points

Unmet need

Anti-VEGF therapy has transformed the retinal exudative disease landscape, but response to treatment is heterogenous, and treatment burden remains a substantial challenge

Multifactorial etiology

The pathophysiology of retinal vascular and hyperpermeability disorders is multifactorial and multiple cytokines beyond VEGF are thought to be involved

- VEGF and IL-6 are key mediators of inflammation, hyperpermeability and angiogenesis, three major components of pathophysiology in these diseases.

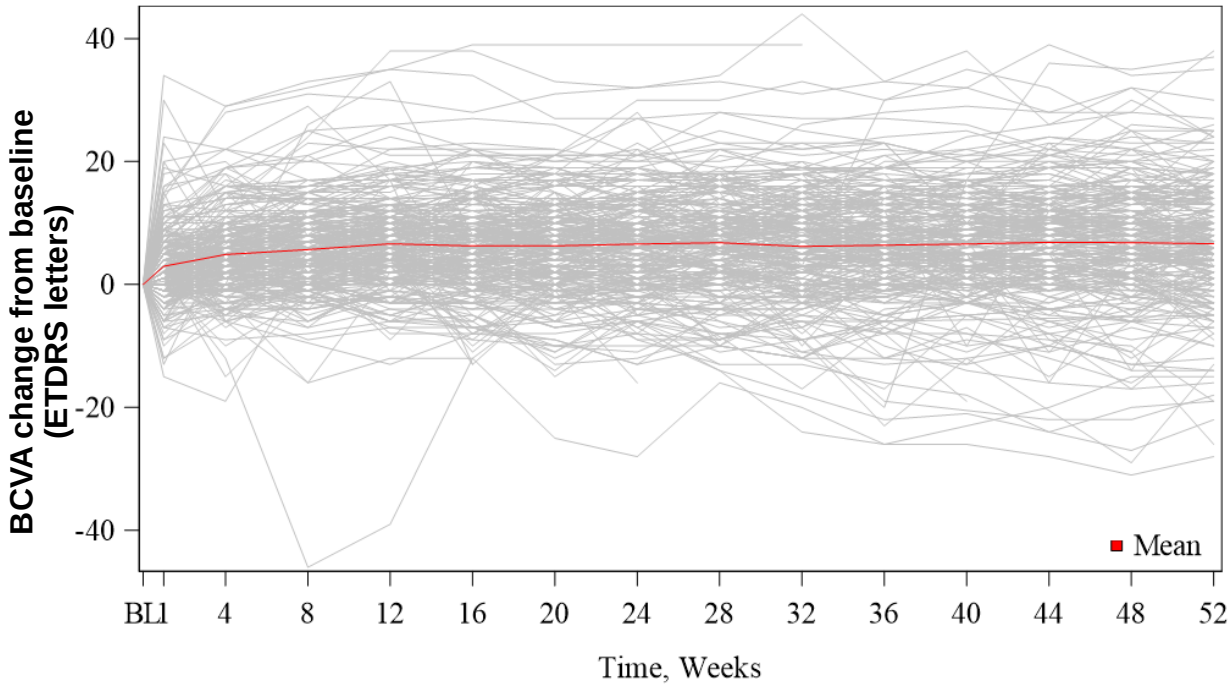
KSI-501 - new category of retinal medicine inhibiting IL-6 and VEGF

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

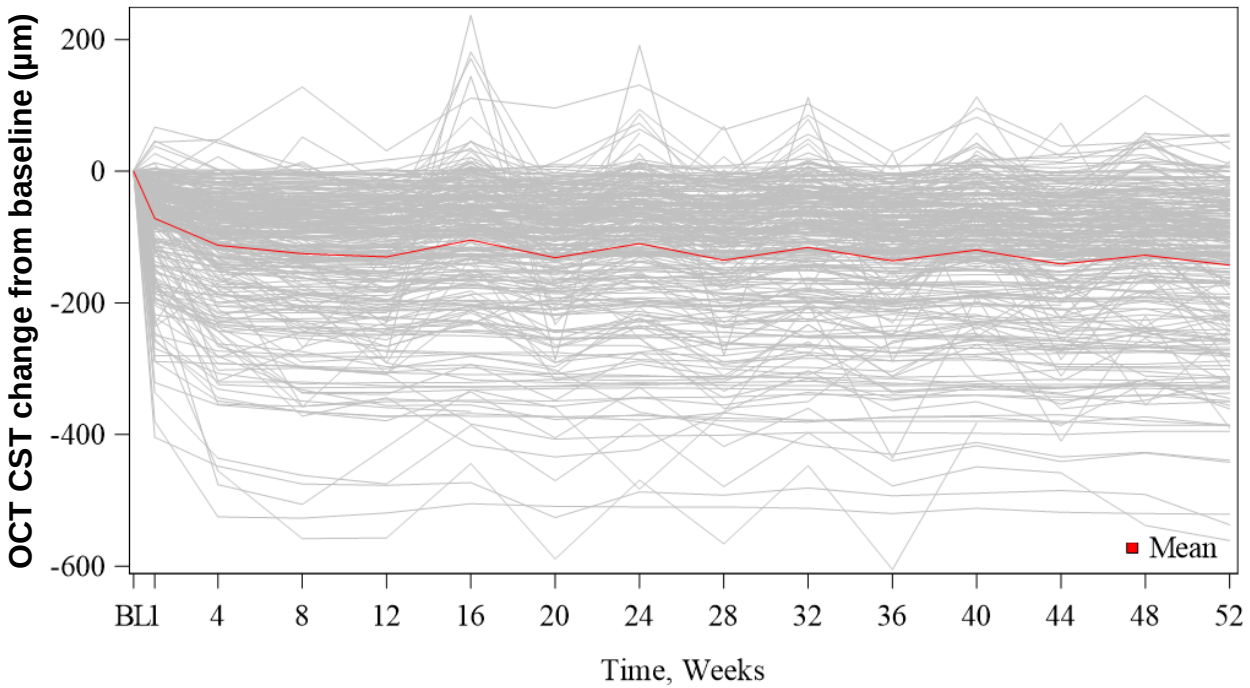
First-in-human Phase 1 multiple ascending dose study is currently ongoing in the US, initially in DME patients. Additional disease cohorts anticipated later in 2023.

