Bispecific trap-antibody inhibiting interleukin-6 and vascular endothelial growth factor (KSI-101): first-time results from the Phase 1b APEX Study in patients with macular edema secondary to inflammation (MESI)

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on behalf of the APEX Study Group

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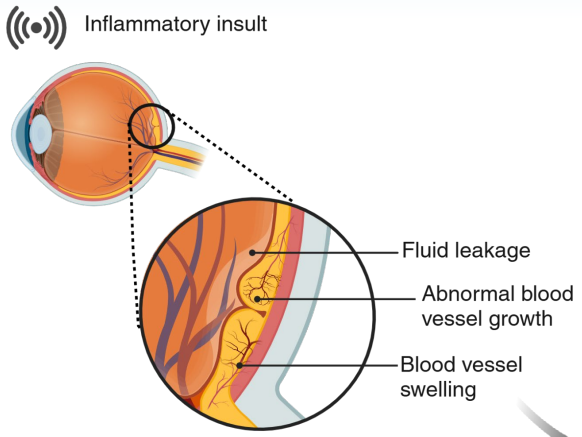
Dr. Chang, Dr. Fitzpatrick, Dr. Perlroth and Dr. Velazquez-Martin are employees of Kodiak Sciences

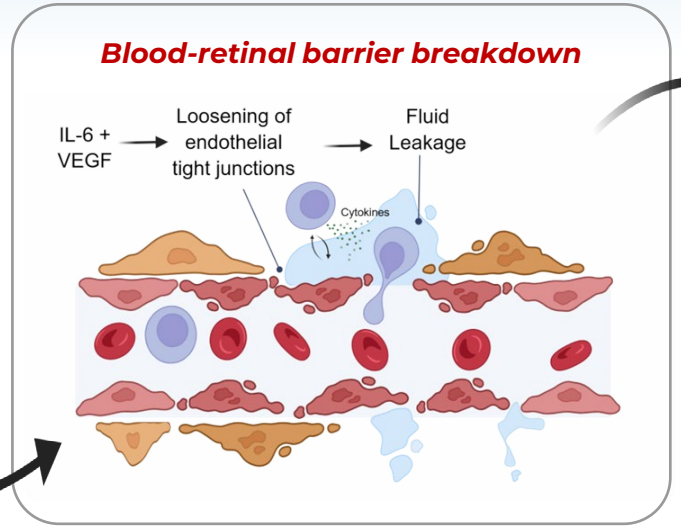
Dysregulation of the immune system causes a series of insults to the blood-ocular barrier, leading to breakdown of the barrier and release of inflammatory mediators

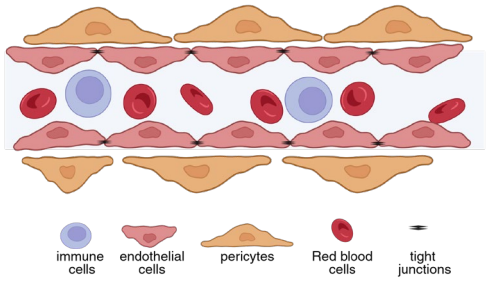
1 **Inflammatory insults** (e.g., autoimmune diseases) can **disrupt the blood-retinal barrier**

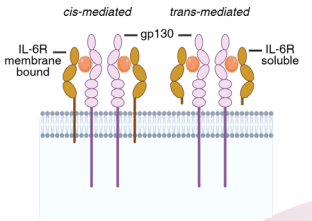
2 **Blood-retinal barrier breakdown** allows immune cells and blood plasma into the retina, causing **inflammation, leakage and macular edema**

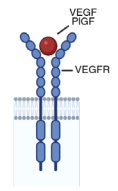
3 **IL-6 and VEGF are co-induced:** IL-6 sustains inflammation and upregulates VEGF, which promotes vascular leak and neovascularization. Together, IL-6 and VEGF compound damage to the blood-retinal barrier











INFLAMMATION

- VEGF ↑
- **Endothelial dysfunction**
- **Vascular permeability (Endothelial cells, RPE cells)**
- Immune cell recruitment
- Endothelial activation

VASCULAR REMODELING

- Endothelial proliferation
- Endothelial migration
- Endothelial survival

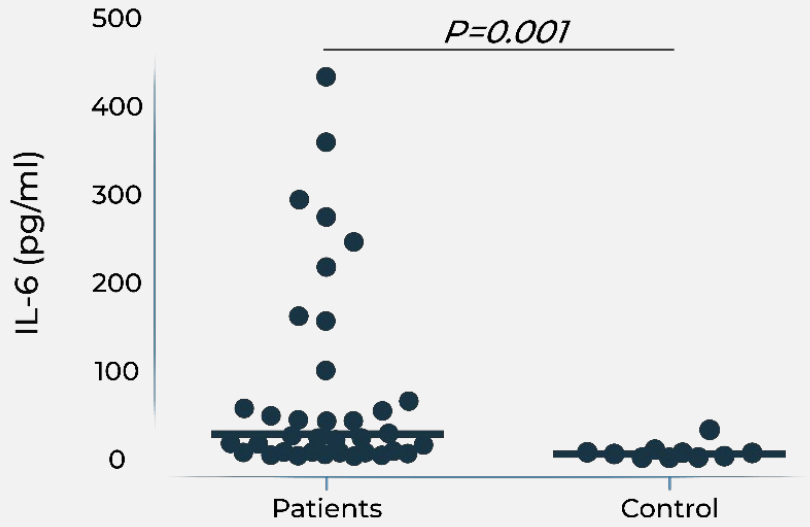
Yang et al. Int. J. Mol. Sci. 2023, 24: 4676. Metcalfe et al. Front. Immunol. 2020, 11: 1424. Shaik et al. Biomolecules. 2020, 10: 1673. Valle et al. Exp Eye Res. 2019, 178: 27. Mesquida et al. Trans Vis Sci Tech. 2019, 8: 32.

