Extended Durability in Exudative Retinal Diseases Using the Novel Intravitreal Anti-VEGF Antibody Biopolymer Conjugate KSI-301

Phase 1b Study in Patients with wAMD, DME and RVO

Year 1 Results

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Disclosures

- **Financial:**

  Aerie (C, R), Allergan (C), Asclepix (C, R), Boehringer Ingelheim (C, R), Genentech (C), Kodiak (C, S) Novartis (C, R), Regeneron (C, R) , Santen (C, R)

- **Study Disclosures:**

  This study of an investigational product includes research conducted on human subjects. Institutional Review Board (IRB) approval was obtained prior to study initiation.

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

KSI-301 Phase 1b Study – Year 1 Results
Key Questions

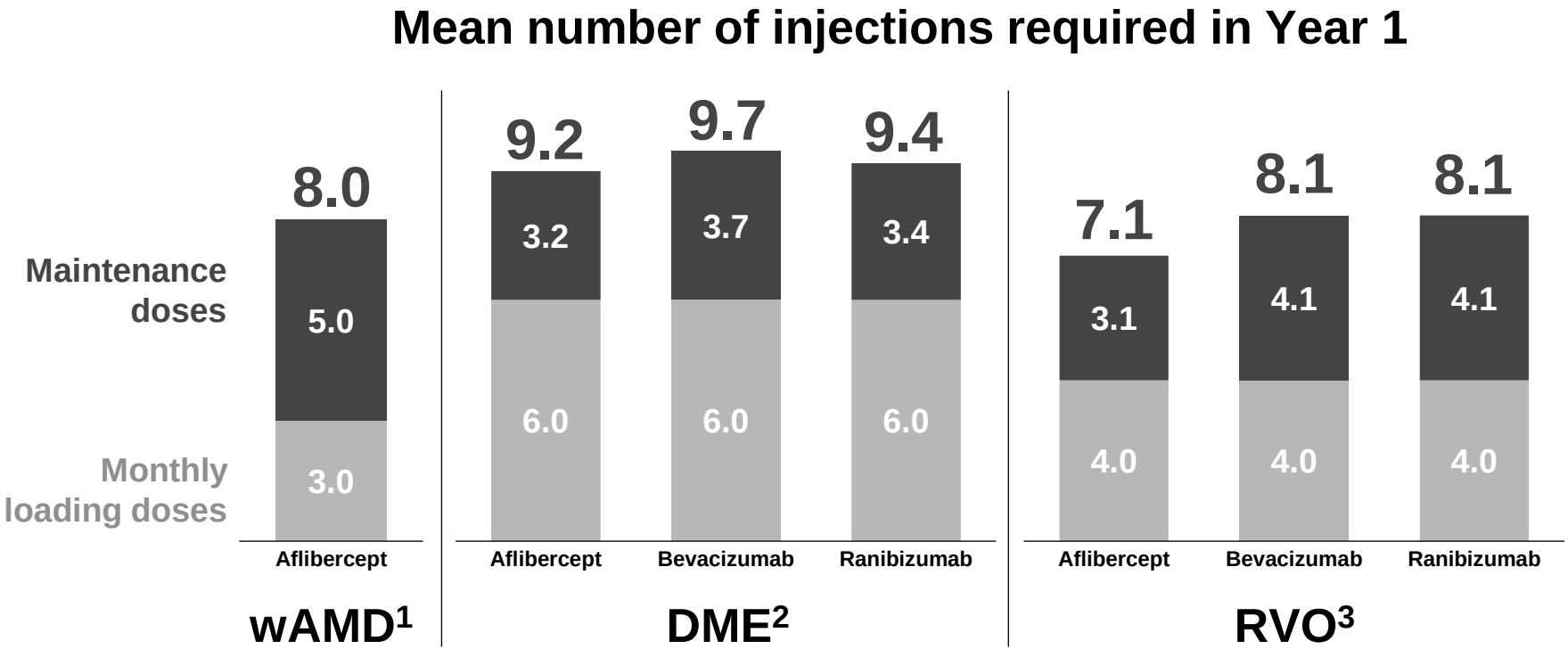
Do the data support the potential for KSI-301 to meaningfully advance the treatment paradigm for major retinal vascular diseases?

Can KSI-301 provide the expected **efficacy gains in line with current anti-VEGF agents**?

Can KSI-301 achieve **clinical durability of 6-months or longer** in the majority of patients, and **with fewer loading doses**?