Substantial patient-to-patient variability is the norm for patients treated with anti-VEGF monotherapy

BCVA change from baseline during year 1 for individual patients treated with Q8W aflibercept



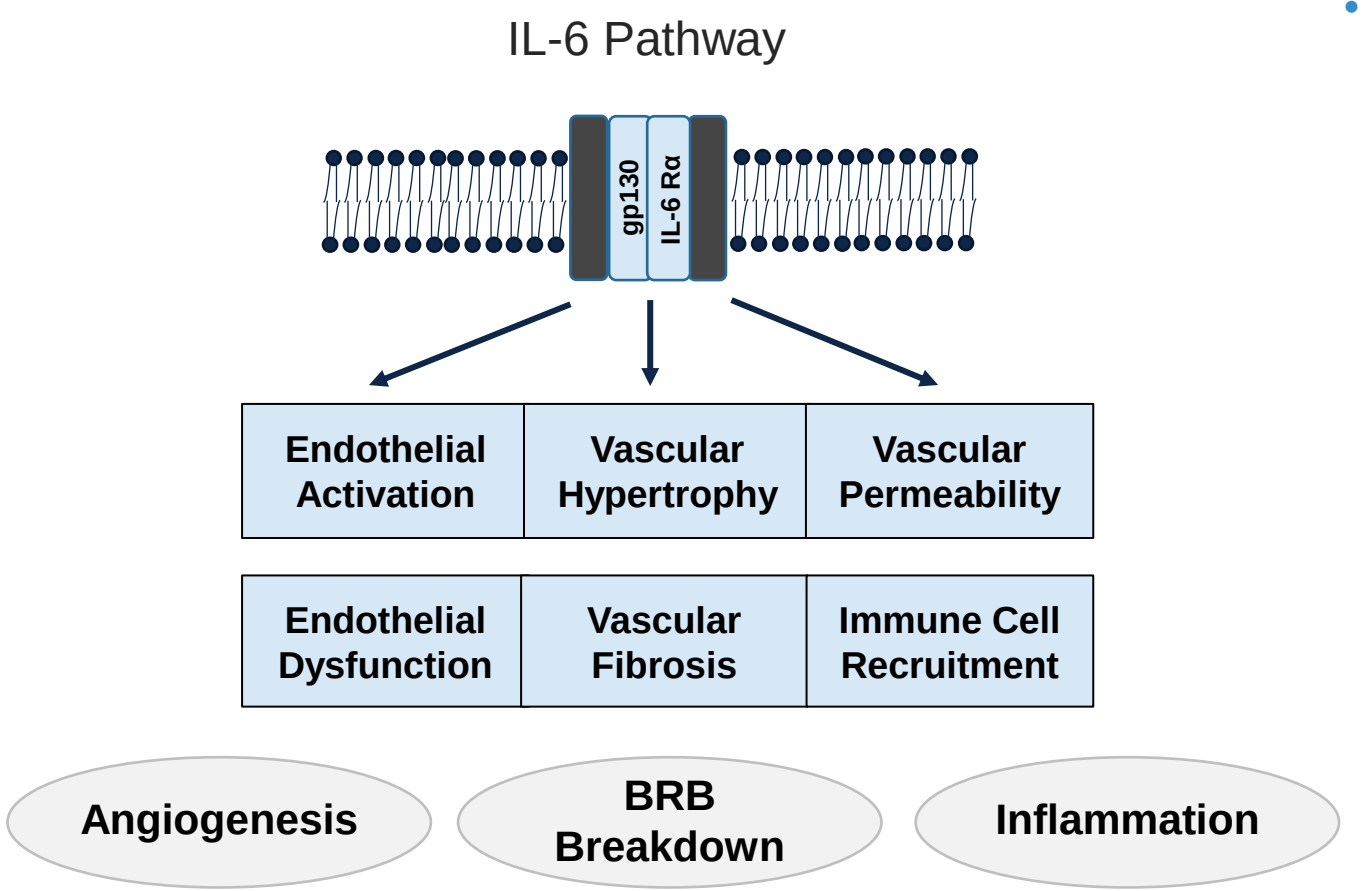
OCT CST change from baseline during year 1 for individual patients treated with Q8W aflibercept