Both IL-6 and VEGF are implicated in the pathogenesis of inflammatory macular edema

IL-6

- IL-6 levels are elevated in patients with ocular inflammation and further elevated in patients with inflammatory macular edema

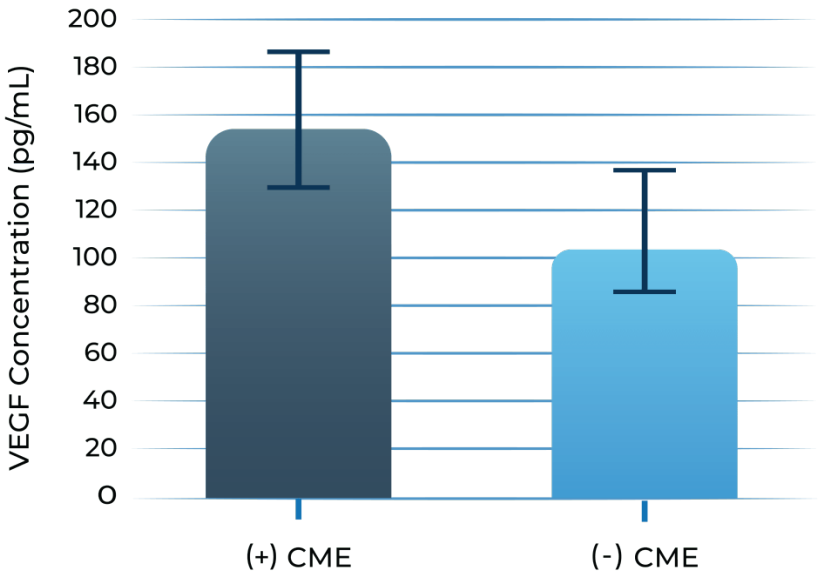
Aqueous humor IL-6 levels in patients with intermediate uveitis[1]



VEGF

- Persistent inflammation triggers VEGF upregulation. VEGF levels are found to be elevated in eyes with inflammatory macular edema

VEGF levels in aqueous humor of uveitis patients with macular edema vs without macular edema[2]



CME: cystoid macular edema
1. Adapted from Valentincic et al. Molecular Vision 2011; 17: 2003-2010. 2. Adapted from Fine et al. Am J Ophthal. 2001; 132: 794-796.

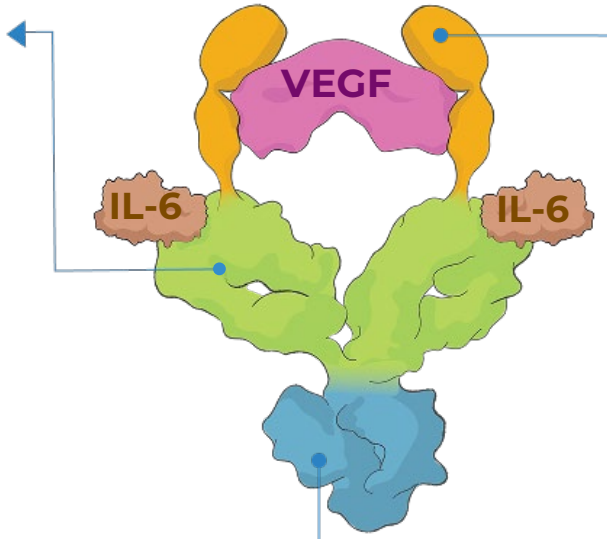
KSI-101 is a first-in-class, high-strength intravitreal biologic designed to target IL-6 mediated inflammation and VEGF-mediated vascular permeability simultaneously

KSI-101: high formulation strength (100 mg/mL)

Anti-IL-6 Antibody

Potent Anti-Inflammatory Effect

The anti-IL-6 antibody can inhibit up to two IL-6 molecules to block inflammation and normalize the blood retinal barriers



VEGF Trap

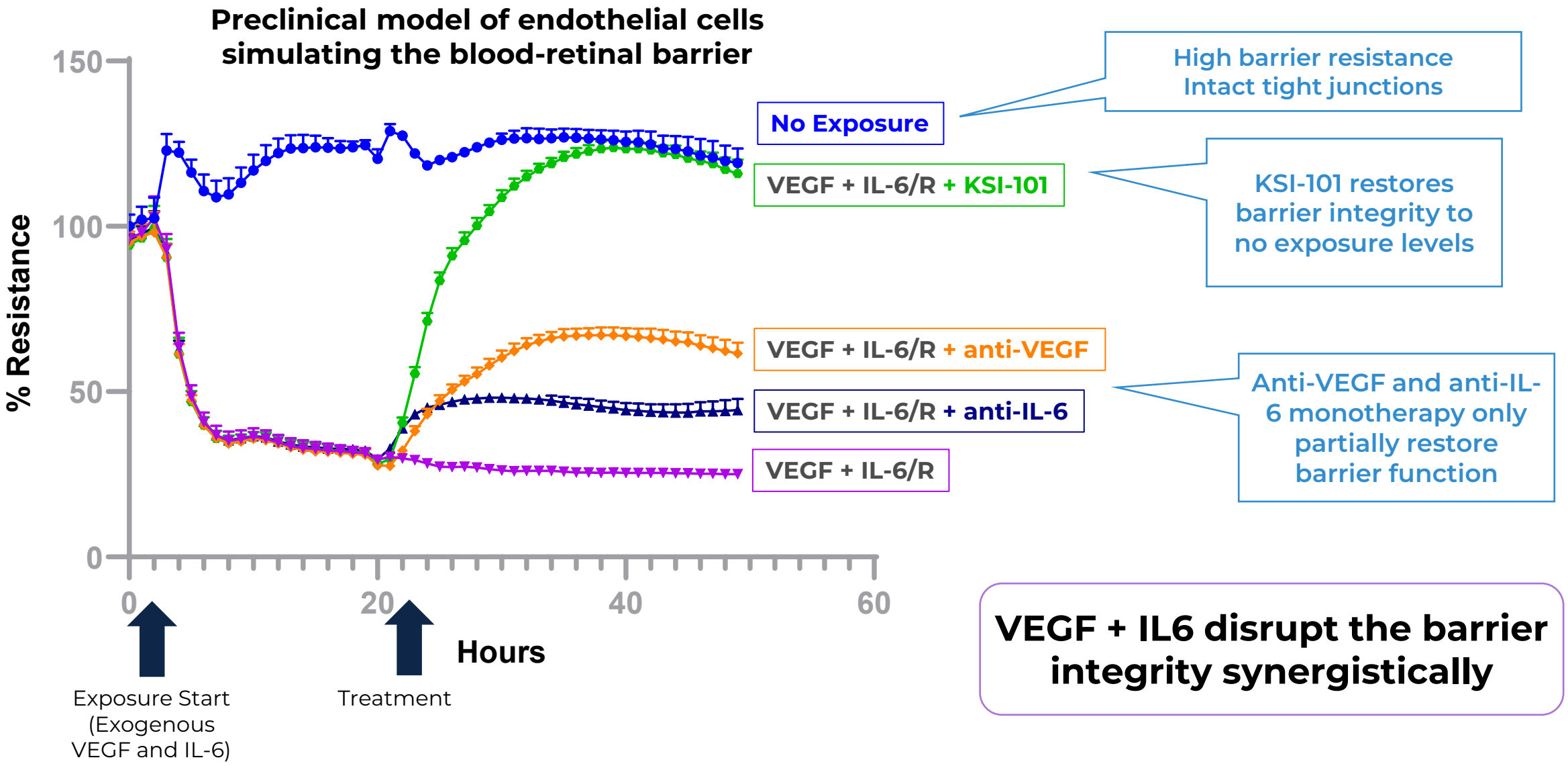
Broad VEGF Inhibition

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

Modified Fc

Immunologically inert antibody

Bispecific KSI-101 restores barrier resistance from pre-existing insult greater than anti-IL-6 or anti-VEGF monotherapies alone