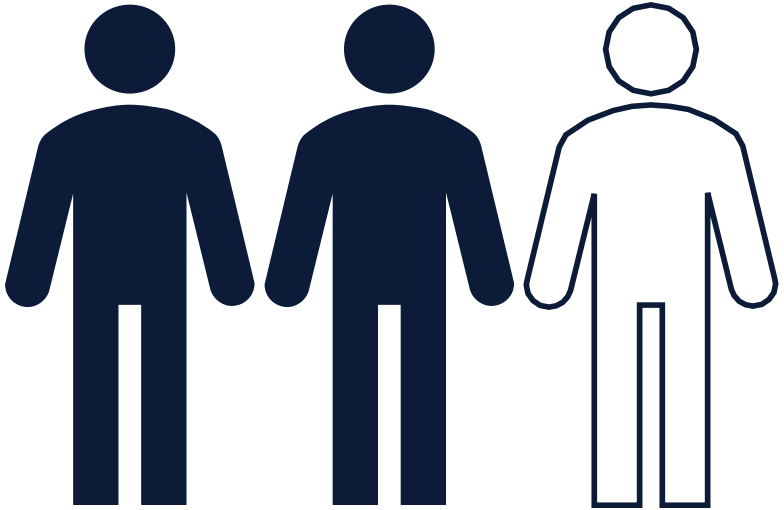
Does KSI-301 have the **excellent safety profile** expected for intravitreal anti-VEGF agents ranibizumab and aflibercept?

Current anti-VEGF agents depend on high-frequency treatment to be most efficacious



1. Heier JS. VIEW Studies. Ophthalmology. 2012 Dec;119(12):2537-48.
2. Wells JA. DRCR.net Protocol T. N Engl J Med. 2015 Mar 26;372(13):1193-203 (supplemental data).
3. Hykin P. LEAVO trial. JAMA Ophthalmol. 2019 Aug 29;137(11):1256-1264.

KSI-301 shows impressive and consistent durability across retinal vascular diseases in Year 1



2 in every 3 patients are on a ≥ 6-month treatment-free interval at Year 1 after only 3 loading doses

Interval at Year 1	wAMD n=50	DME n=32	RVO n=32
≥6 months	66%	69%	66%

Phase 1b interim data. 2.5 & 5 mg doses pooled. Includes only patients that received all (3) loading doses and either a) received a dose before Week 52 or b) did not receive a dose and were followed for at least six months after the last loading dose (Week 32 visit). Two RVO patients were not included as they discontinued at the Week 12 and 16 visits, respectively, without receiving a retreatment dose. Interval at Year 1 reflects the treatment interval ongoing at the Week 52 visit (where available) or the last interval before Week 52.

KSI-301

Clinical Data

130 patients dosed in Phase 1a/1b Program

168+ patient years of clinical experience

KSI-301 Phase 1b Study Design

Randomized, open label study to evaluate multidose safety, efficacy & durability

wAMD (n=51) | **DME** (n=35) | **RVO** (n=35)

Randomized 1:3

KSI-301 2.5 mg (50 μL) | KSI-301 5 mg (100 μL)

	Loading Phase			Durability Assessment Phase	Extension Study
Weeks	0	4	8	12 to 72 (months 3 to 18)	76 to 148 (months 19 to 36)
	■	■	■	Monthly monitoring with protocol guided retreatment	Monthly monitoring with protocol guided retreatment

wAMD = wet age-related macular degeneration; DME = diabetic macular edema; RVO = retinal vein occlusion; Clinicaltrials.gov ID: NCT03790852

■ Fixed Treatment

KSI-301 Phase 1b Retreatment Criteria

- **wAMD**
  - Increase in CST ≥75 µm with a decrease in BCVA of ≥ 5 letters compared to Week 12, *OR*
  - Decrease in BCVA of > 5 letters compared to Day 1, due to worsening wAMD activity, *OR*
  - Decrease in BCVA of ≥ 10 letters compared to the best prior BCVA, due to worsening wAMD activity, *OR*
  - 6 months have elapsed since the last retreatment
- **DME and RVO**
  - Increase in CST ≥75 µm with a decrease in BCVA of ≥ 5 letters compared to Week 12 or the prior visit, *OR*
  - Decrease in BCVA of ≥ 10 letters compared to the best prior BCVA, due to worsening DME/RVO disease activity

For all subjects, investigators can retreat at their discretion if significant disease activity is present that does not meet the above criteria

wAMD = wet age-related macular degeneration; DME = diabetic macular edema; RVO = retinal vein occlusion; CST = central subfield retinal thickness; BCVA = best corrected visual acuity.
Clinicaltrials.gov ID: NCT03790852

