Clinical Trials at the Summit 2024
Salt Lake City – June 8, 2024

Bispecific Anti-VEGF / Anti-IL-6 Programs: KSI-501 in Retinal Vascular Diseases and KSI-101 in Macular Edema Secondary to Inflammation

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Stanford OPHTHALMOLOGY
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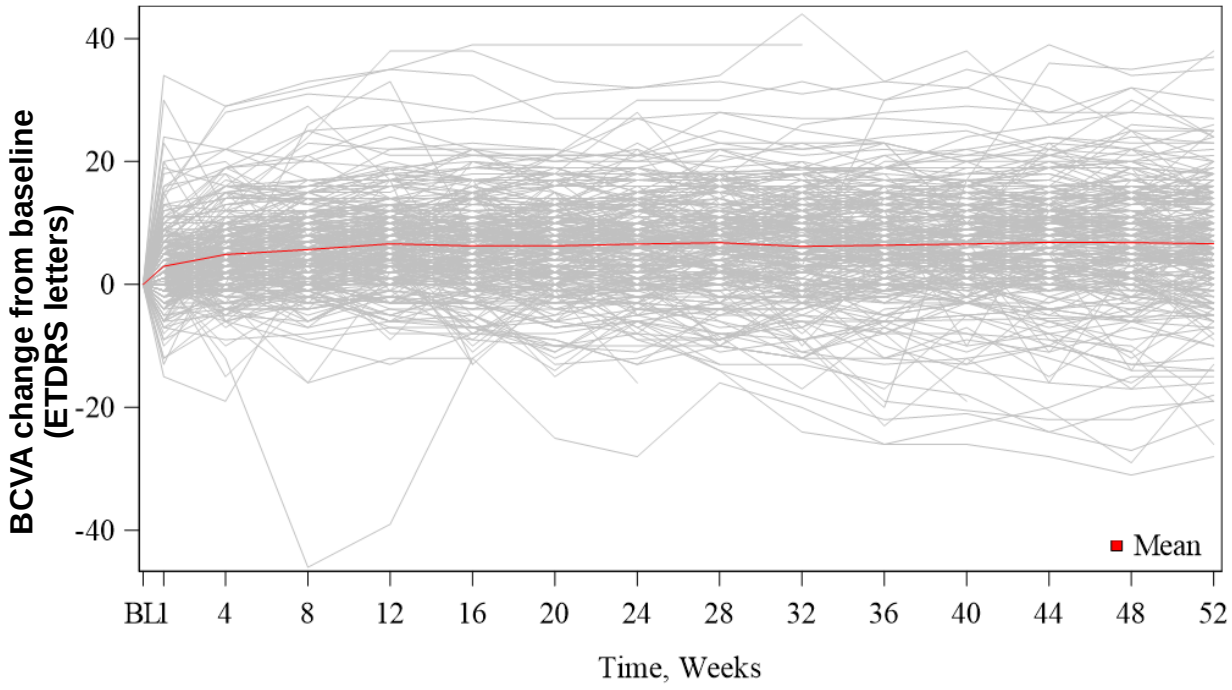
Disclosures

- Stanford University, the employer of Dr. Nguyen, has received research funding from Boehringer-Ingelheim, Genentech, Priovant, and Regeneron, among others
- Dr. Nguyen serves on the scientific advisory boards for Acelyrin, Alumis, Boehringer-Ingelheim, Genentech, Regeneron, and Rezolute, among others
- Dr. Nguyen also holds stock options in Kodiak
- The presentation will discuss IRB/IEC approved research of an investigational medicine

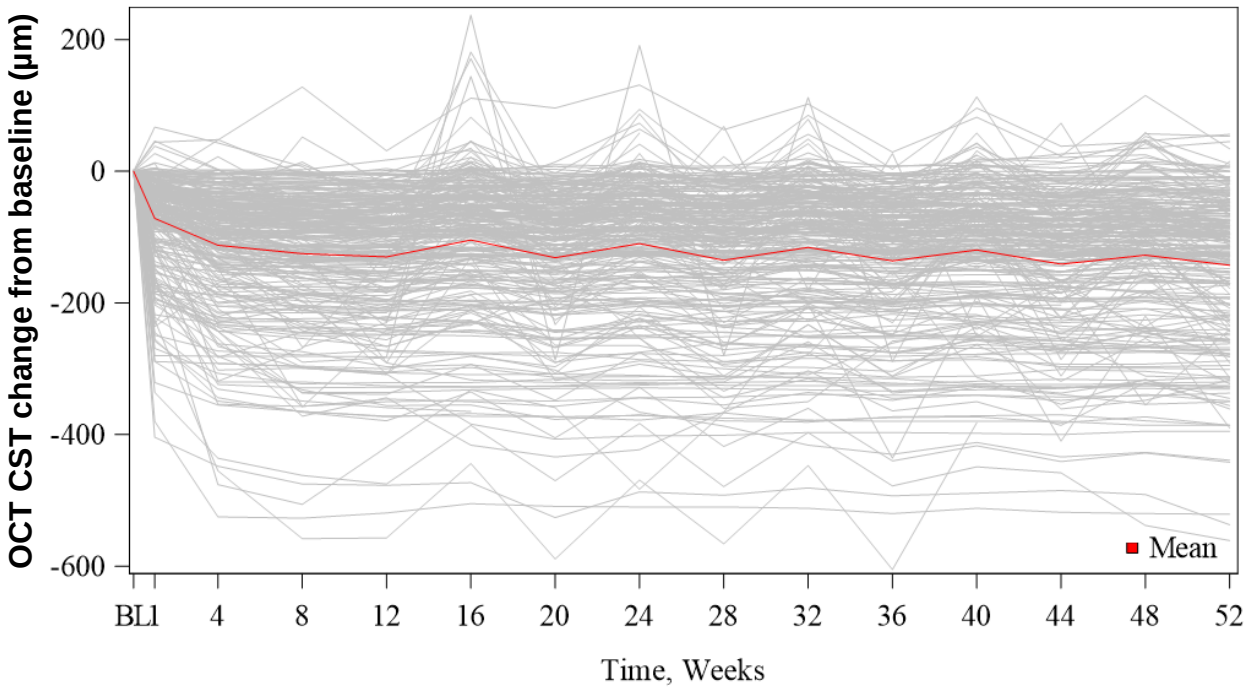
(C): Consultant; (S): Stock/shareholder; (R): Grants/Research Support