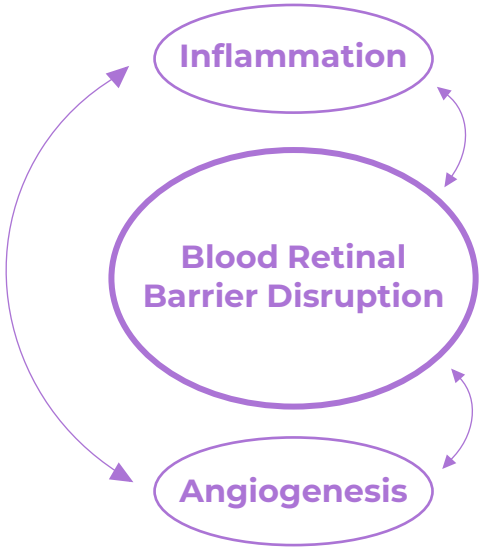


VEGF + IL6 disrupt the barrier integrity synergistically

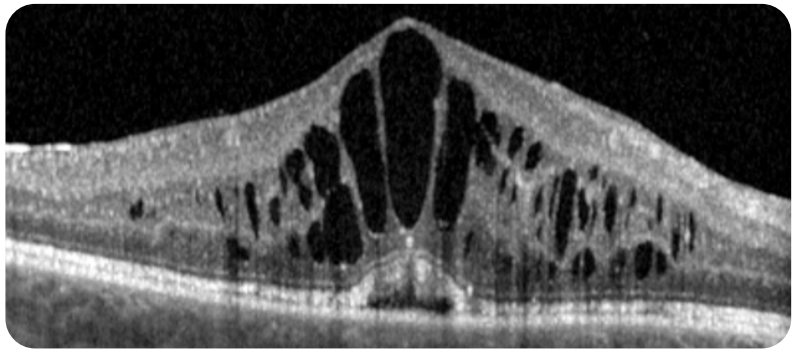
HUVEC cells were treated as indicated after growth to establish barrier

What is macular edema secondary to inflammation (MESI)?

Common Pathophysiology

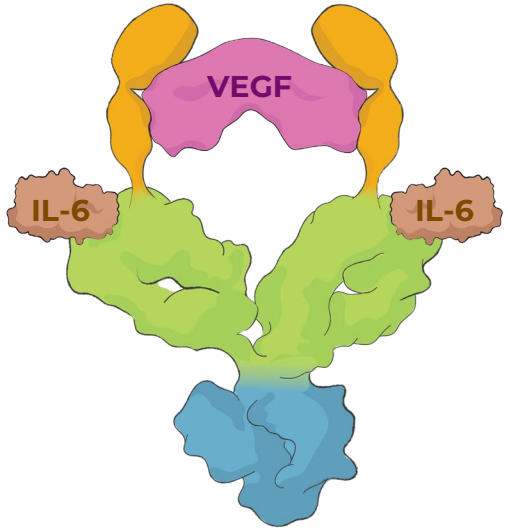


Common Clinical Presentation



Macular Edema with visual impairment

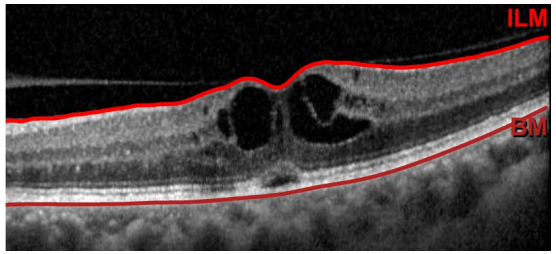
Potential common therapy

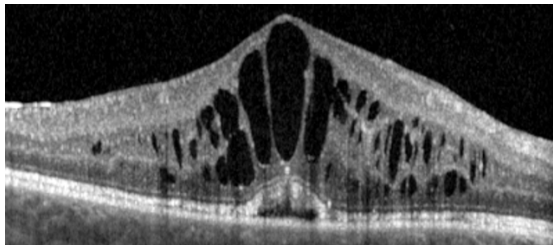


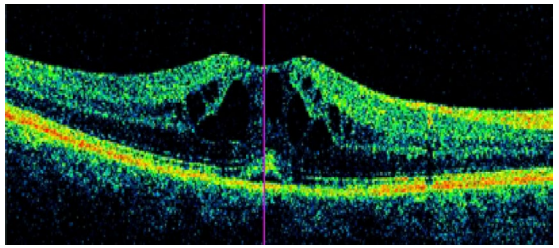
KSI-101

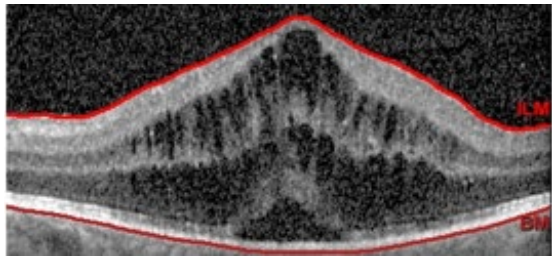
MESI is a heterogenous group of diseases that clinically present with macular edema and visual impairment, which are caused by a common pathophysiology: inflammation and blood retinal barrier disruption

MESI comprises a heterogenous group of diseases with a common, readily identifiable clinical presentation: macular edema with visual impairment







