KSI-501 Bispecific Anti-VEGF Anti-IL-6 Antibody Biopolymer Conjugate: First Time Results of the Multiple Ascending Dose Phase 1 Study

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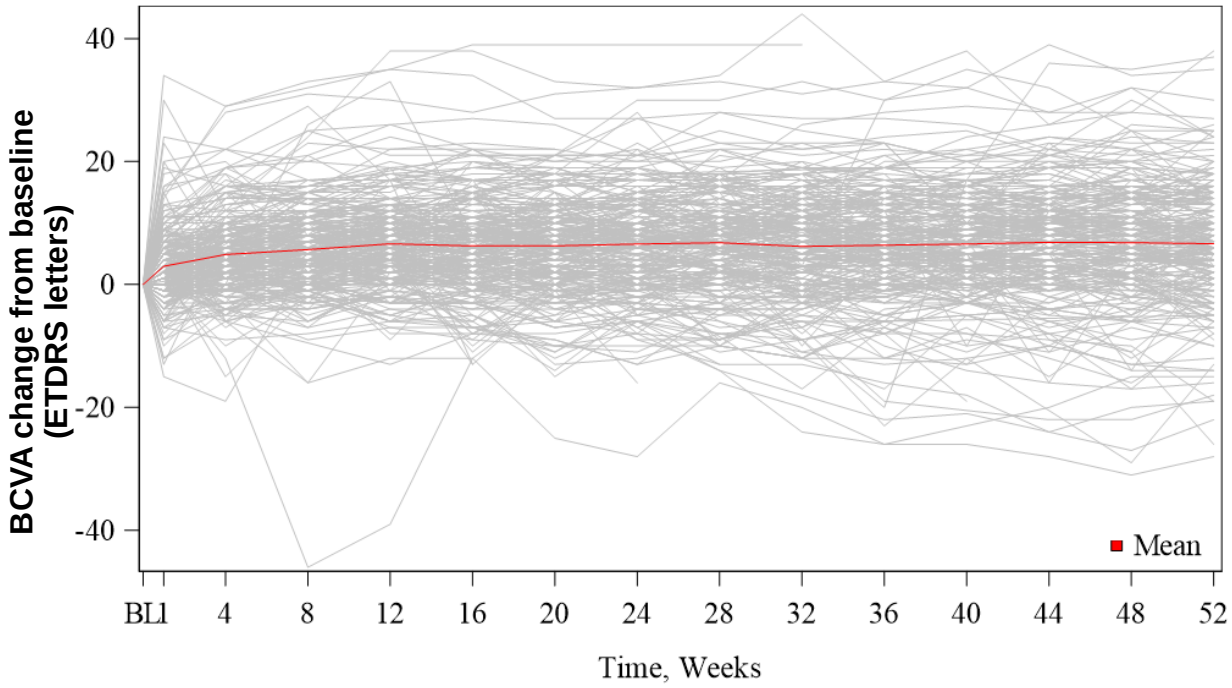
Disclosures

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

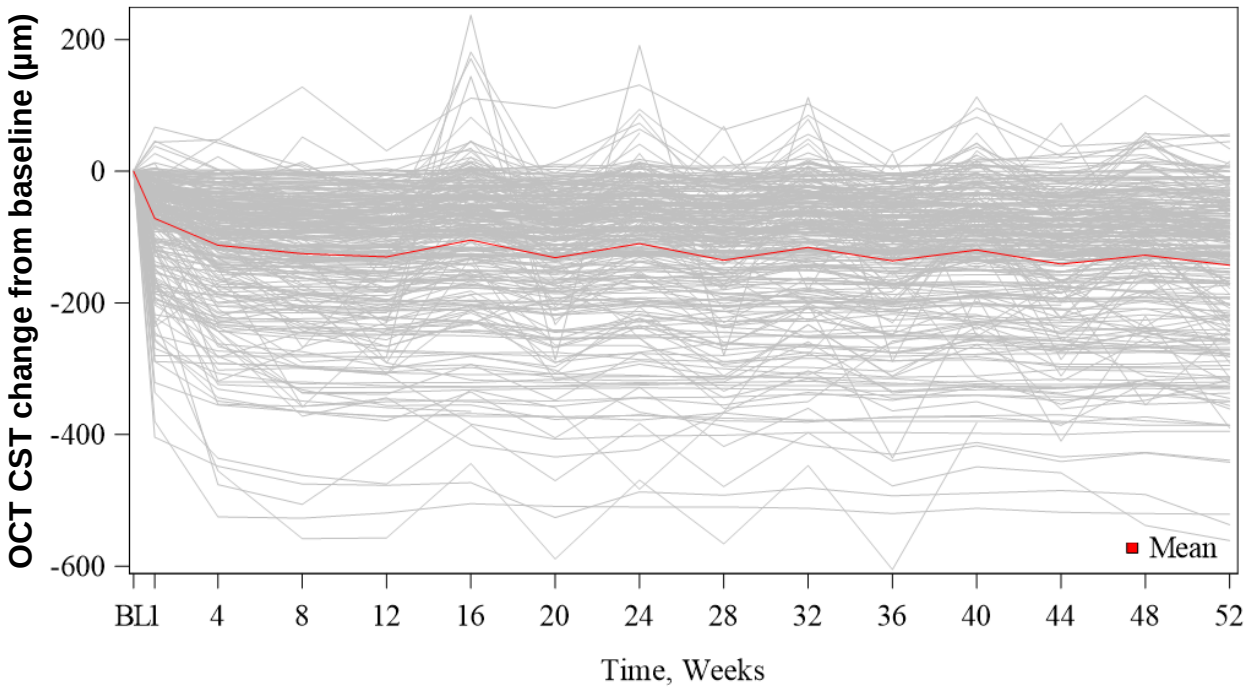
(C): Consultant; (S): Stock/shareholder; (R): Grants/Research Support