Substantial patient-to-patient variability is observed 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

Increased levels of IL-6 are associated with poor functional outcomes in wAMD and DME patients treated with anti-VEGF monotherapy

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ARTICLE OPEN

Check for updates

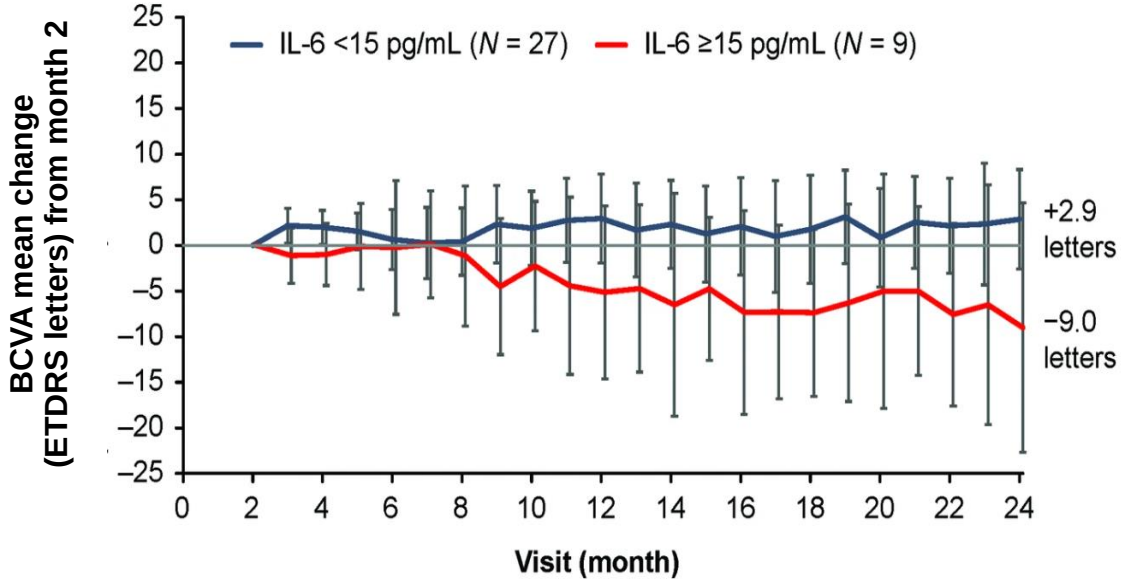
Aqueous humour interleukin-6 and vision outcomes with anti-vascular endothelial growth factor therapy

Yasir Jamal Sepah[1], Diana V. Do[1], Marina Mesquida[2], Bann-Mo Day[3], Steven Blotner[3], Rubbia Afridi[1,4], Muhammad Sohail Halim[1,4], Kyu Hong[3], Eric Wakshull[3], Sascha Fauser[2], Ivaylo Stoilov[3]✉, Quan Dong Nguyen[1]✉, on behalf of the HARBOR* and READ-3 Investigators*

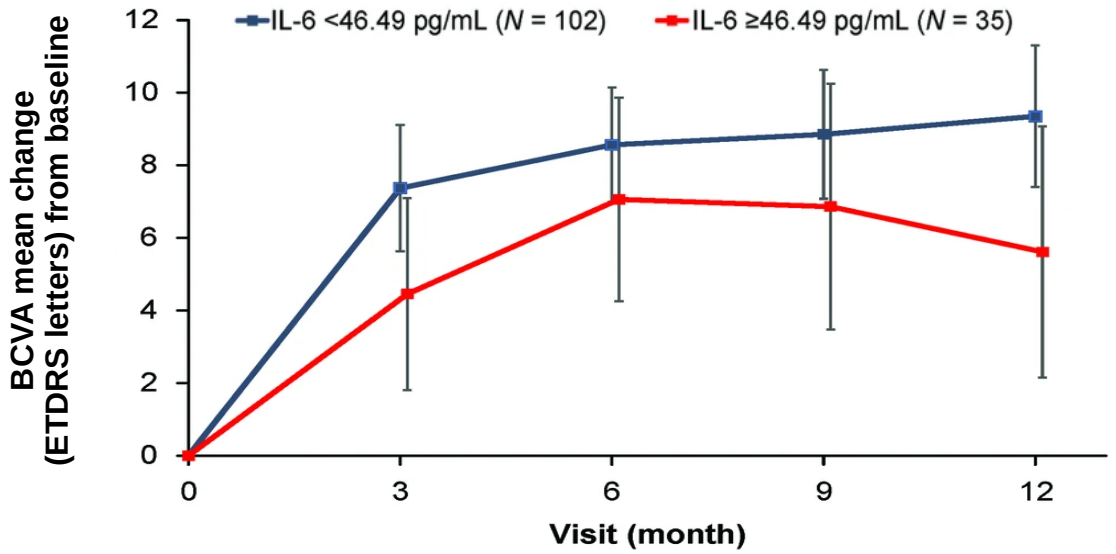
Eye, 2024

Increased levels of IL-6 are associated with poor functional outcomes in wAMD and DME patients treated with anti-VEGF monotherapy