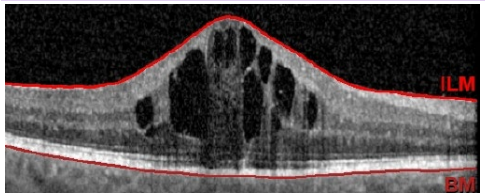
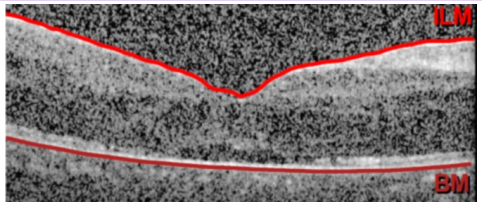
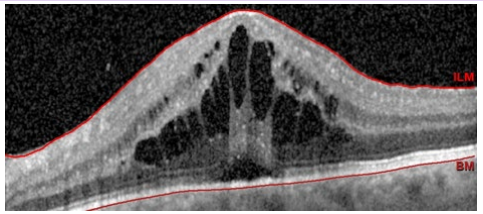
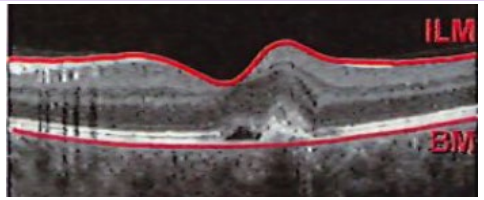
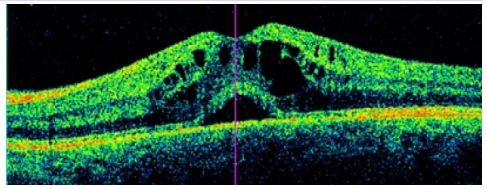


Anterior | **Intermediate** | **Posterior** | **Panuveitis**

Location of inflammation

Irrespective of the anatomical location of the inflammation or the specific etiology, the clinical presentation is the same: macular edema

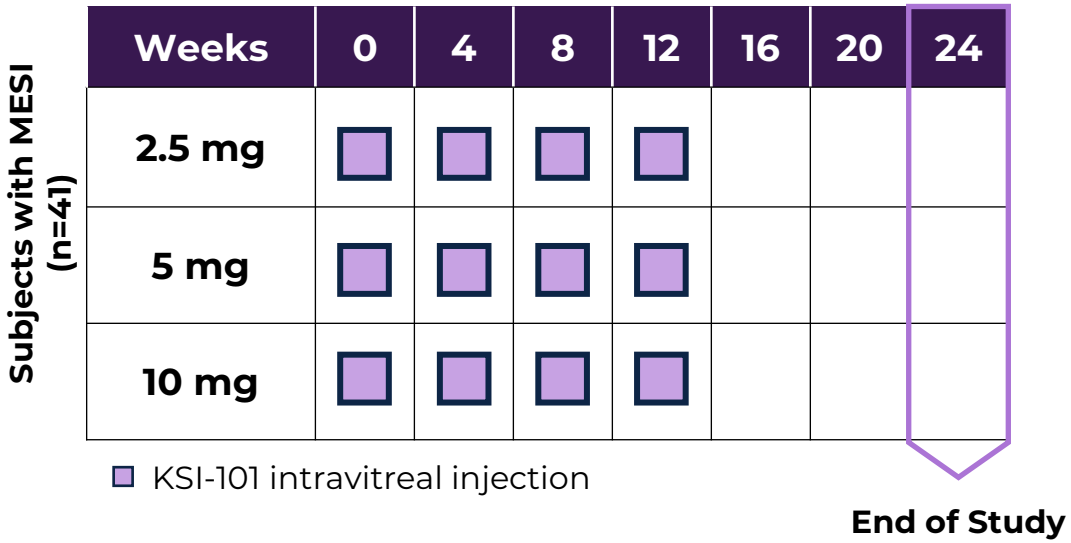
Specific Etiology

Idiopathic	Juvenile Idiopathic Arthritis	Focal Chorioretinal inflammation	Punctate Inner Choroidopathy	Post-Operative Macular Edema
				

Phase 1b APEX study: multiple dose study of KSI-101 in patients with MESI

Enrollment complete

Study Design: Ongoing, Open-label Phase 1b in MESI



Key inclusion criteria

- Macular edema secondary to inflammation (MESI)
- Diagnosis of active or inactive non-infectious intraocular inflammation, acute or chronic.
- Active leakage as evidenced by fluorescein angiogram.
- OCT CST of ≥320 microns
- BCVA score ≤75 and ≥25 (20/32 to 20/320 Snellen equivalent)