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



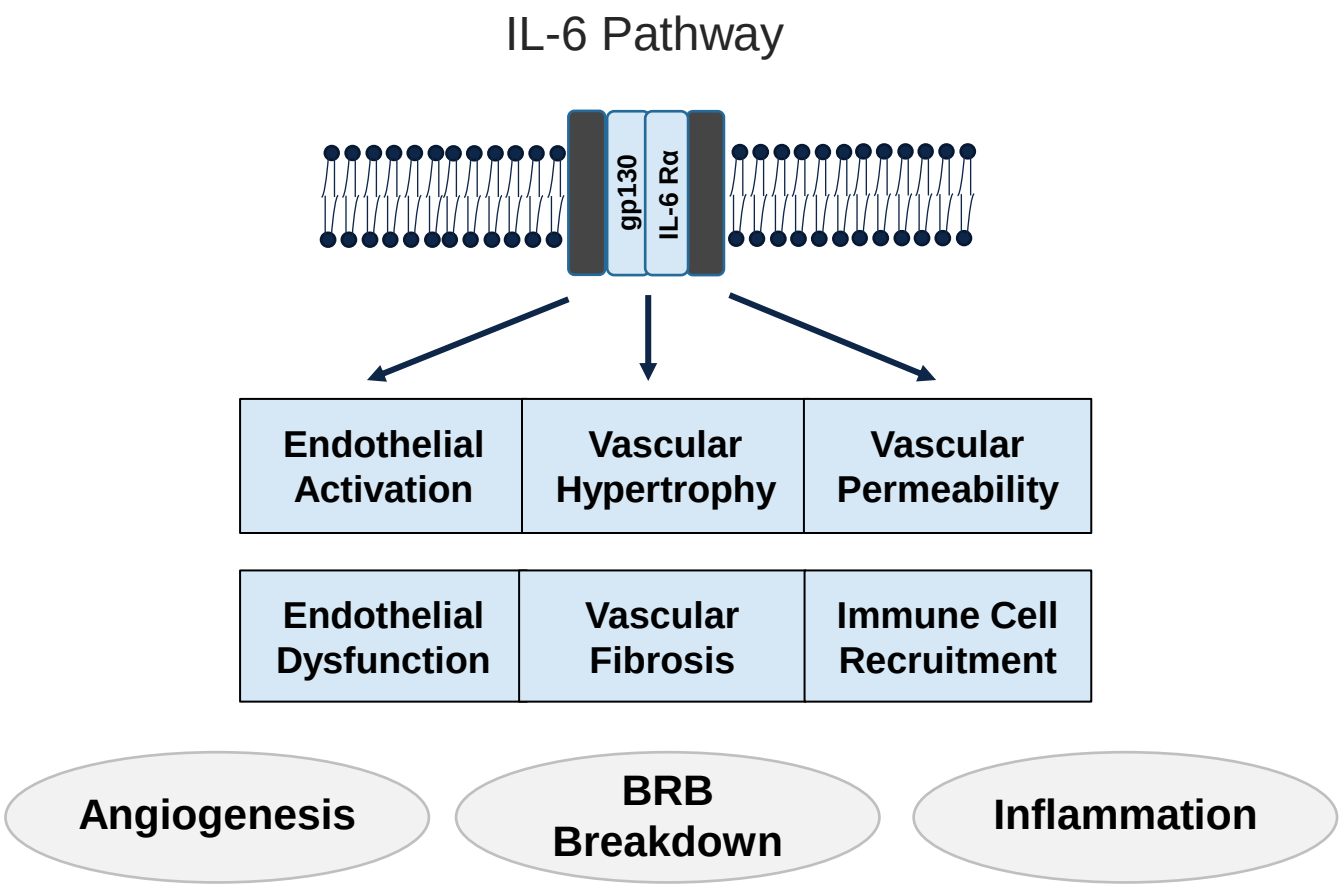
OCT CST change from baseline during year 1 for individual patients treated with Q8W aflibercept



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.
VEGF, vascular endothelial growth factor; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; OCT, optical coherence tomography; CST, central subfield thickness; Q8W: every 8 weeks

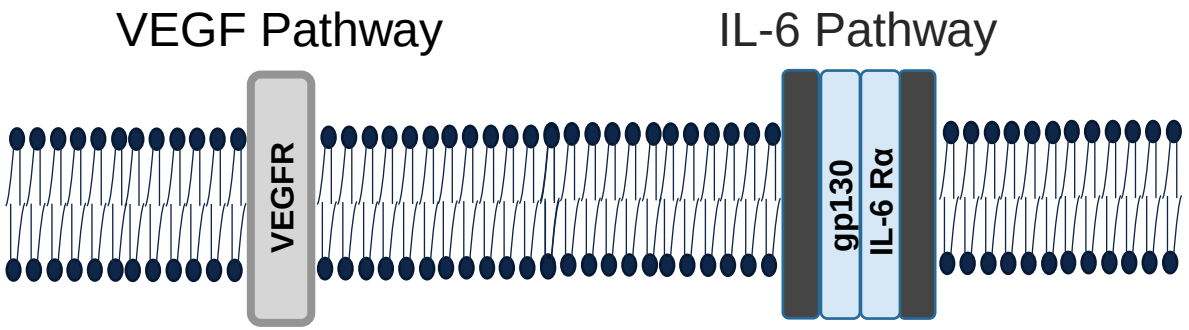
IL-6 plays an important role in the pathophysiology of retinal vascular and hyperpermeability disorders



- **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

IL-6: Interleukin-6; VEGF: vascular endothelial growth factor; DR: diabetic retinopathy; AMD: age-related macular degeneration; RVO: retinal vein occlusion; 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