BCVA change from month 2 over time in **wAMD** patients with high and low aqueous IL-6 levels



BCVA change from baseline over time in **DME** patients stratified by baseline aqueous IL-6 levels



Higher levels of IL-6 in aqueous humor are correlated with poorer BCVA outcomes over time in retinal vascular diseases, which suggests that IL-6 inhibition in combination with anti-VEGF therapy could lead to improved outcomes

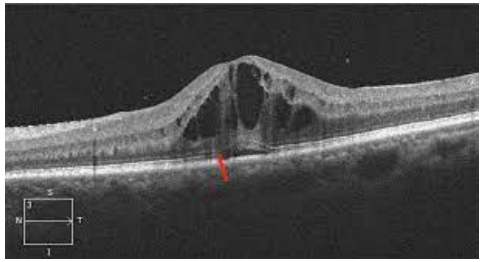
Sepah, Y.J., Do, D.V., Mesquida, M. et al. Aqueous humour interleukin-6 and vision outcomes with anti-vascular endothelial growth factor therapy. Eye (2024). https://doi.org/10.1038/s41433-024-03015-2; VEGF, vascular endothelial growth factor; BCVA, best corrected visual acuity; ETDRS, Early Treatment Diabetic Retinopathy Study; OCT, optical coherence tomography; CST, central subfield thickness; Q8W: every 8 weeks

Macular edema is the leading cause of vision loss among patients with uveitis and IL-6 mediated pro-inflammatory signaling is a key disease driver

Uveitis is the 4th leading cause of vision loss in the developed world

- Up to 50% of patients experience reduced vision
- 10-15% of patients become blind

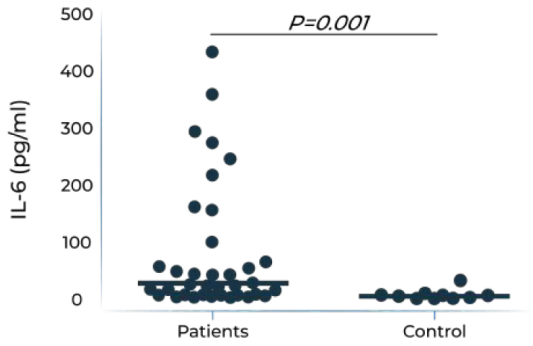
Macular edema is the leading cause of vision loss among uveitis patients



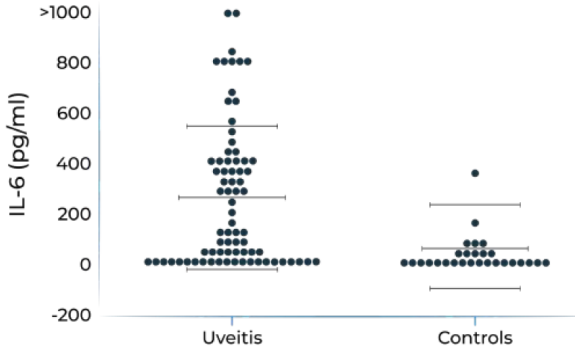
1/3 of uveitis patients (~110,000 patients in the U.S.) develop macular edema

IL-6 is a key disease driver of uveitic macular edema (UME), leading to disruption of the inner and/or outer blood-retinal barrier

Aqueous humor IL-6 levels are elevated in patients with intermediate uveitis[5]