Individual patient variability underlies the mean BCVA and OCT curves for patients treated with anti-VEGF monotherapy, suggesting need for additional mechanisms of action

Aflibercept-treated subjects completing Year 1 of Phase 2b/3 study of tarcocimab tedromer in wet AMD, NCT04049266.
BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; OCT, optical coherence tomography; CST, central subfield thickness

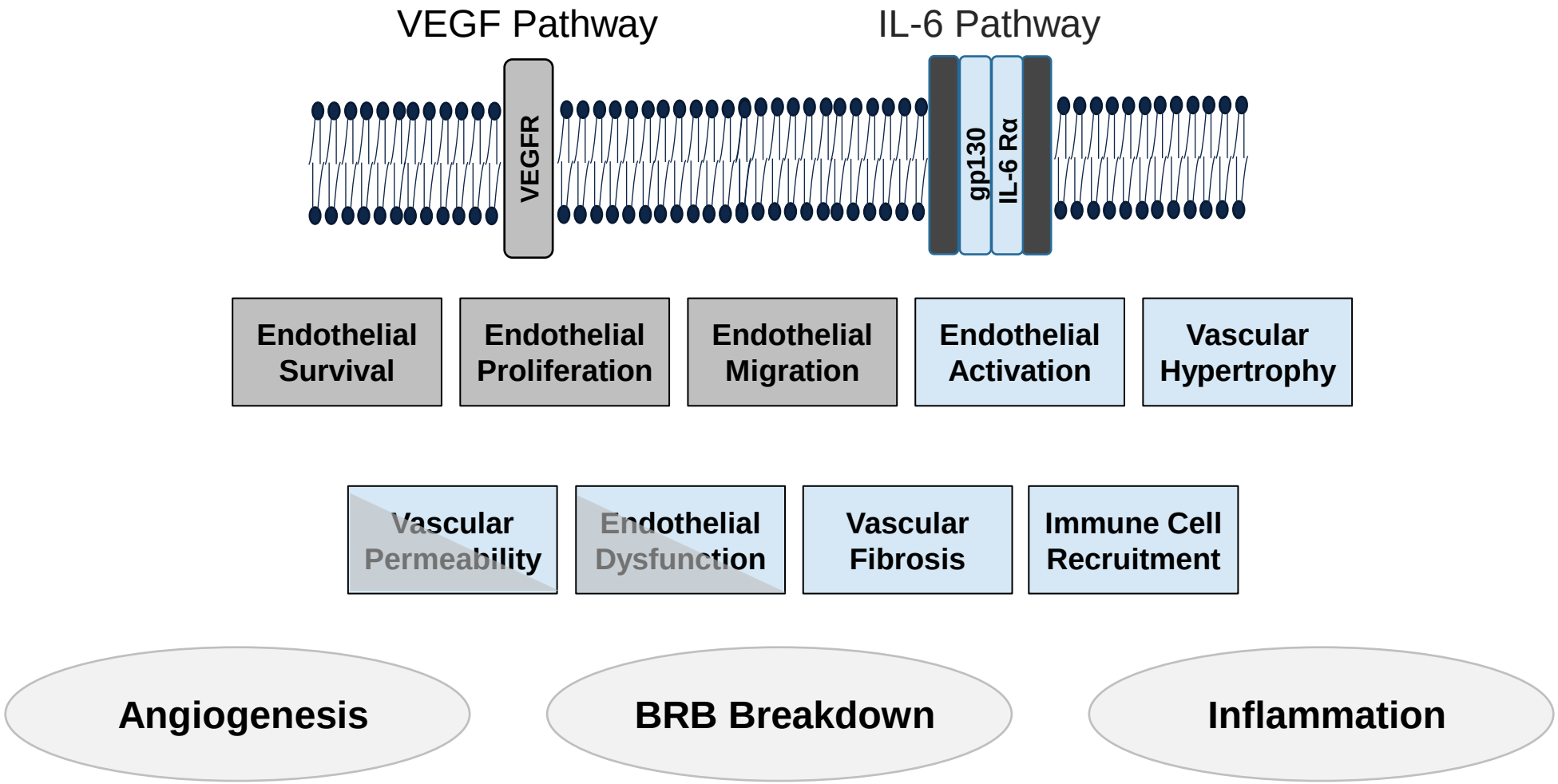
The pathophysiology of retinal vascular and hyperpermeability disorders involves multiple cytokines



- **IL-6 is a pro-inflammatory cytokine and immune growth factor 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

BRB: blood retinal barrier

KSI-501 is a first-in-class bispecific that inhibits two powerful pathophysiologic mechanisms in retinal disease – IL-6 and VEGF