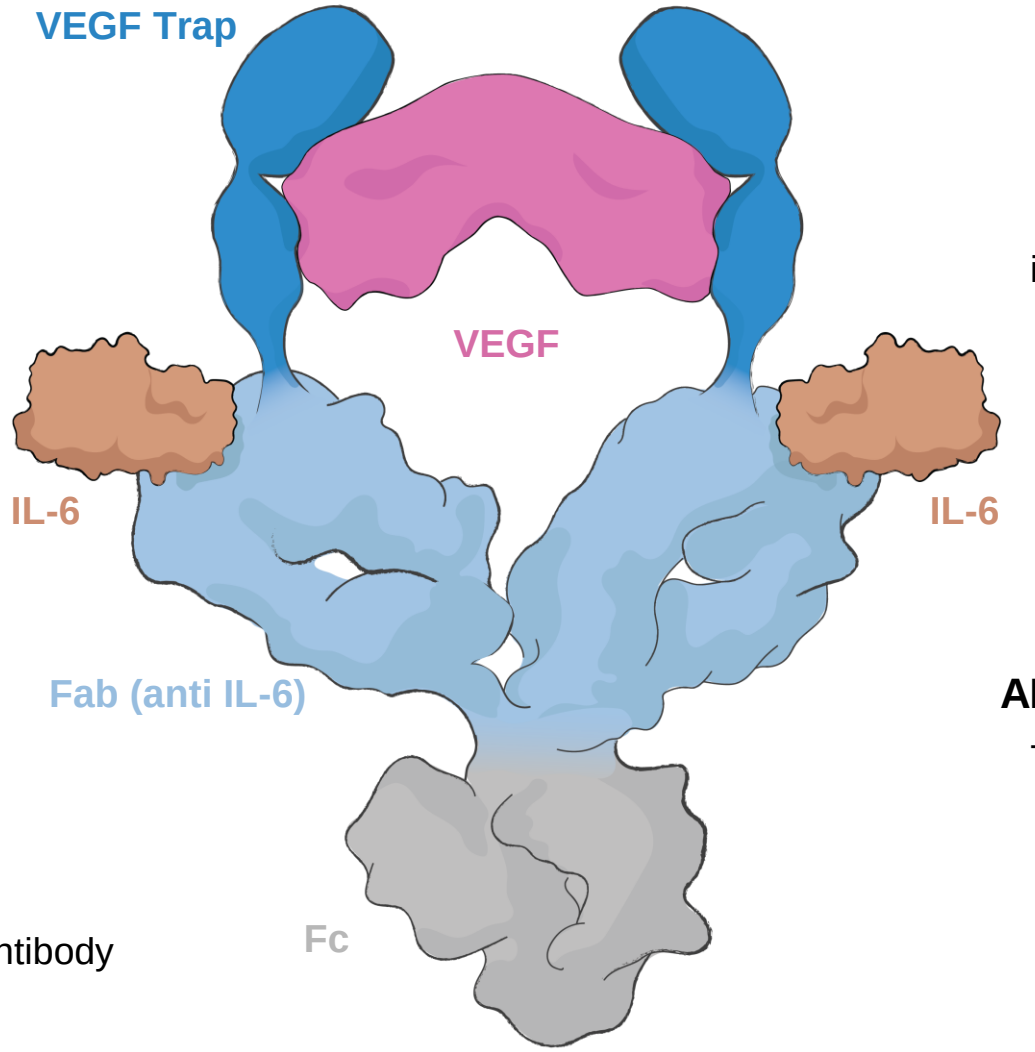
- Endothelial Survival
- Endothelial Proliferation
- Endothelial Migration
- Endothelial Activation
- Vascular Hypertrophy
- Vascular Permeability
- Endothelial Dysfunction
- Vascular Fibrosis
- Immune Cell Recruitment

Angiogenesis | **BRB Breakdown** | **Inflammation**

IL-6: Interleukin-6; VEGF: vascular endothelial growth factor; BRB: blood retinal barrier

KSI-501 bispecific protein features a unique design that enables highly efficient binding to both IL-6 and VEGF

“Two hands on the ball”



BINDING CAPACITY OF UP TO 3 MOLECULES

This first in class bispecific has the capability of inhibiting **one VEGF dimer**, **in addition to two IL-6 molecules, simultaneously**

BEST-IN-CLASS VEGF INHIBITION

The **VEGF trap** mimics the native receptor and binds multiple targets including **VEGF-A, VEGF-B and PlGF**

ADDITIONAL ANTI-INFLAMMATORY INHIBITION

The **anti-IL-6 Fab** blocks inflammation and normalizes the blood retinal barriers

MODIFIED Fc

Immunologically inert antibody

IL-6: Interleukin-6; VEGF: vascular endothelial growth factor; PlGF: placental growth factor; Fab: fragment antigen-binding; Fc: fragment crystallizable

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

BISPECIFIC

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

BIOPOLYMER

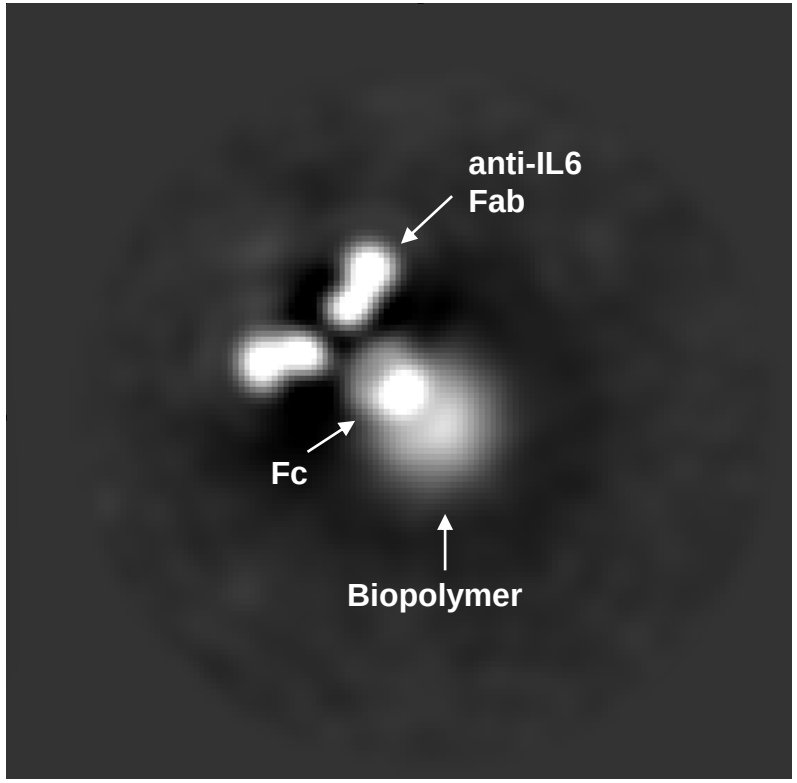
Branched, Optically Clear,
High Molecular Weight
Phosphorylcholine Polymer