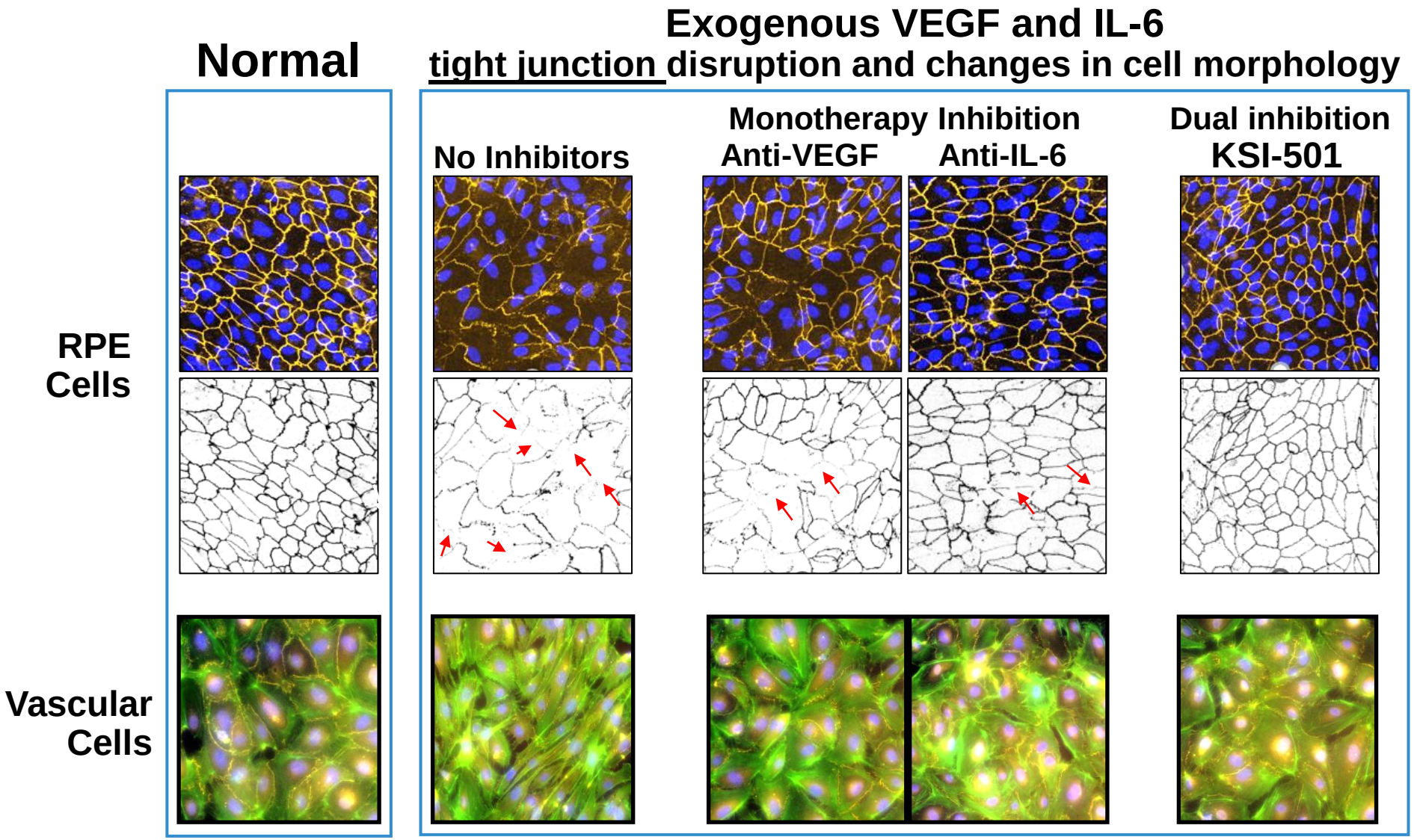


IL-6 levels are elevated in the vitreous of patients with active uveitis[6]



1. Thorne et al. *JAMA Ophthalmol.* 2016 Nov 1;134(11):1237-1245. 2. Rosenbaum et al. *Semin Arthritis Rheum*. 2019 Dec;49(3):438-445. 3. Massa et al. *Clinical Ophthalmology 2019*: 13, 1761-1777. 4. Joltikov and Lobo-Chan (2021) Front. Med. 8:695904. 5. Valentincic et al. Molecular Vision 2011; 17: 2003-2010. 6. de Boer et al. Curr Eye Res. 1992;11 Suppl:181-186. 5. Sepah et al. STOP Uveitis. *Am J Ophthal* 2017

Dual inhibition of VEGF and IL-6 confers superior normalization of complex biologies compared to either anti-VEGF or anti-IL-6 monotherapy alone



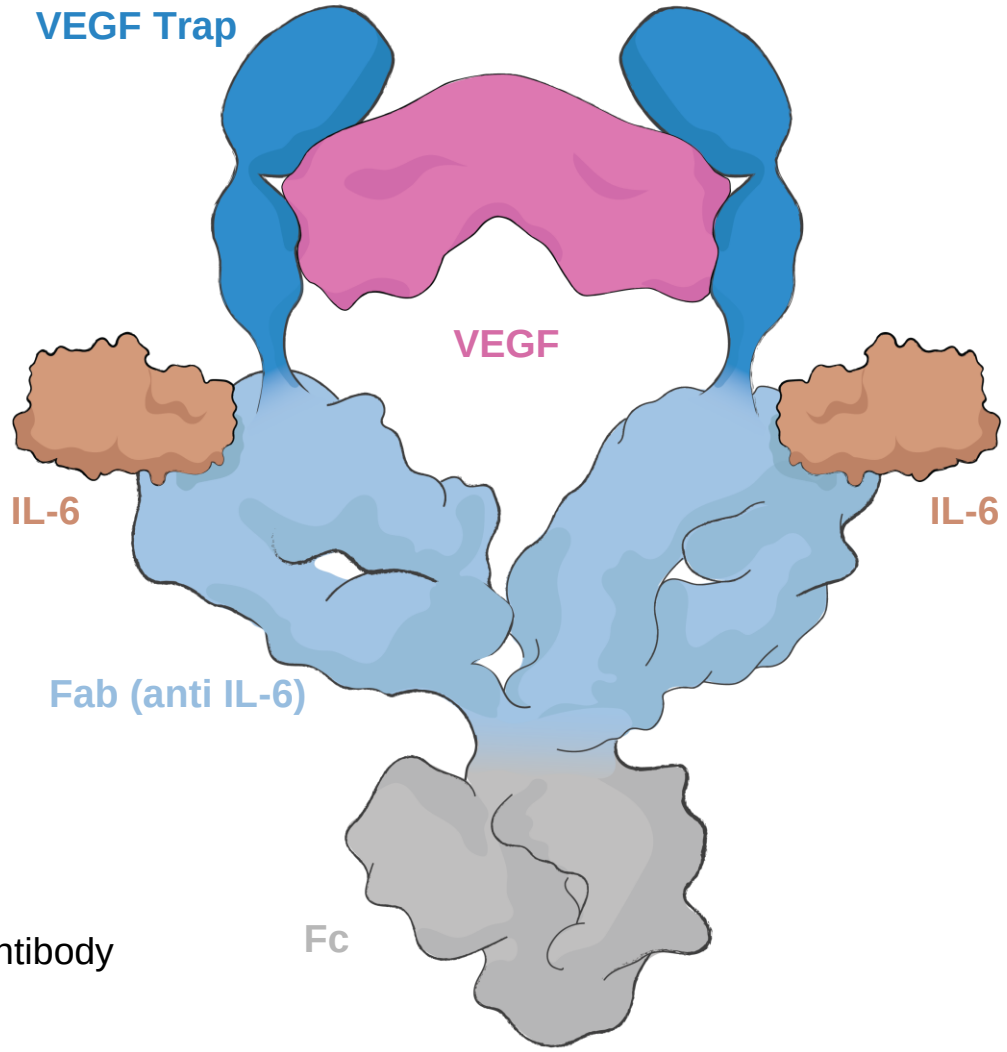
In additional studies, KSI-501 has been shown to inhibit endothelial cell proliferation and tube formation to a greater extent than anti-VEGF or anti-IL-6 monotherapy