BRB: blood retinal barrier

By leveraging the Antibody Biopolymer Conjugate (ABC) platform KSI-501 has an increased molecular size, and in turn an extended ocular half-life

BISPECIFIC

lgG1 anti-IL-6 Antibody
+ VEGF Trap
Fusion Protein

BIOPOLYMER

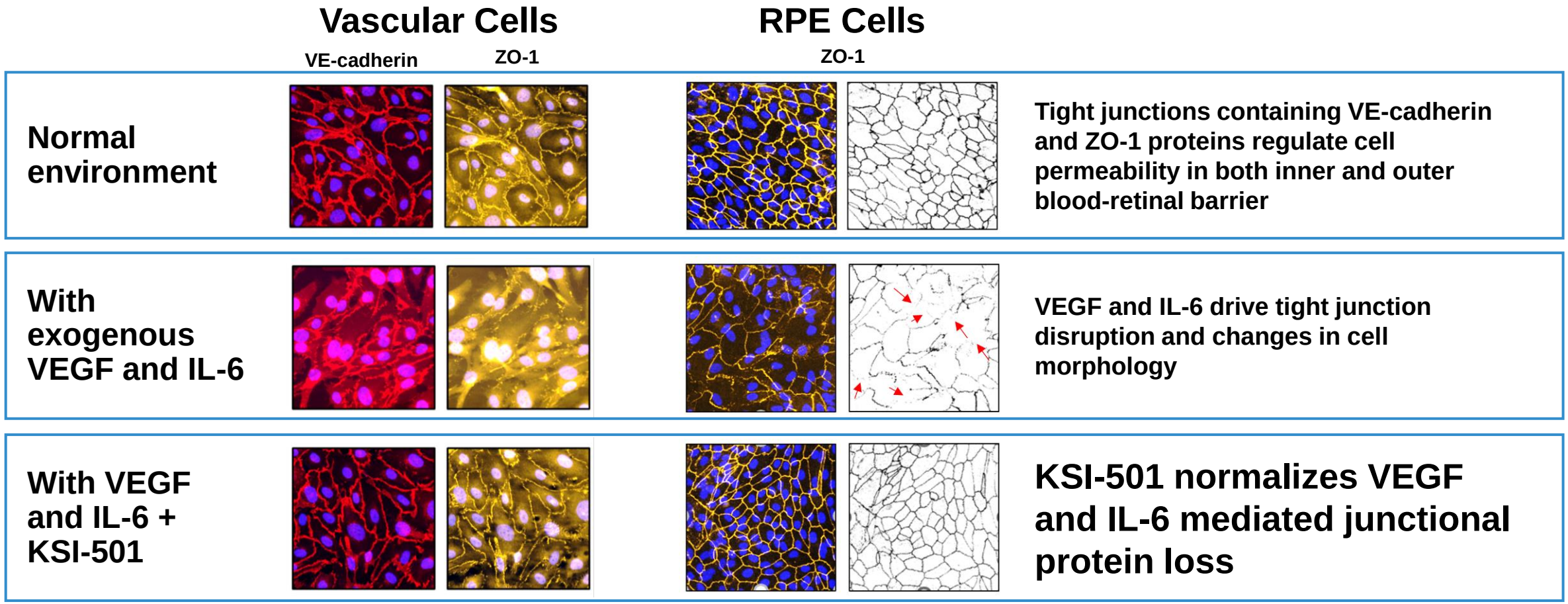
Branched, Optically Clear,
High Molecular Weight
Phosphorylcholine Polymer