CONJUGATE

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

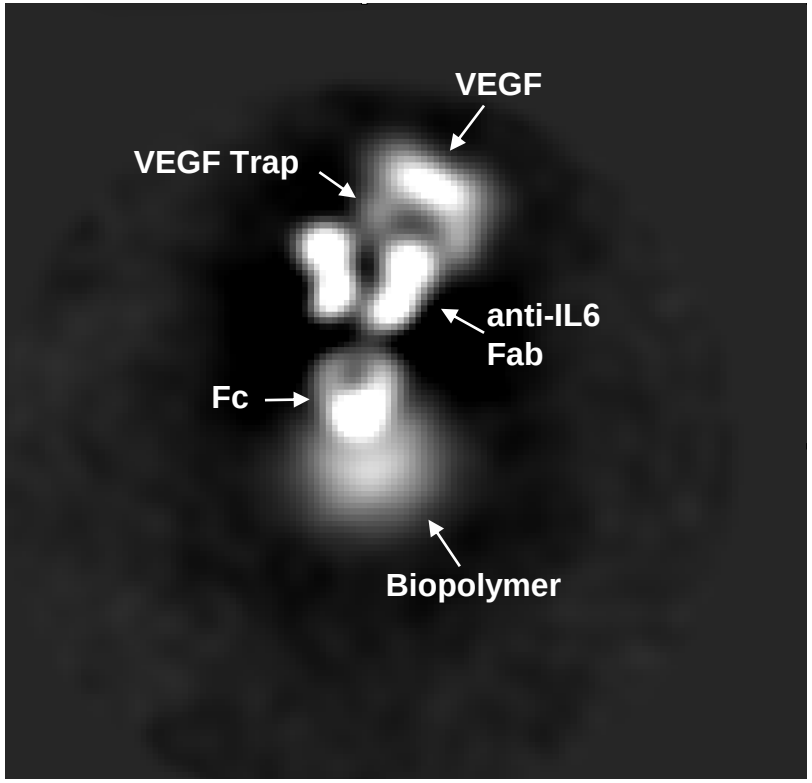
Negative-stain electron microscopy images of KSI-501ABC illustrate real time activation of the anti-VEGF trap in the presence of VEGF

KSI-501ABC



In the absence of VEGF, VEGF trap arms are not seen

KSI-501ABC + VEGF



Upon VEGF binding, VEGF trap arms are oriented in an optimal configuration and become visible

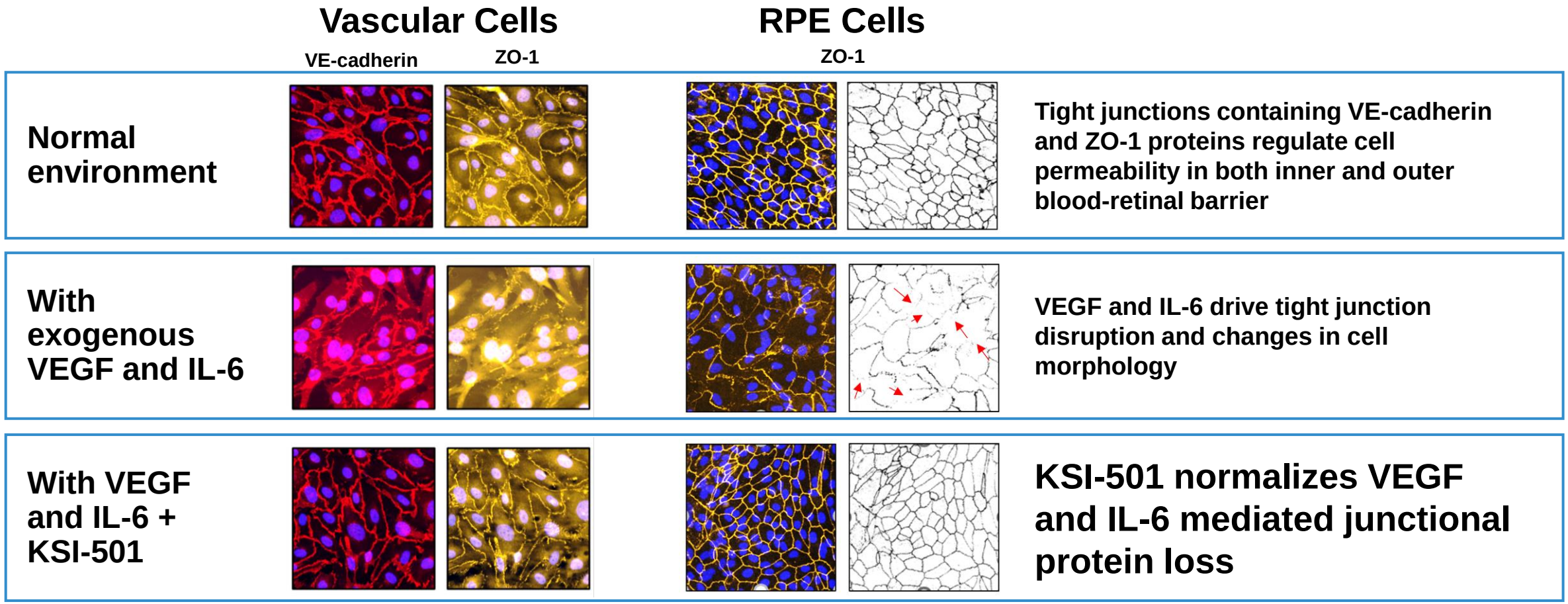
KSI-501 demonstrates comparable VEGF binding affinity and potency to aflibercept and comparable IL-6 potency as vamikibart

Key disease drivers in retinal diseases	**Aflibercept**	**Vamikibart (anti-IL-6 mAb)**	**KSI-501^**
Inflammation	✗	✓	✓
Angiogenesis	✓	✗	✓
Barrier function	✗	✓	✓
Vascular leakage	✓	✗	✓
Preclinical potency			
Binding affinity to VEGF-A*	0.49 pM	N / A	1.02 pM
Inhibition of VEGF-A binding to VEGF-R^^	IC_{50}=129.6 pM	N / A	IC_{50}=163.7 pM
Inhibition of IL-6 *cis* signaling	N / A	IC_{50} = 41 pM	IC_{50} = 66 pM
Inhibition of IL-6 *trans* signaling	N / A	IC_{50}= 1.0 nM	IC_{50}= 2.1 nM
Target inhibition	**VEGF-A, VEGF-B and PlGF**	**IL-6**	**VEGF-A, VEGF-B, PlGF *and* IL-6**

mAb: monoclonal antibody; *VEGF-A binding affinity determined by Kodiak from Kinetic Exclusion Assay for tarcocimab and KSI-501 and determined by Regeneron from Biacore assay for aflibercept; ^^IC50 determined by Kodiak from VEGF bioluminescent cell-based assay; ^Values for KSI-501P are shown, except for VEGF-A binding affinity, for which values for KSI-501ABC was shown.