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

KSI-101 and KSI-501 are based on a first-in-class 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**

POTENT ANTI-INFLAMMATORY EFFECT

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

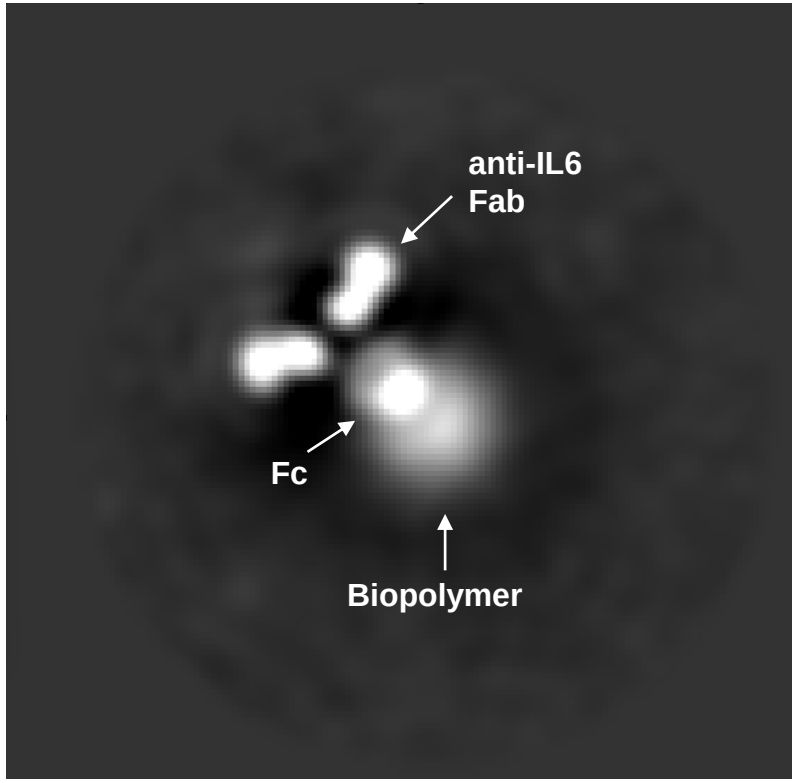
MODIFIED Fc

Immunologically inert antibody

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

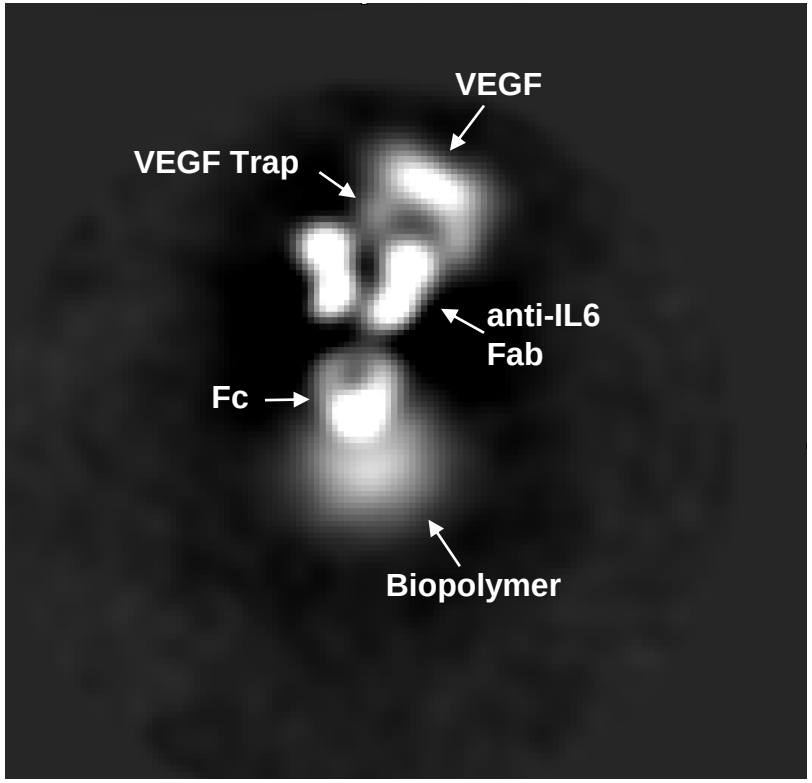
Negative-stain electron microscopy images of KSI-501ABC illustrate real time activation of the anti-VEGF trap in the presence of VEGF

KSI-501



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

KSI-501 + VEGF



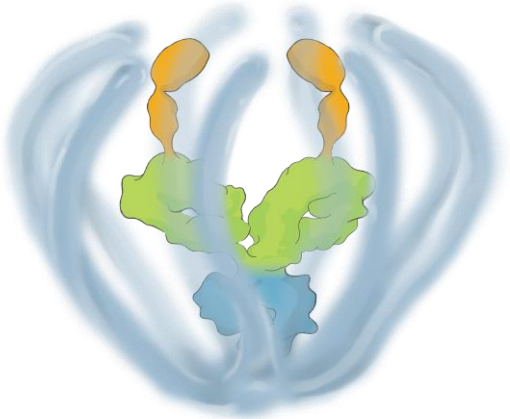
Upon VEGF binding, VEGF trap arms are oriented in an optimal configuration and become visible

KSI-501 and KSI-101 demonstrate 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/KSI-101^
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 KSI-501 and determined by Regeneron from Biacore assay for aflibercept; ^^IC50 determined by Kodiak from VEGF bioluminescent cell-based assay; ^Values for KSI-101 are shown, except for VEGF-A binding affinity, for which values for KSI-501 was shown.