CONJUGATE

KSI-501 is a Trap - Antibody ABC that blocks VEGF/PlGF and IL-6

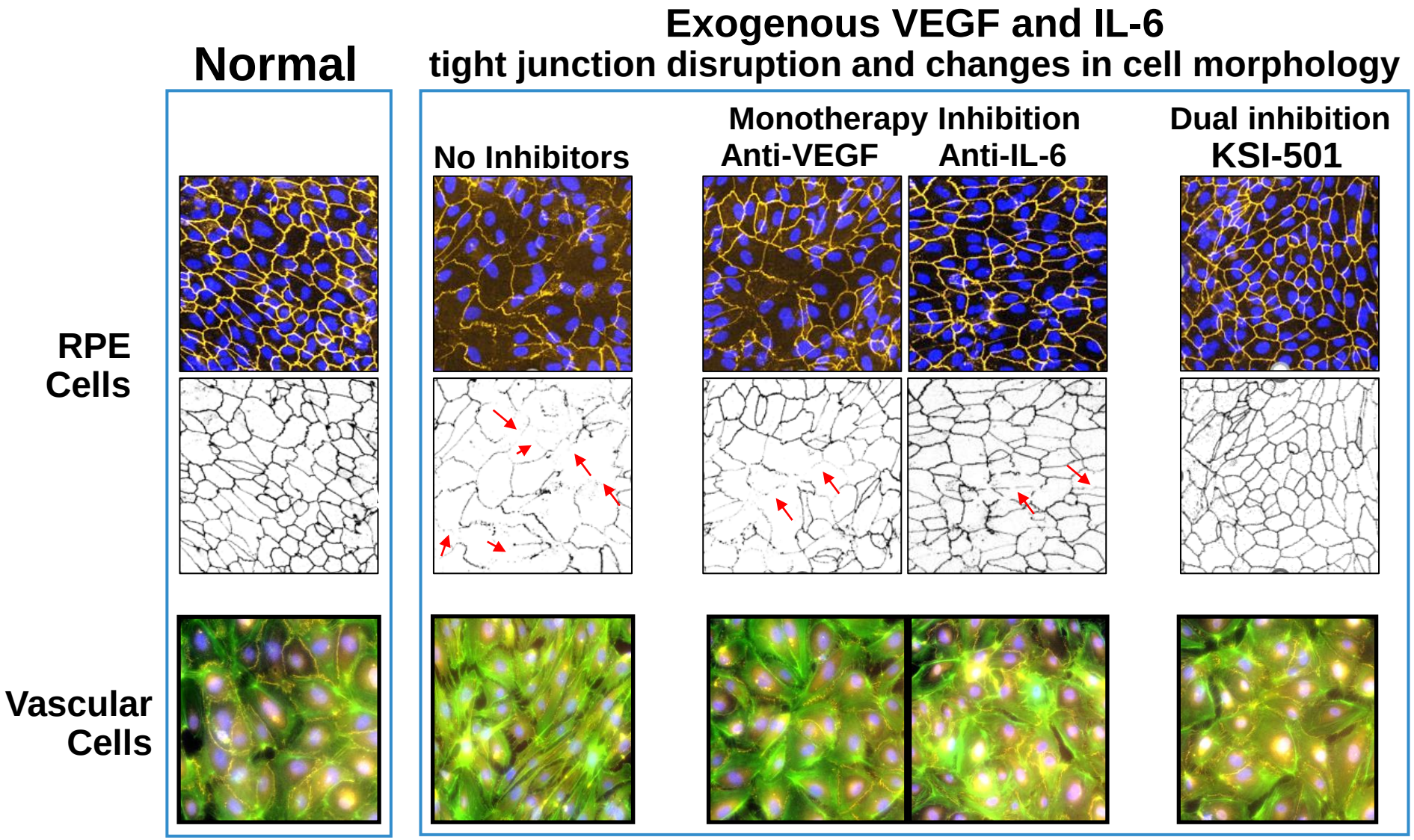
KSI-501 inhibits angiogenesis and normalizes the inner and outer blood retinal barriers

- **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]



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.
K Williams et al, "Biological Benefits of KSI-501: Novel Bispecific Anti-Inflammatory and Anti-Angiogenic Therapy for the Treatment of both Retinal Vascular and Inflammatory Diseases" Poster 2215 at 2023 ARVO Annual Meeting

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.

K Williams et al, "Biological Benefits of KSI-501: Novel Bispecific Anti-Inflammatory and Anti-Angiogenic Therapy for the Treatment of both Retinal Vascular and Inflammatory Diseases" Poster 2215 at 2023 ARVO Annual Meeting

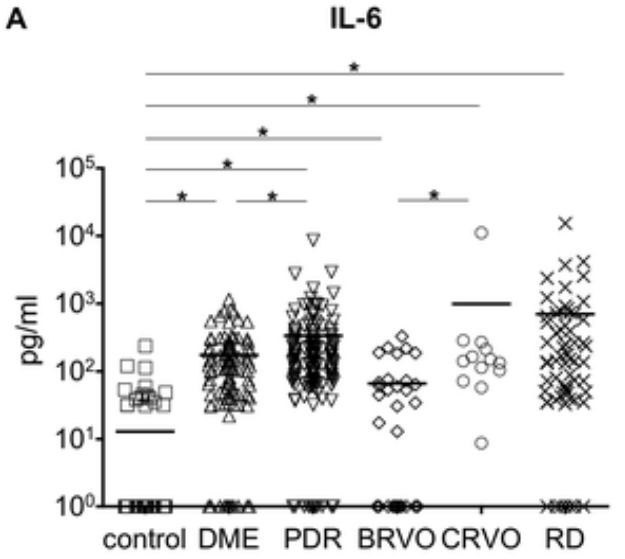
Dual inhibition of IL-6 and VEGF provides ample opportunity for clinical use of KSI-501 across a range of retina disease indications

- Preclinical and clinical data support the role of IL-6 as a key inflammatory modulator in retinal vascular diseases and seems to be related to the potential response to VEGF inhibition alone.
- In Uveitic Macular Edema, the underlying inflammatory component of the pathophysiological process is not addressed by inhibiting VEGF alone.