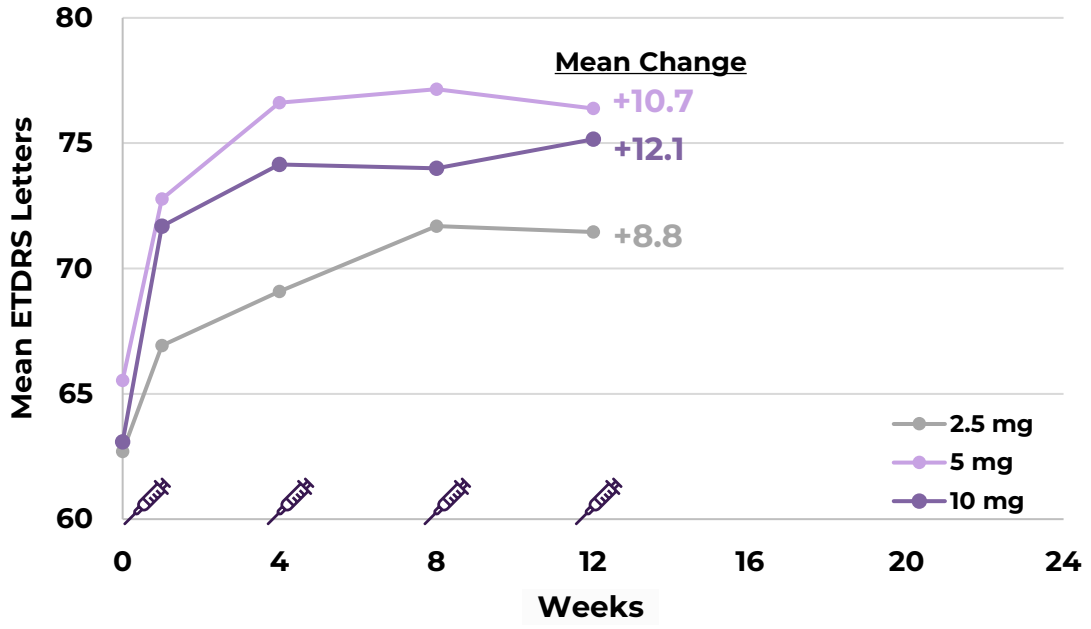
Baseline Characteristics

	KSI-101 2.5 mg (n=13)	KSI-101 5 mg (n=14)	KSI-101 10 mg (n=14)	All KSI-101 (N=41)
Age, years, mean (SD)	74.2 (11.6)	67.4 (8.1)	67.5 (18.8)	69.6 (13.7)
Female, n (%)	8 (61.5)	7 (50.0)	8 (57.1)	23 (56.1)
Race, White, n (%)	11 (84.6)	11 (78.6)	14 (100)	36 (87.8)
MESI disease duration, months, mean (SD)	12.2 (20.1)	1.7 (1.2)	15.8 (37.2)	11.1 (26.5)
Inflammation anatomical location, n (%)				
Anterior	0	2 (14.3)	0	2 (4.9)
Intermediate	1 (7.7)	0	2 (14.3)	3 (7.3)
Posterior	10 (76.9)	6 (42.9)	10 (71.4)	26 (63.4)
Panuveitis	2 (15.4)	6 (42.9)	2 (14.3)	10 (24.4)
Patients with active inflammation, n (%)	3 (23.1)	10 (71.4)	5 (35.7)	18 (43.9)
Unilateral MESI, n (%)	9 (69.2)	6 (42.9)	5 (35.7)	20 (48.8)
BCVA, ETDRS Letters, mean (SD)	62.7 (7.4)	65.5 (7.8)	62.1 (8.4)	63.5 (7.8)
Snellen equivalent	~20/50	~20/50	~20/63	~20/50
OCT CST, µm, mean (SD)	461.7 (137.7)	487.0 (124.1)	528.6 (157.3)	493.2 (139.7)
Lens Status, pseudophakic, n (%)	9 (69.2)	13 (92.9)	11 (78.6)	33 (80.5)

The APEX study is ongoing. Final results may be different due to data cleaning.

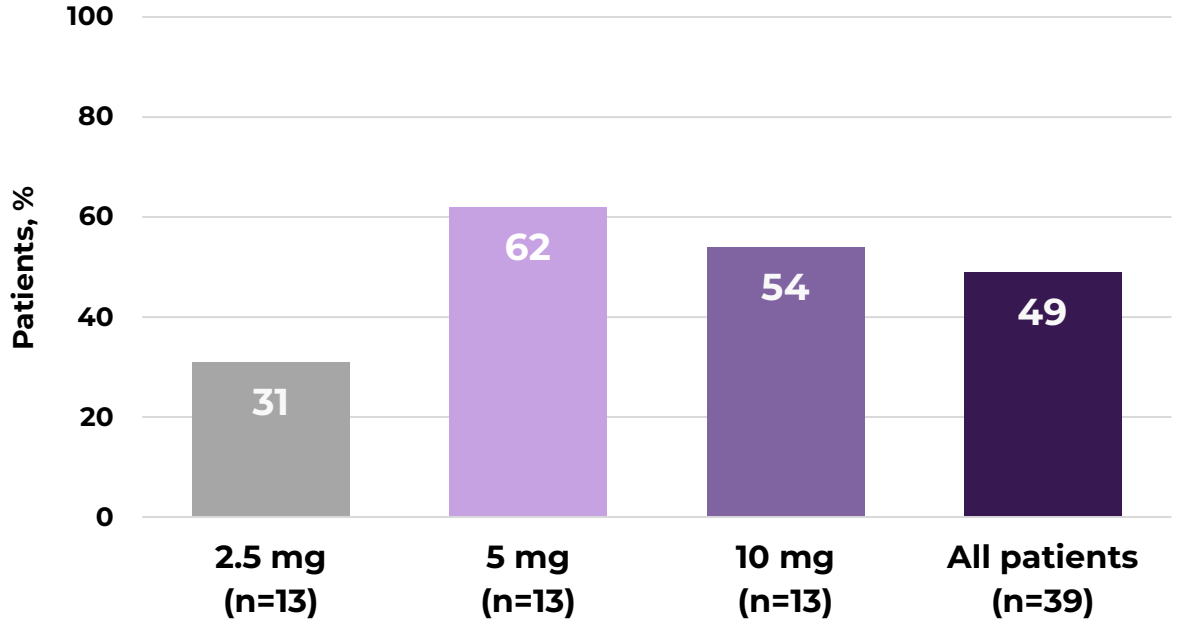
APEX KSI-101 in MESI – Meaningful vision gains are rapidly achieved as early as Week 4 and ≥half of patients in the top two dose levels achieved a ≥15 letter gain

Observed BCVA over time



Dose Level	Sample Size				
2.5 mg	13	13	13	13	13
5 mg	13	13	13	13	13
10 mg	13	13	13	13	13

Proportion of ≥15 letter gainers

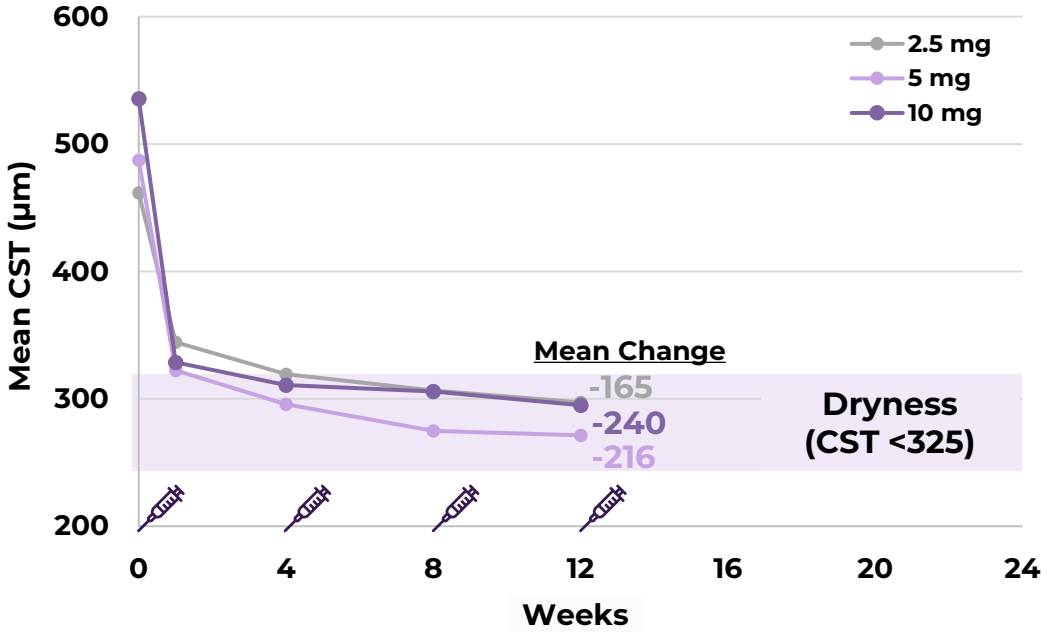


Preliminary analysis: all patients have completed Week 12

The APEX study is ongoing. Final results may be different due to data cleaning. Includes patients in the per protocol set that completed the Week 12 visit and met all the eligibility criteria. Excludes one patient in the 5 mg dose that discontinued treatment before Week 4, and one patient in the 10 mg dose with a significant epiretinal membrane at baseline (exclusion criterion).