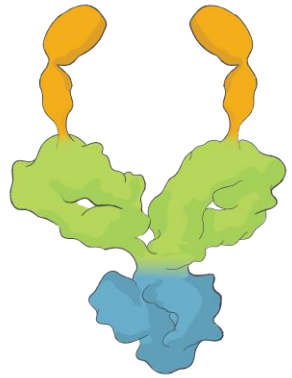
Both KSI bispecific programs, KSI-501 and KSI-101, will be developed in parallel, addressing two different unmet needs



KSI-501
Bispecific Anti-IL-6 VEGF Trap
Antibody Biopolymer Conjugate (ABC)

ABC biologic for
retinal vascular diseases

- A protein therapeutic, engineered for high affinity and specificity, is combined with a **bioinspired polymer designed for extended ocular half life and therapeutic benefit**
- Designed to provide 6-month durability to the majority of patients in high prevalence retinal diseases
- **50 mg/mL** formulation of unconjugated and conjugated forms balances towards durability without compromising immediacy



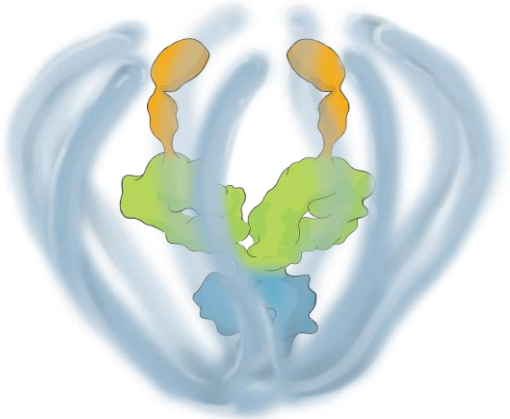
KSI-101
Bispecific Anti-IL-6 VEGF Trap Protein

Unconjugated biologic for
inflammatory retinal diseases

- First-in-class bispecific protein **targets inflammation** and vascular permeability
- Addresses underlying disease mechanisms of vision-threatening retinal inflammatory conditions for which no approved intravitreal biologic therapies exist today
- **100 mg/mL** formulation provides high strength and potency

DME: diabetic macular edema; wAMD: wet age-related macular degeneration; RVO: retinal vein occlusion; DR: diabetic retinopathy;

Both KSI bispecific programs, KSI-501 and KSI-101, will be developed in parallel, addressing two different unmet needs



KSI-501
Bispecific Anti-IL-6 VEGF Trap
Antibody Biopolymer Conjugate (ABC)

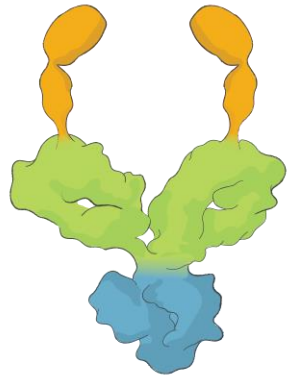
ABC biologic for
retinal vascular diseases

wAMD | DME | RVO | DR

Phase 1 FIH DME
Completed

Phase 3 wAMD DAYBREAK study
Starting mid-2024

2nd Phase 3 study
Planned for 2025



KSI-101
Bispecific Anti-IL-6 VEGF Trap Protein

Unconjugated biologic for
inflammatory retinal diseases

Macular edema secondary to inflammation (MESI)

Phase 1b
Part 2 (DME) and Part 3 (MESI)