Potential Indications for KSI-501

DME	wAMD	Uveitic Macular Edema
Non-Proliferative Diabetic Retinopathy	Retinal Vein Occlusion	Uveitis

Concentration of IL-6 in the vitreous cavity of patients with retinal vascular disease



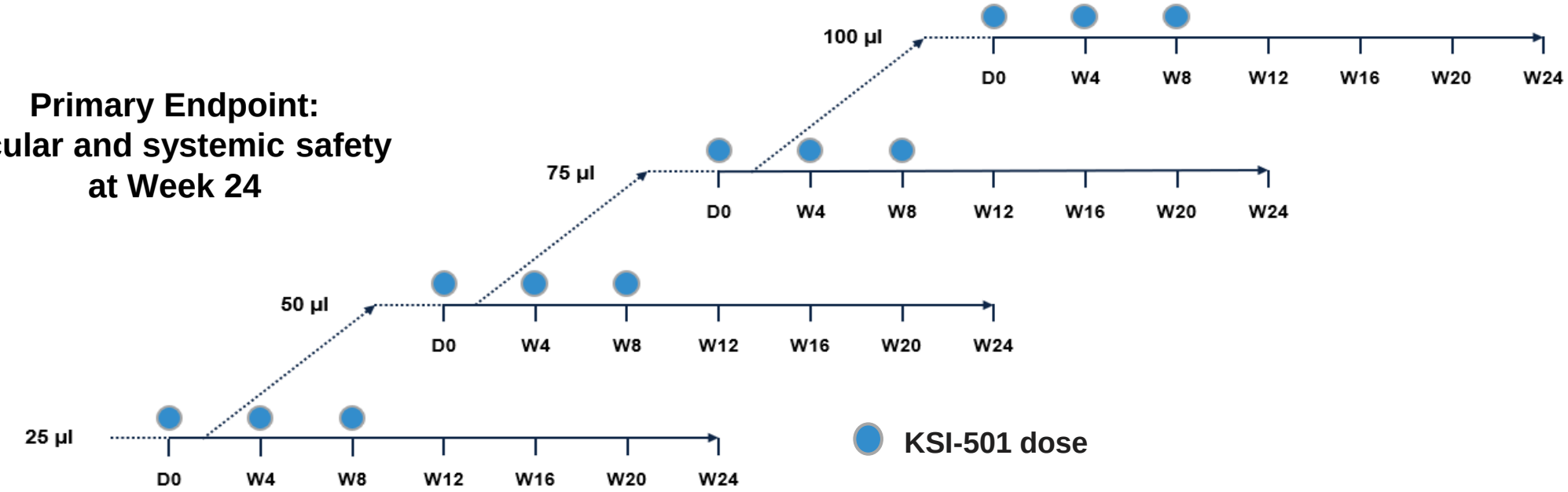
	IL-6
Control	12.1(<30–206.8)
DME	174(<30–1152)
PDR	330.1(<30–8630)
BRVO	65.6(<30–326)
CRVO	985.4(<30–11103)
RRD	701.6(<30–15381)

Values are given as mean (range) in pg/ml with detection limit

Yoshimura T, Sonoda KH, Sugahara M, Mochizuki Y, Enaida H, et al. (2009) Comprehensive Analysis of Inflammatory Immune Mediators in Vitreoretinal Diseases. PLOS ONE 4(12): e8158. https://doi.org/10.1371/journal.pone.0008158

KSI-501 is now being evaluated in a phase 1 multiple ascending dose study in patients with diabetic macular edema – plan to study additional disease indications later this year

Primary Endpoint:
Ocular and systemic safety at Week 24



Key Inclusion Criteria

Adults ≥21 years of age
Diabetes mellitus type 1 and 2 (HbA1c ≤12%)
Vision loss due to DME
- BCVA between 25 and 70 ETDRS letters (20/40 – 20/320 Snellen)
- DME (CST 320 microns)

Treatment naïve or previously treated with defined washout period

- Multiple ascending dose design
- Underway at 5 sites in the US
- 3 subjects planned to be enrolled for each dosing group, with option for expansion of each group if indicated
- Each subject receives 3 monthly doses and will be followed for 24 weeks total

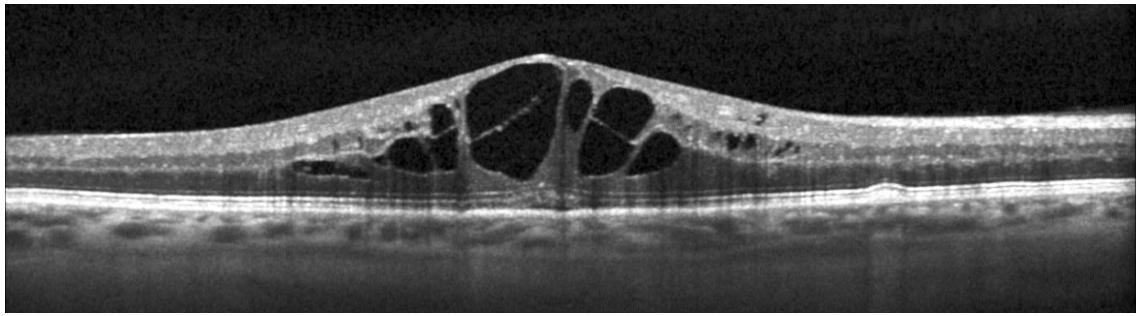
HbA1c: Hemoglobin A1c; DME: Diabetic Macular Edema; BCVA: best-corrected visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; CST: Central Subfield Thickness; D: Day; W: Week