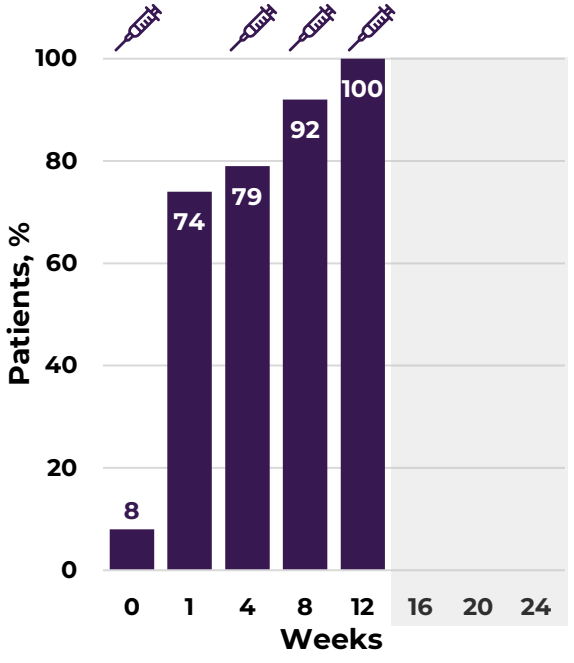
APEX KSI-101 in MESI – A single dose of KSI-101 results in the majority of patients achieving dryness. Over 90% of patients achieve dryness by Week 8

Observed OCT CST over time[a]



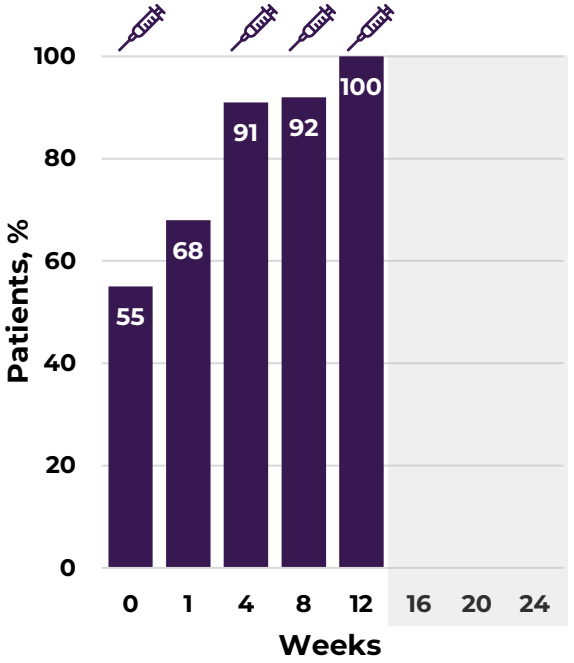
Dose Level	Sample Size				
2.5 mg	13	13	13	13	13
5 mg	13	13	13	13	13
10 mg	13	13	13	13	13

Proportion of patients achieving absence of IRF[b]



N values Pooled KSI-101					
	38	38	33	25	21

Proportion of patients achieving absence of SRF[b]



N values Pooled KSI-101					
	38	38	33	25	21

The APEX study is ongoing. Final results may be different due to additional data collection or data cleaning.

[a] Includes patients in the per protocol set that completed the Week 12 visit and met all the eligibility criteria. Excludes one patient in the 5 mg dose that discontinued treatment before Week 4, and one patient in the 10 mg dose with a significant epiretinal membrane at baseline (exclusion criterion).

[b] Includes patients in the per protocol set that meet all the eligibility criteria. Excludes one patient in the 10 mg dose with a significant epiretinal membrane at baseline (exclusion criterion). Includes all data available by the 14-Jul-25 reporting date.

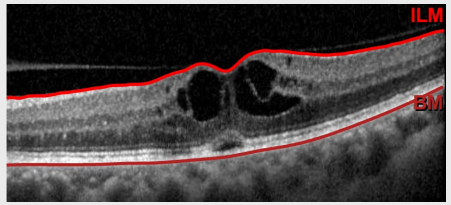
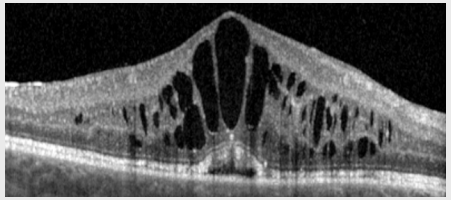
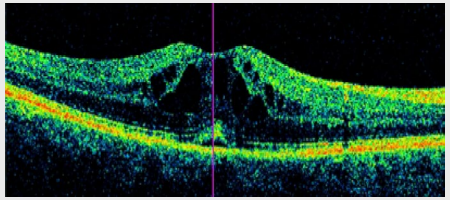
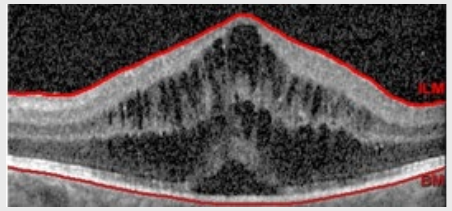
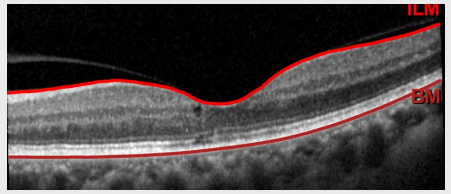
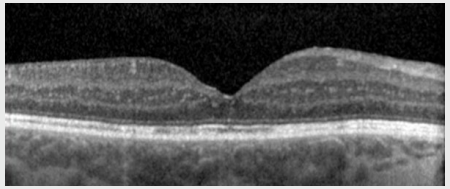
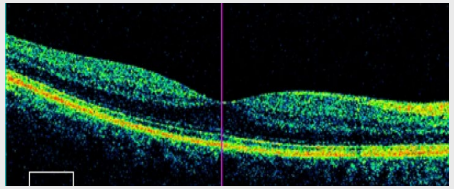
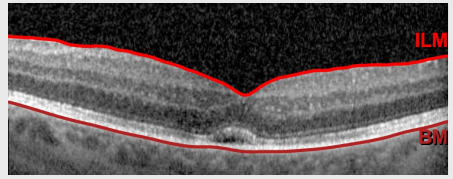
APEX KSI-101 in MESI – KSI-101 was well-tolerated