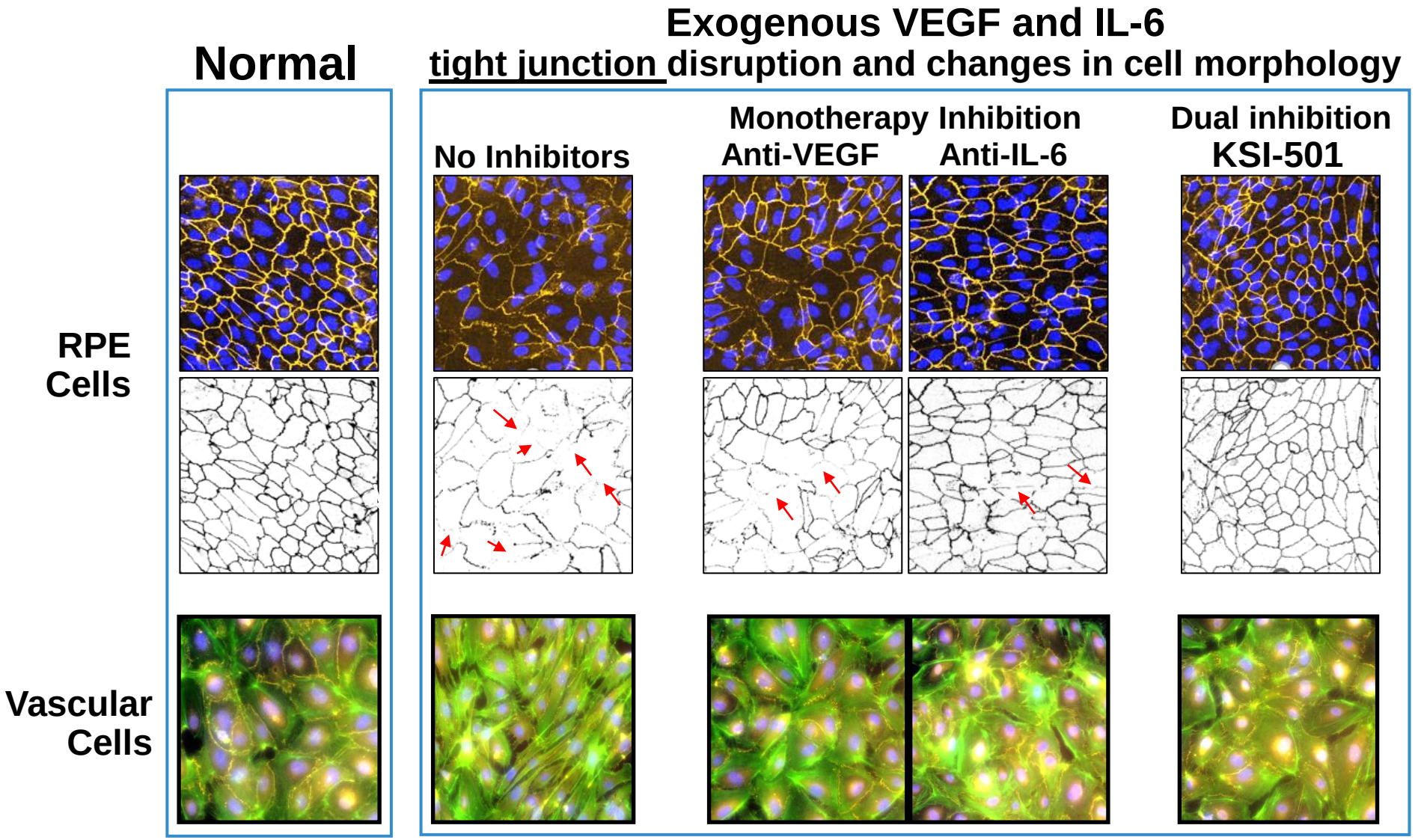
KSI-501 inhibits angiogenesis and normalizes the inner and outer blood retinal barriers

- **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 of complex biologies 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

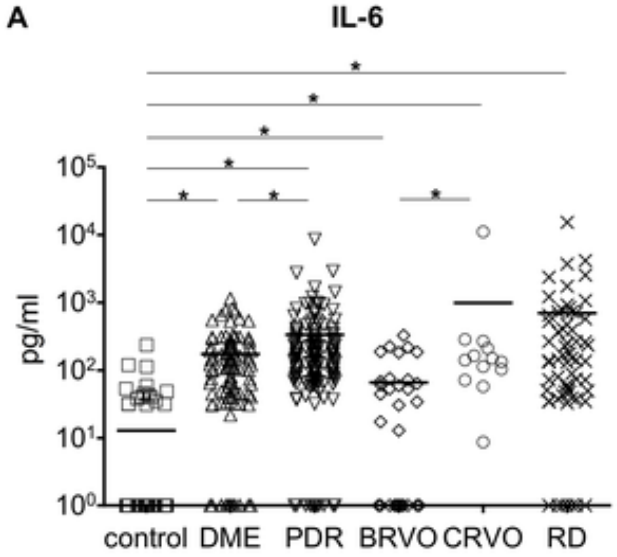
RPE cells: nuclei in blue, ZO1 (tight junction protein) in yellow. Vascular cells: nuclei in purple, ZO1 (tight junction protein) in yellow, actin in green.

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 can provide 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.
- Patients with macular edema secondary to inflammation (prior or concurrent), the underlying inflammatory component of the pathophysiological process is not addressed by inhibiting VEGF alone.