KSI-501 Phase 1 Study

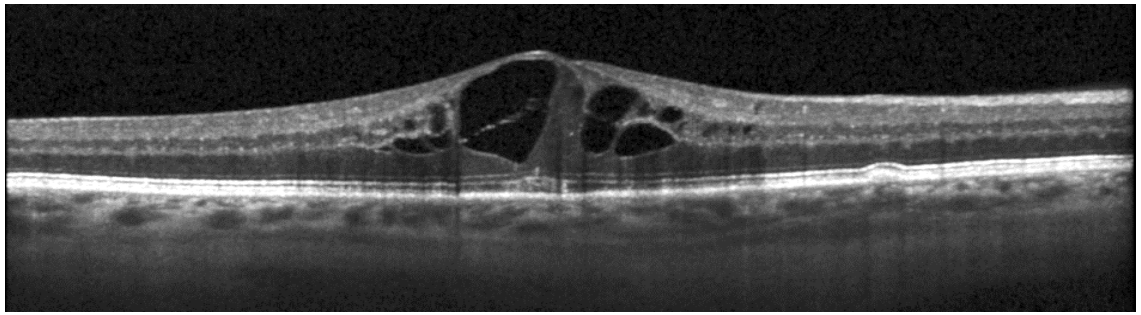
Early clinical cases from ongoing dose escalation

Study KS501P101 - Clinical Case – lowest dose tested (25 µL)