	KSI-101 2.5 mg (n=13)	KSI-101 5 mg (n=14)	KSI-101 10 mg (n=14)	All KSI-101 (N=41)
Summary of AEs in the Study eye, n (%)				
Subjects with ≥1 AEs	2 (15.4)	3 (21.4)	2 (14.3)	7 (17.1)
Treatment-related AEs	1 (7.7)[a]	1 (7.1)[b]	0	2 (4.9)
Serious AEs	0	0	0	0
Treatment-related serious AEs	0	0	0	0
Severe AEs	0	0	0	0
AEs leading to study discontinuation	0	1 (7.1)[b]	0	1 (2.4)
Selected AEs in the Study Eye, n (%)				
Intraocular inflammation (recurrent uveitis flare-up)	1 (7.7)[a]	1 (7.1)[b]	0	2 (4.9)
Occlusive retinal vasculitis	0	0	0	0
Cataract	0	0	0	0
Elevated IOP	0	0	0	0
Eye Pain	1 (7.7)[a]	0	0	1 (2.4)
Vitreous hemorrhage	1 (7.7)[a]	0	0	1 (2.4)

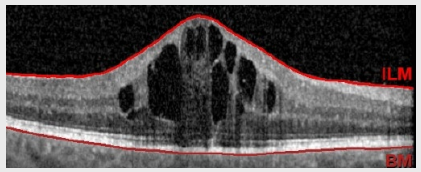
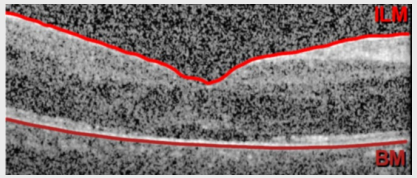
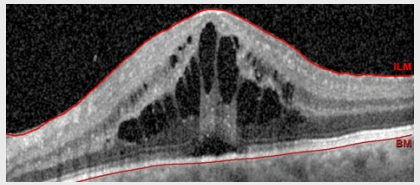
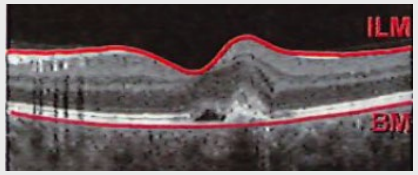
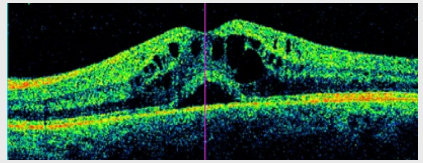
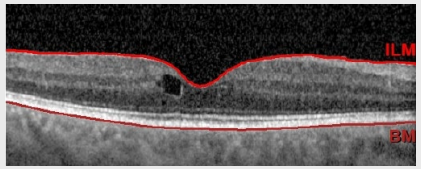
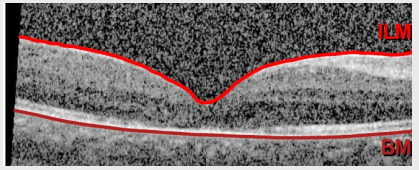
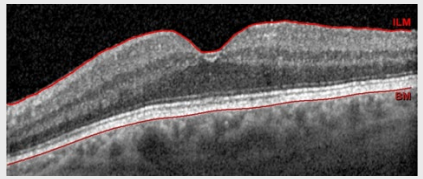
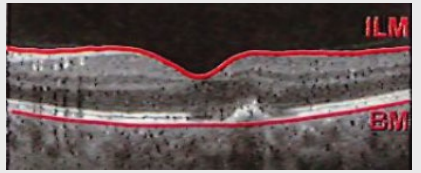
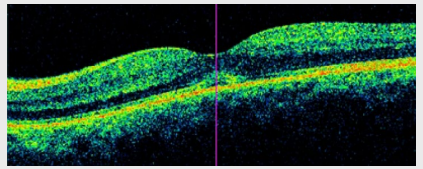
The APEX study is ongoing. Final results may be different due to additional data collection or data cleaning.
AE, Adverse event; IOP, intraocular pressure. Events are investigator reported. Adverse events are treatment-emergent events with start date ≥first study drug date and ≤last study drug date + 28 days.
[a] Same patient. Vitreous hemorrhage secondary to aqueous humor sampling at the Day 1 visit (pre-dose). The patient had 3+ AC cells and flare and 2+ vitreous haze ***prior*** to the Day 1 KSI-101 dose. The patient safely received all 4 doses of KSI-101 and is +26 letters in BCVA at their last visit and no intraocular inflammation.
[b] Same patient. Uveitis flare-up consistent with underlying disease

After a single dose of KSI-101, heterogenous MESI diseases show rapid and meaningful responses to the simultaneous IL-6 and VEGF inhibition, irrespective of the location of the inflammation or the specific macular edema diagnosis

Location of inflammation

	Anterior	Intermediate	Posterior	Panuveitis
Day 1				
Week 4 Effect of a single dose of KSI-101				

Specific Macular Edema Etiology

	Idiopathic	Juvenile Idiopathic Arthritis	Focal Chorioretinal inflammation	Punctate Inner Choroidopathy	Post-Operative Macular Edema
Day 1					
Week 4 Effect of a single dose of KSI-101					

APEX KSI-101 in DME – Meaningful visual and anatomical gains were achieved with KSI-101, with additional benefits with continued dosing. KSI-101 was well-tolerated

Study Design: Ongoing, Open-label Phase 1b in treatment-naïve DME

Subjects with DME (n=12)