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 (<3-326)
CRVO	985.4 (<30-11103)
RRD	701.6 (<30-15381)

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

Potential Indications for KSI-501

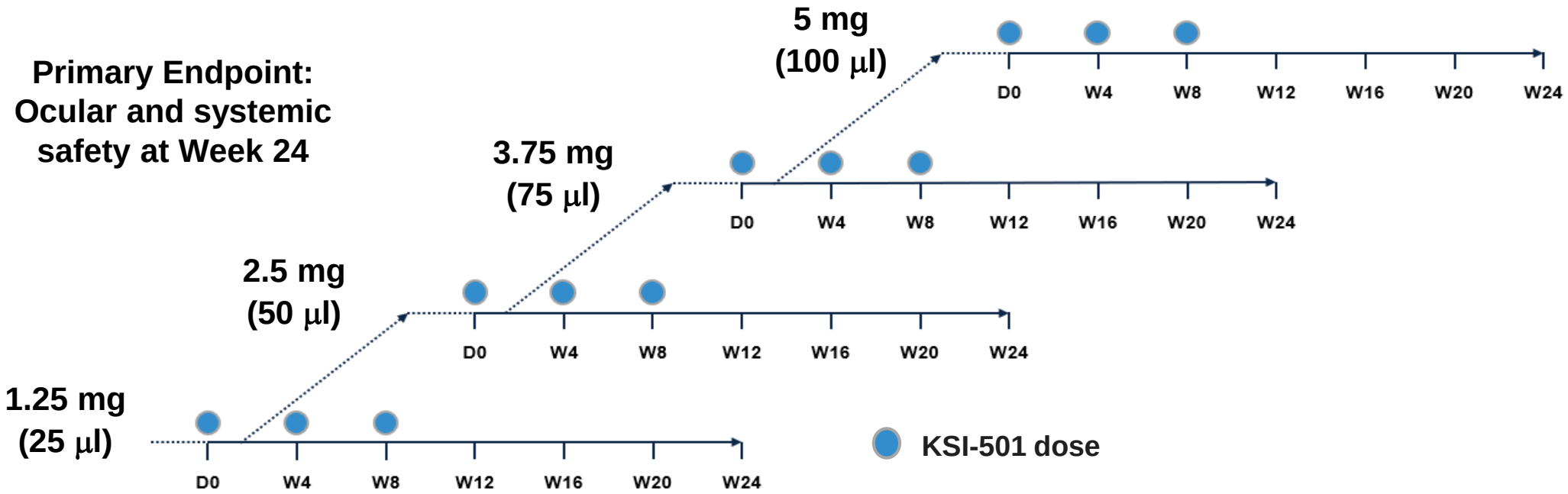
DME	**wAMD**	**Retinal Vein Occlusion**
Diabetic Retinopathy	**Inflammatory macular edema**	**Uveitis**

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-501ABC Phase 1 Study
First Time Results

KSI-501ABC Phase 1 multiple ascending dose study in patients with diabetic macular edema

Primary Endpoint: Ocular and systemic safety at Week 24



Study design

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

Key Inclusion/Exclusion 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 and previously treated with an 8-week washout period

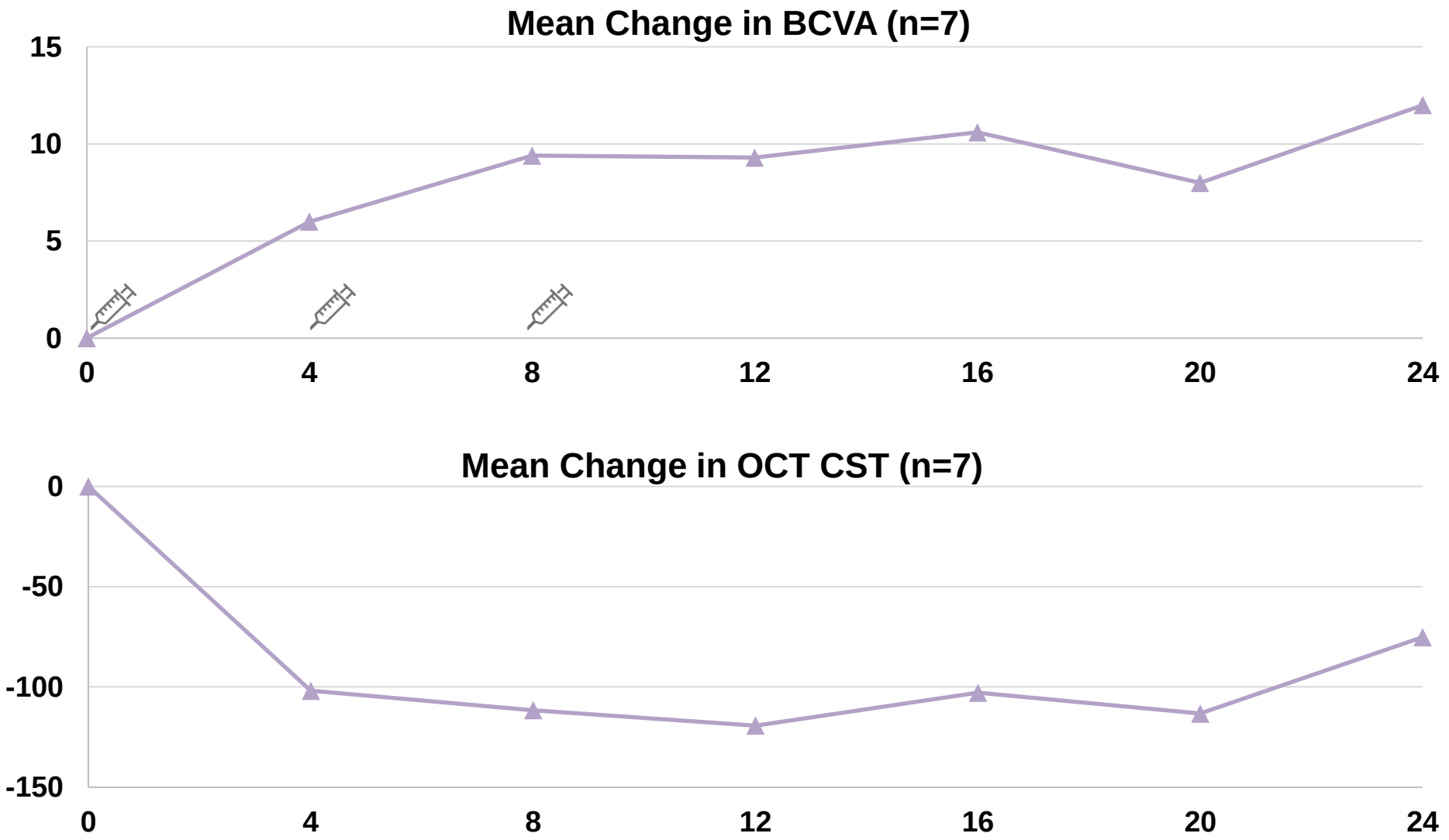
HbA1c: Hemoglobin A1c; DME: Diabetic Macular Edema; BCVA: best-corrected visual acuity; ETDRS: Early Treatment Diabetic Retinopathy Study; CST: Central Subfield Thickness; D: Day; W: Week