APEX study
Starting mid-2024

Phase 2b/3 MESI
PEAK study

Starting late-2024

Phase 2b/3 MESI
PINNACLE study

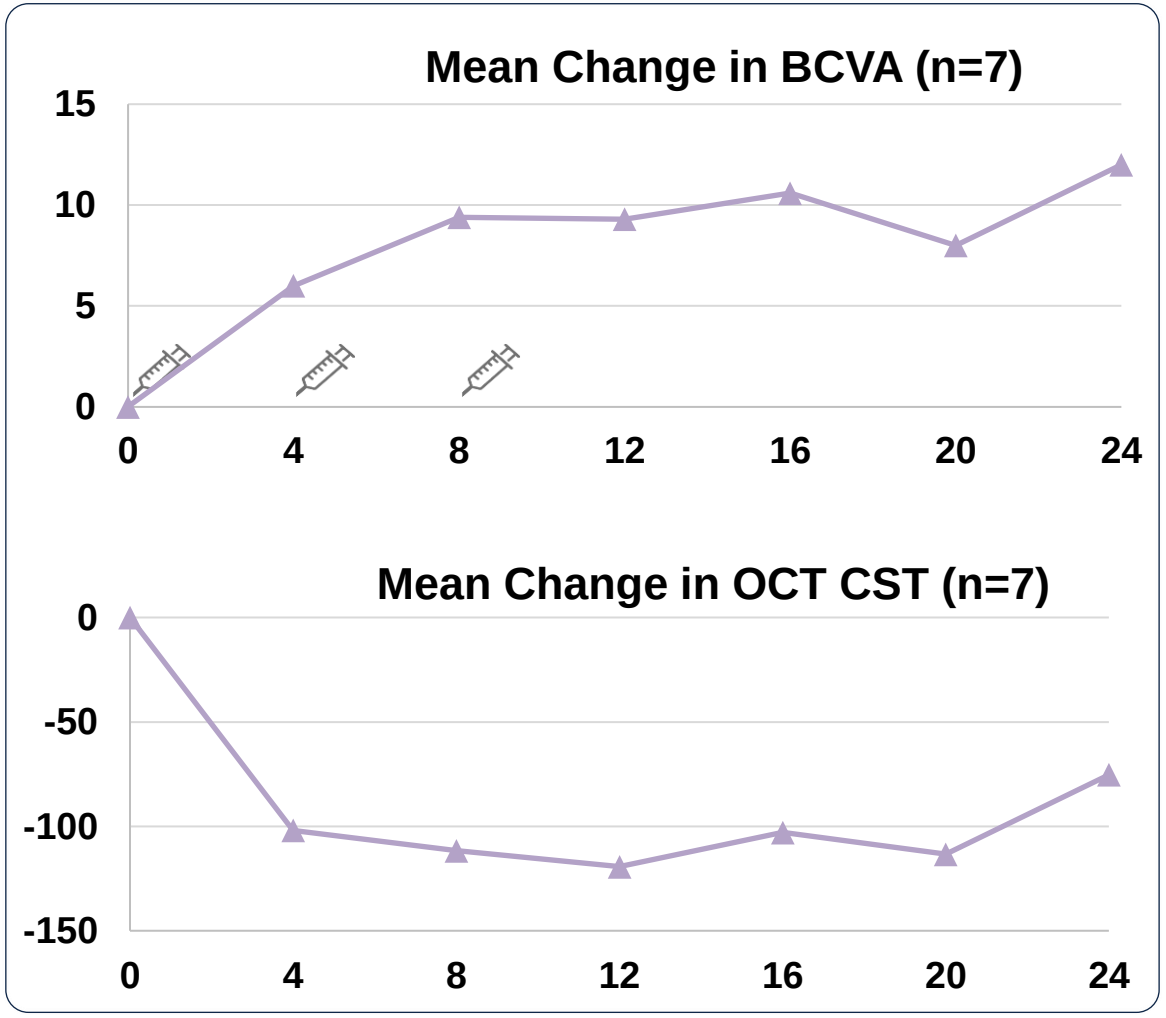
Starting late-2024

DME: diabetic macular edema; wAMD: wet age-related macular degeneration; RVO: retinal vein occlusion; DR: diabetic retinopathy;

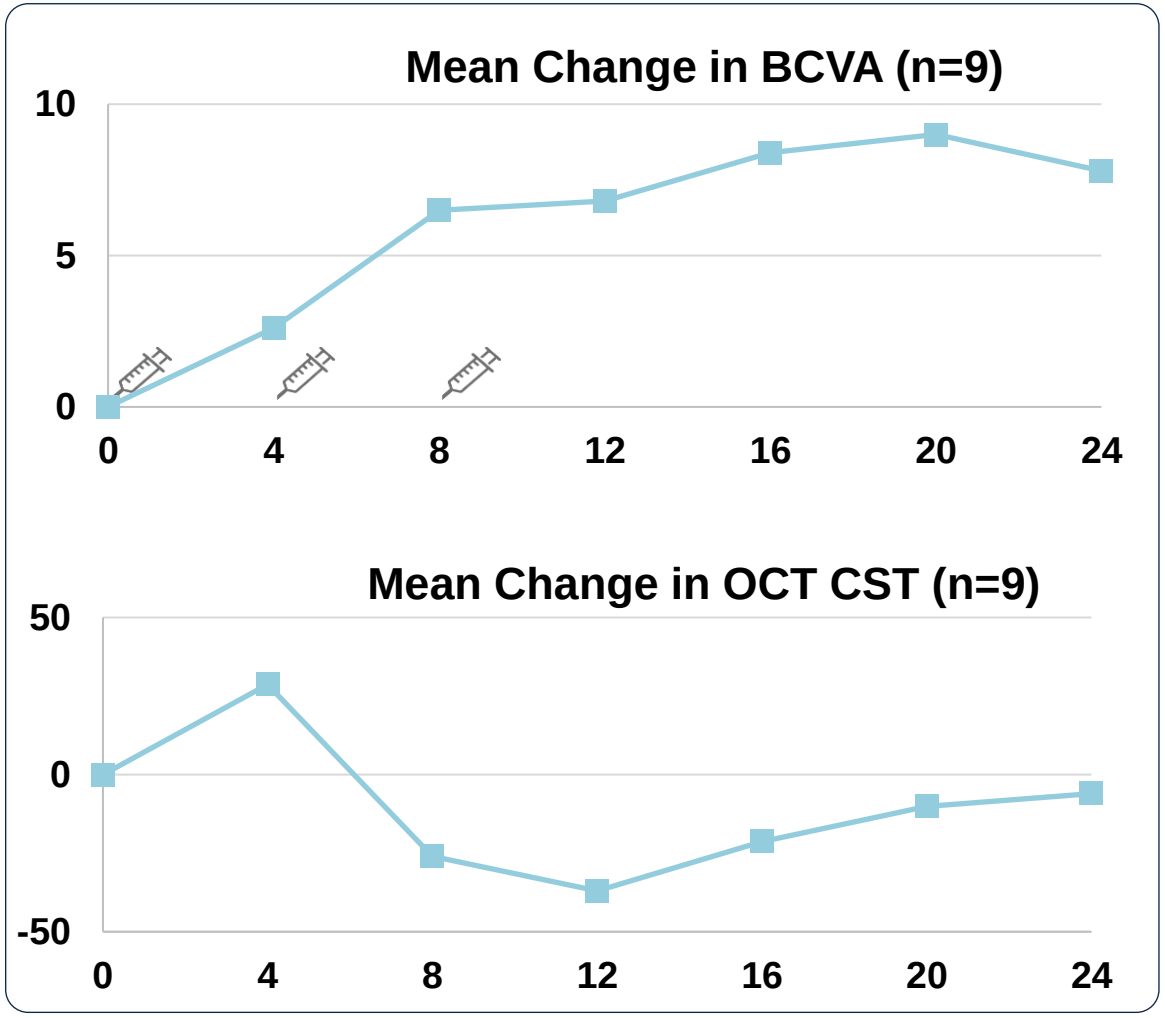
KSI-501 Phase 1 Study Results

Dosing with KSI-501 in DME patients resulted in robust visual and anatomical gains that were sustained over 16 weeks after the last dose