Weeks	0	4	8	12	16	20	24
2.5 mg	■	■	■	■	■		
5 mg	■	■	■	■	■		
10 mg	■	■	■	■	■		

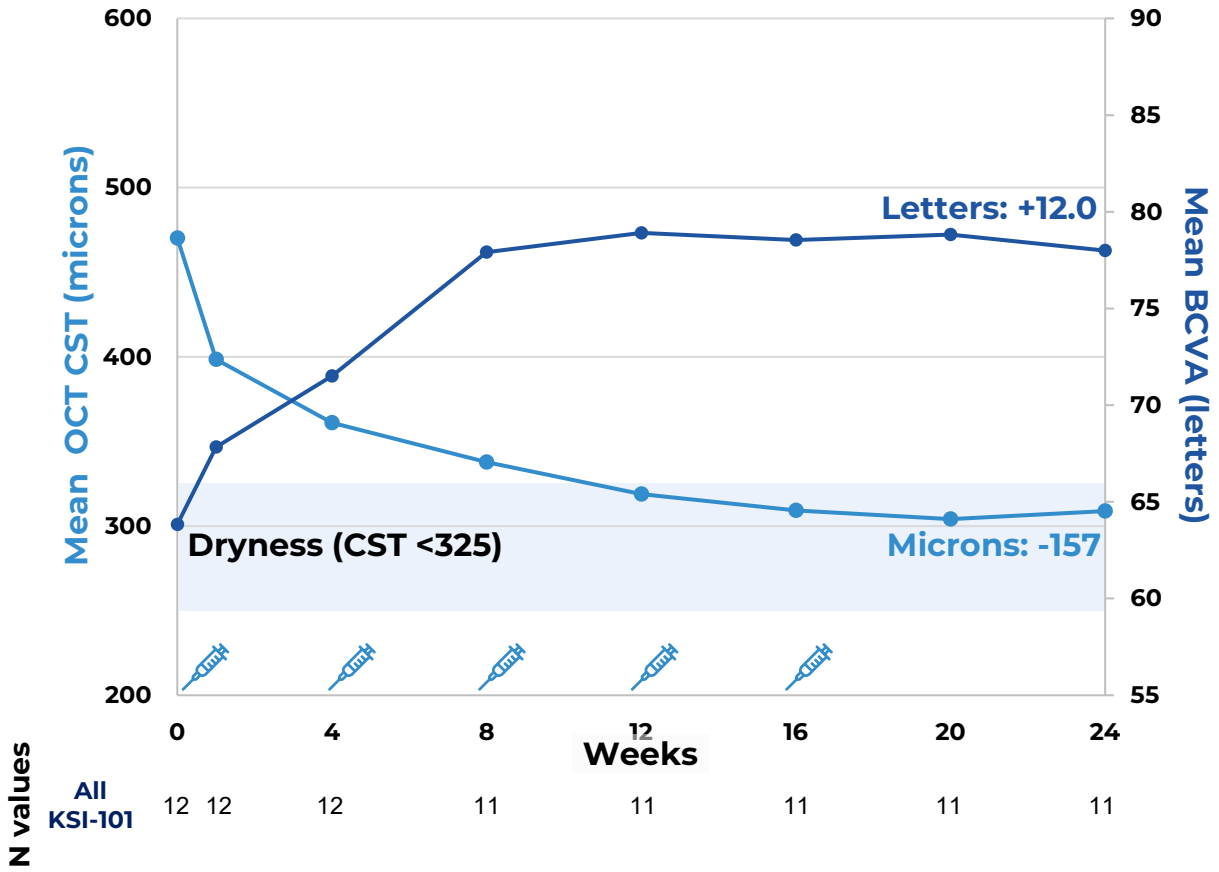
■ KSI-101 intravitreal injection

End of Study

Safety

	All KSI-101 (N=12)
Summary of AEs in the Study eye, n (%)	
Subjects with ≥1 AEs	1 (8.3)
Treatment-related AEs	0
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	0
Occlusive retinal vasculitis	0
Cataract	0
Cataract traumatic*	1 (8.3)

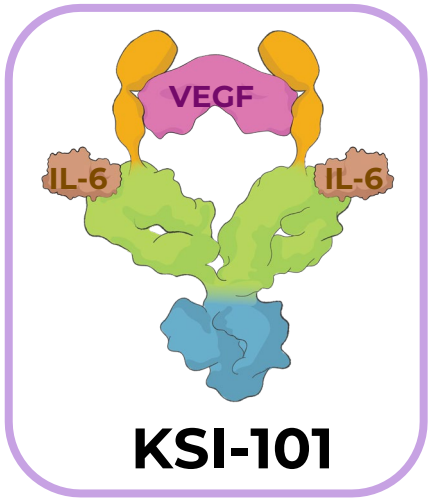
Mean Change in BCVA and OCT CST in DME
All KSI-101 dose levels combined



The APEX study is ongoing. Final results may be different due to additional data collection or data cleaning.
AE, Adverse event; IOP, intraocular pressure. Events are investigator reported. Adverse events are treatment-emergent events with start date ≥first study drug date and ≤last study drug date + 28 days.
* Anterior traumatic cataract due to aqueous humor routine sample

Conclusions: KSI-101 demonstrated meaningful visual and anatomical improvements in patients with MESI in the APEX Study

- **MESI:** group of diseases with a shared pathophysiology — inflammation & BRB disruption
- **Treatment with KSI-101 in MESI patients in APEX, 12-week analyses:**
  - **Robust anatomic and visual responses to date**
    - Half of patients achieved a ≥15 letter gain.
    - >90% resolution of both IRF & SRF by Week 8
    - Consistent response with different underlying etiologies
- **Two Phase 3 trials of KSI-101 in MESI actively enrolling**



	Fixed monthly dosing						Individualized dosing						
Weeks	**D1**	**4**	**8**	**12**	**16**	**20**	**24**	**28**	**32**	**36**	**40**	**44**	**48**
KSI-101 5 mg (n~50)													
KSI-101 10 mg (n~50)													
Sham (n~50)													

Primary endpoint

- KSI-101 5 mg injection
- KSI-101 10 mg injection
- Sham injection
- Individualized treatment (PRN)
- Sham PRN

Key inclusion criteria

- Macular edema secondary to inflammation (MESI)
- Diagnosis of active or inactive non-infectious intraocular inflammation, acute or chronic.
- Active leakage as evidenced by fluorescein angiogram
- OCT CST of ≥320 microns
- BCVA score ≤78 and ≥25 (~20/25 to 20/320 Snellen)

PEAK

Moderate to severe edema with moderate to severe vision impairment

PINNACLE

Moderate to severe edema with good vision

Mild edema with any vision impairment

PEAK and PINNACLE are actively enrolling

PEAK: NCT06990399. PINNACLE: NCT06996080