Demographics, general characteristics and baseline ocular characteristics were typical of DME patients

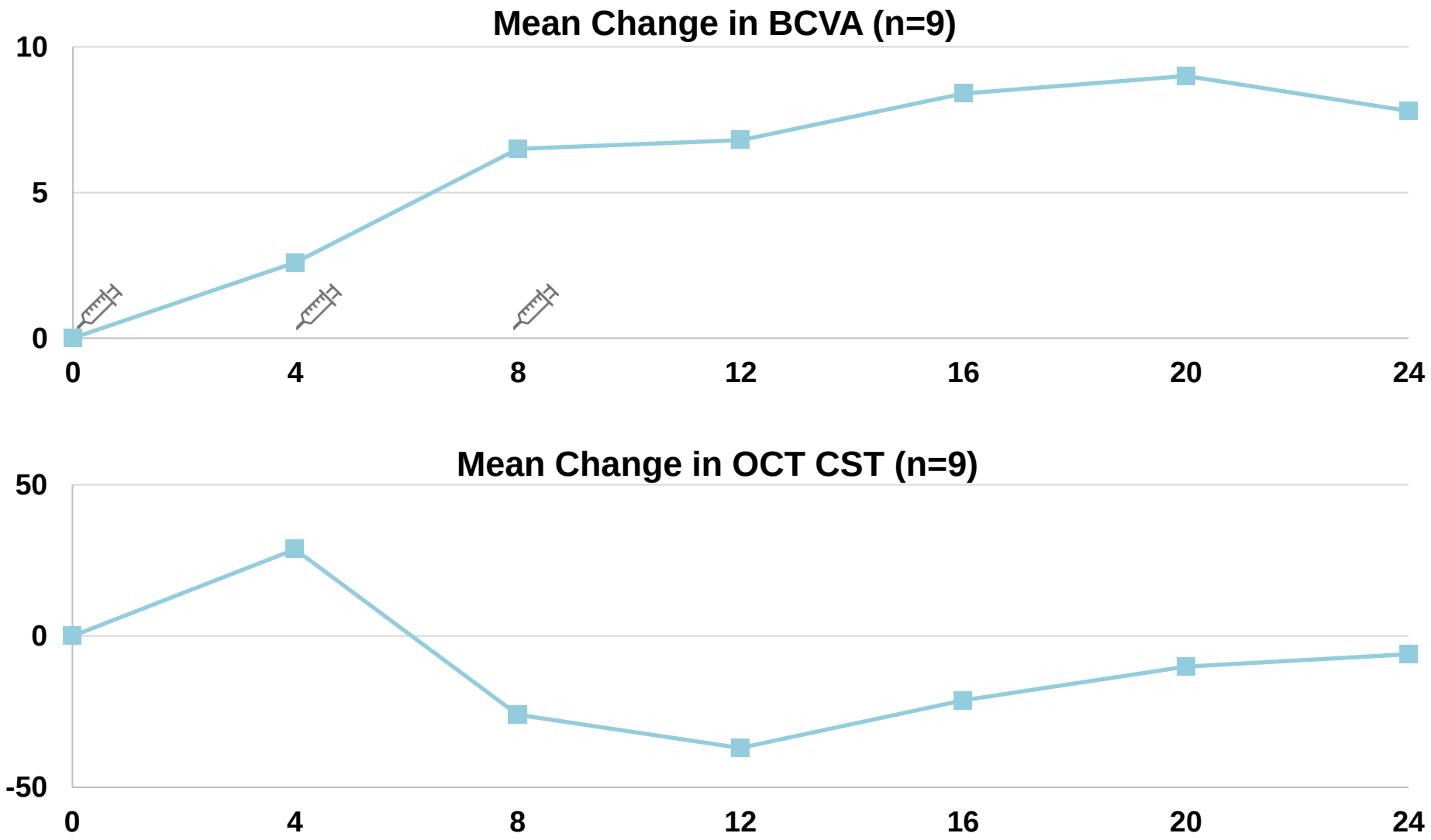
	KSI-501ABC n=16
Age, years, mean (SD)	67.3 (7.4)
Female, n (%)	6 (37.5)
Hemoglobin A1c, % (SD)	7.2 (1.2)
Diabetes Type 2, n (%)	14 (87.5%)
DME disease duration, months, mean (SD)	38.3 (40.4)
BCVA, ETDRS Letters, mean (SD)	61.7 (9.2)
Snellen equivalent	~20/63
OCT Central Subfield Thickness (CST), µm, mean (SD)	446.0 (109.9)
Lens Status, n (%)	
Phakic	11 (68.8)
Pseudophakic	5 (31.3)
Intraocular Pressure, mmHg, mean (SD)	15.3 (2.9)

n = Number of participants treated;
BCVA: best-corrected visual acuity; ETDRS: early treatment diabetic retinopathy study; DRSS: diabetic retinopathy severity scale; OCT: optical coherence tomography