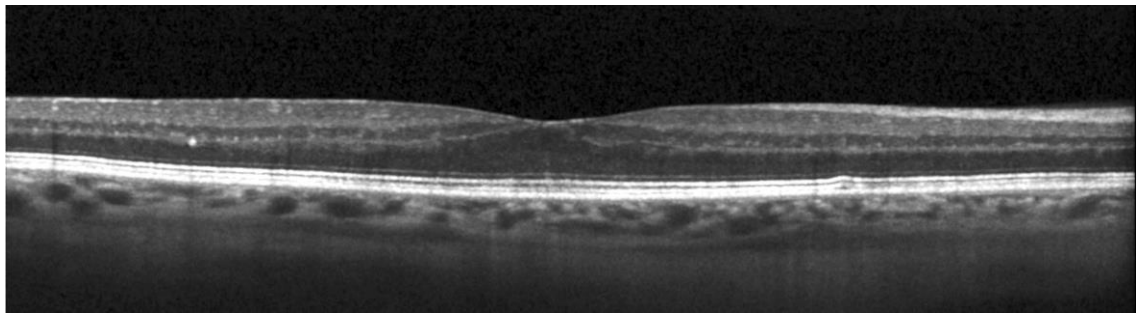
Day 1
70 Letters
641 microns



Week 1
+9 Letters
-79 microns

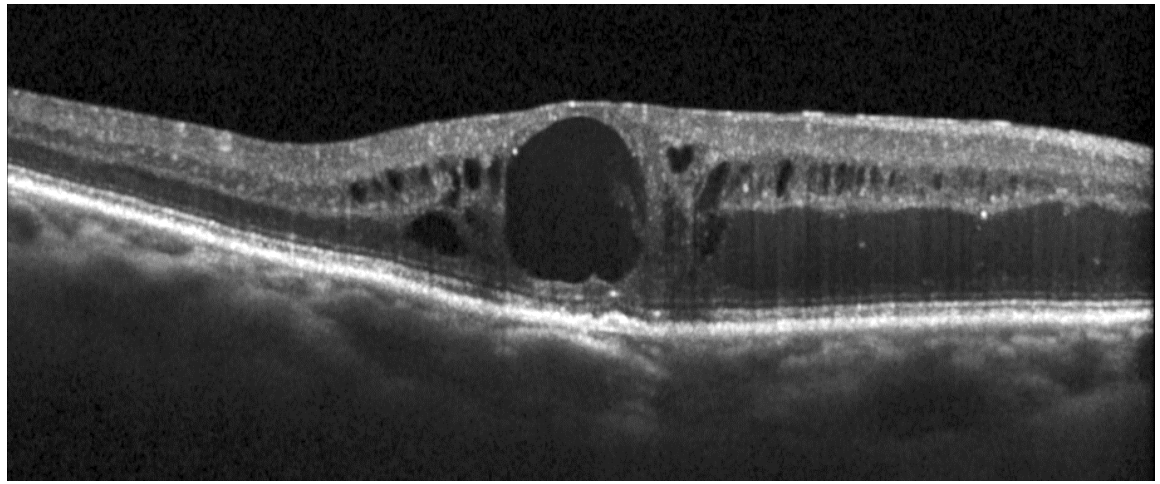


Week 4
+12 Letters
-269 microns

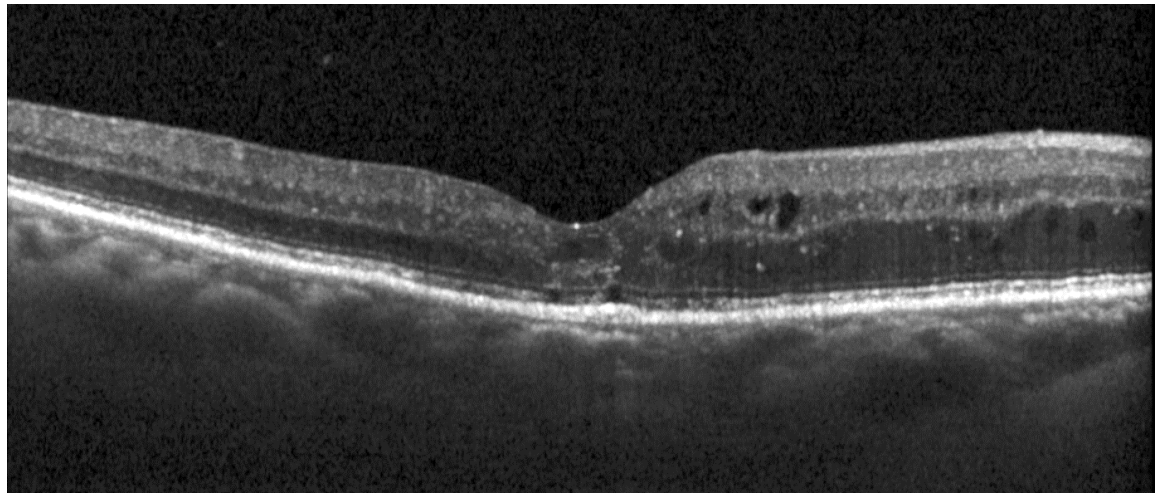


Study KS501P101 - Clinical Case mid-level dose (50 µL)

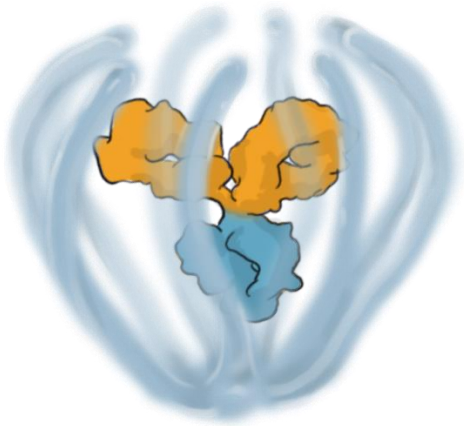
Day 1
35 Letters
609 microns



Week 1
+5 Letters
-277 microns



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



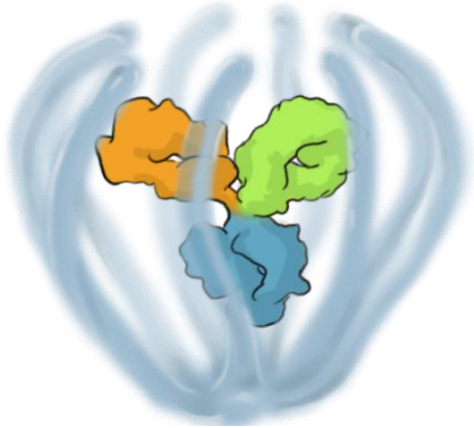
MONOSPECIFIC

1 Molecule, **1 Target**

Antibody conjugated to phosphorylcholine biopolymer

Tarcocimab tedromer (KSI-301)

Inhibits VEGF – In Phase 3 clinical development



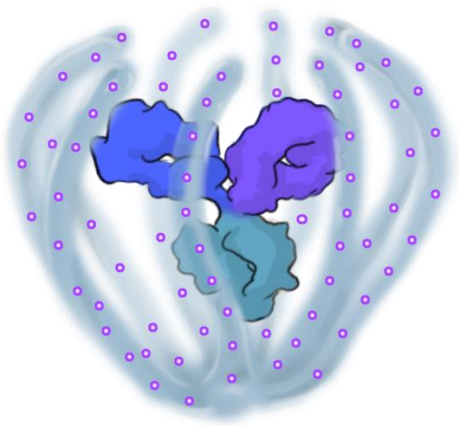
BISPECIFIC

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 – Phase 1 study ongoing



TRIPLET

1 Molecule, **Many Targets**

A new generation of multi-mechanism, multi-modality targeted therapy – biologic embedded with 100’s of copies of small-molecule drugs

KSI-601

For high-prevalence multifactorial diseases

Key Points

Unmet need

Anti-VEGF therapy has transformed the retinal vascular disease landscape, but response to treatment is heterogenous, and treatment burden remains a substantial challenge

Multifactorial etiology

The pathophysiology of retinal vascular and hyperpermeability disorders is multifactorial and multiple cytokines beyond VEGF are thought to be involved

- IL-6 and VEGF are key mediators of inflammation, hyperpermeability and angiogenesis, the three main components driving the pathogenesis of neovascular retinal diseases.

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

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

First-in-human Phase 1 multiple ascending dose study is currently ongoing in the US, initially in DME patients. Additional disease cohorts anticipated later in 2023.