Treatment Naïve Patients

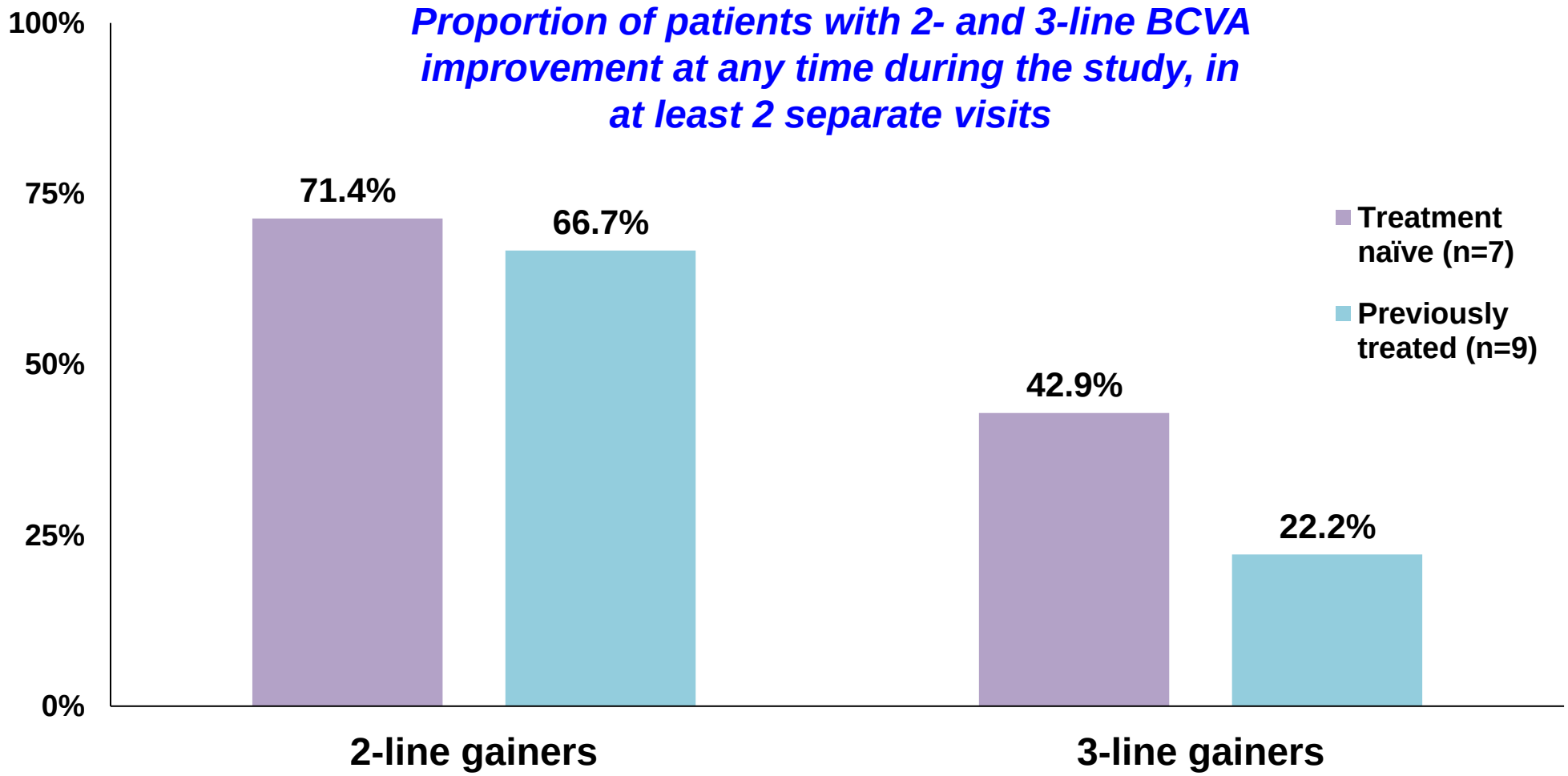


Previously Treated Patients



n = Number of participants treated;
BCVA: best-corrected visual acuity in ETDRS letters; OCT CST: optical coherence tomography central subfield thickness

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



BCVA: best corrected visual acuity

KSI-501 was safe and well tolerated

Adverse Events (AEs) in the Study Eye	KSI-501 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-501 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.

Summary

Retinal diseases multifactorial etiology

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

- IL-6 and VEGF are key mediators of inflammation, hyperpermeability/angiogenesis and blood retinal barrier disruption
- Dual inhibition of IL-6 and VEGF may provide additional clinical benefits across retinal vascular and inflammatory diseases

KSI-101 is being developed for macular edema secondary to inflammation

- **KSI-101, a potent 100 mg/mL high-strength bispecific protein is being developed for the treatment of macular edema secondary to inflammation**
- The anti-inflammatory effect of IL-6 inhibition is the primary effector, with the anti-permeability effect of VEGF inhibition having an additive and synergistic effect

KSI-501 is being developed for retinal vascular diseases

- **KSI-501, an ABC platform medicine, has a 50 mg/mL formulation of unconjugated and conjugated forms that balances towards durability without compromising immediacy**
- The anti-permeability effect of VEGF inhibition is the primary effector, with the anti-inflammatory effect of IL-6 inhibition offering the potential for additional clinical benefits