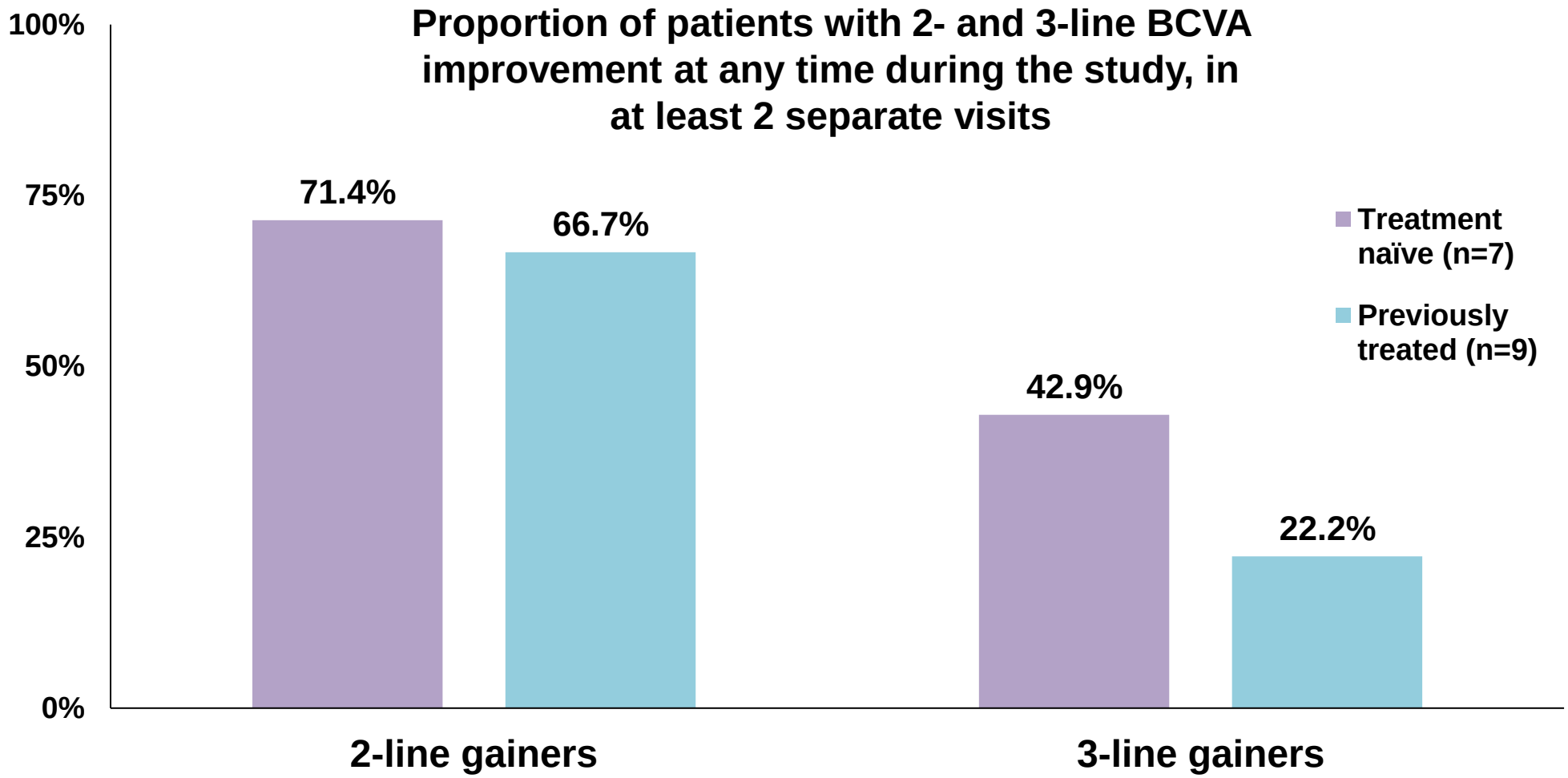
In treatment naïve patients, dosing with KSI-501ABC resulted in robust visual and anatomical gains that were sustained over 16 weeks after the last dose



In previously treated population, dosing with KSI-501ABC resulted in anatomical improvement, as well as meaningful and sustained gains in BCVA



Treatment with KSI-501ABC resulted in a meaningful increase of BCVA for the majority of patients during the study



BCVA: best corrected visual acuity

KSI-501ABC was safe and well tolerated

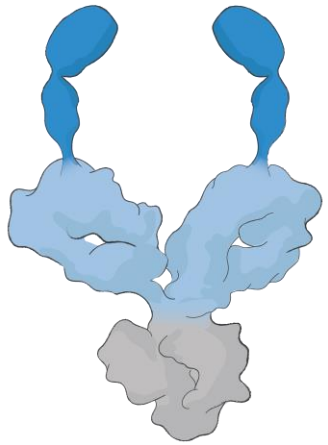
Adverse Events (AEs) in the Study Eye	KSI-501ABC N=16
Summary, n (%)	
Subjects with ≥1 AEs	7 (43.8)
Treatment-related AEs	1 (6.3)
Serious AEs	0
Treatment-related serious AEs	0
Severe AEs	0
AEs leading to study discontinuation	0
AEs in the Study Eye, n (%)	
Intraocular inflammation*	1 (6.3)
Occlusive retinal vasculitis	0
Cataract	0
Elevated IOP	0
Eye Pain	0

* One subject in the 2.5 mg dose level (50 μl), mild, treated with topical steroids. Subject remained in the study and received two additional KSI-501ABC doses with no recurrence of inflammation.

Events are investigator reported. Adverse events are treatment-emergent events with start date ≥first study drug date and ≤last study drug date + 28 days.

The KSI-501 program will be developed in parallel as a “naked” protein and as a bioconjugate, addressing two very different unmet needs

KSI-501P
Unconjugated Protein



There are no available intravitreal biologic therapies addressing the spectrum of inflammatory diseases of the retina.

First-in-class, bispecific anti-IL-6 and anti-VEGF protein – **for macular edema secondary to inflammation**

KSI-501ABC
Antibody Biopolymer Conjugate

Addressing multiple biologies is still a significant unmet need.

First-in-class, bispecific anti-IL-6 and anti-VEGF biopolymer conjugate – **for retinal vascular diseases**

Summary

Retinal diseases 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.**

KSI-501ABC Phase 1 First in Human Study met its objective

- Repeated monthly dosing of KSI-501 was **safe and well-tolerated.**
- **Bioactivity was demonstrated** in both functional (BCVA) and anatomical (OCT CST) measures.
- Meaningful and sustained gains in BCVA were achieved.

KSI-501, a new category of retinal medicine inhibiting IL-6 and VEGF is advancing

Dual inhibition of IL-6 and VEGF may provide additional clinical benefits across retinal vascular and inflammatory diseases.

- **KSI-501P,** the unconjugated protein, is being developed **for the treatment of macular edema secondary to inflammation.**
- **KSI-501ABC,** the antibody biopolymer conjugate, is being developed **for the treatment of high prevalence retinal vascular diseases.**