Baseline Characteristics

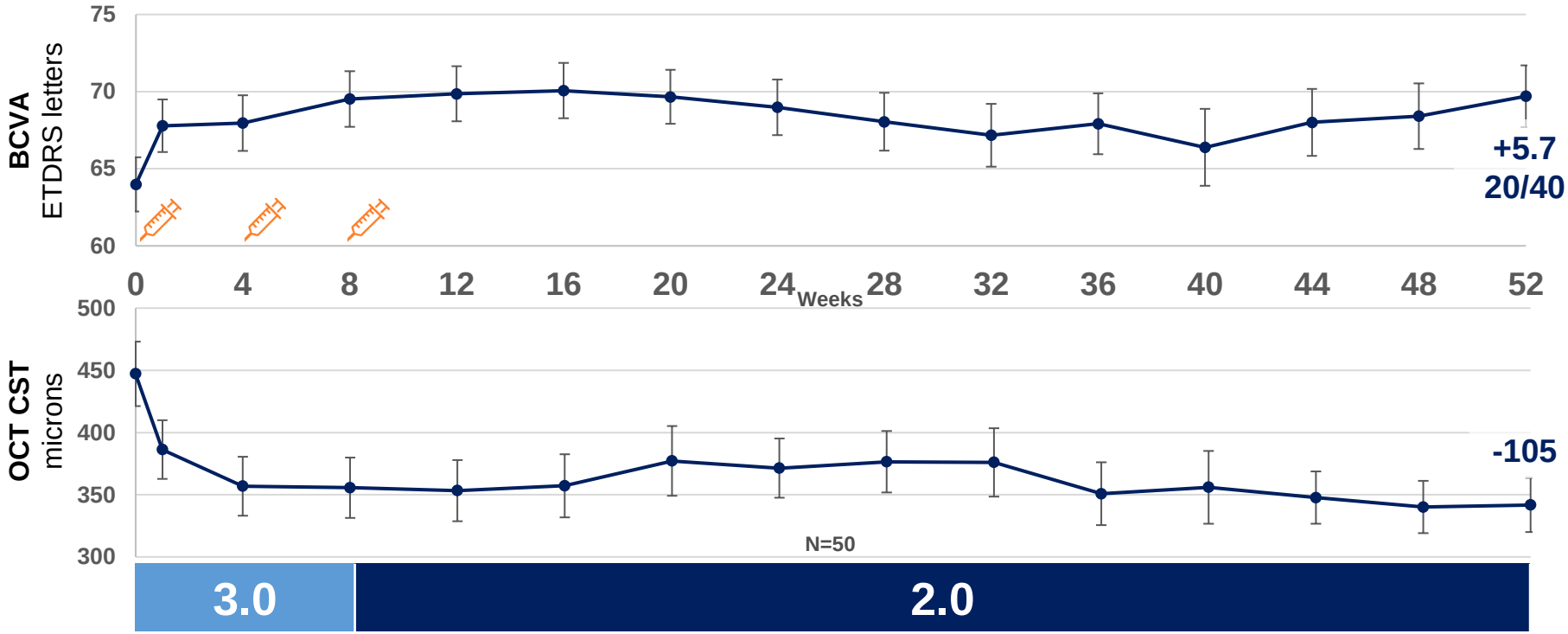
Variable	wAMD Cohort (n=51)	DME Cohort (n=35)	RVO Cohort (n=35)
Age, mean (SD), years	77.9 (10.5)	59.7 (11.7)	63.6 (12.6)
Gender, n (%), female	32 (62.7)	14 (40.0)	13 (37.1)
Race, n (%), White	48 (94.1)	28 (80.0)	31 (88.6)
BCVA, mean (SD), ETDRS letters	**63.3 (13.3)**	**66.8 (10.2)**	**54.9 (15.4)**
Snellen equivalent	~20/50	~20/50	20/80
Snellen 20/40 or better, n (%)	20 (39.2)	16 (45.7)	6 (17.1)
OCT CST, mean (SD), microns	450 (182)	453 (110)	675 (237)

Includes all patients randomized. SD= standard deviation; BCVA= best corrected visual acuity; OCT= optical coherence tomography; CST= central subfield thickness

KSI-301 Phase 1b
wAMD
Year 1 Data

Efficacy of KSI-301 in Wet AMD

Change from baseline to Week 52 in mean BCVA & OCT

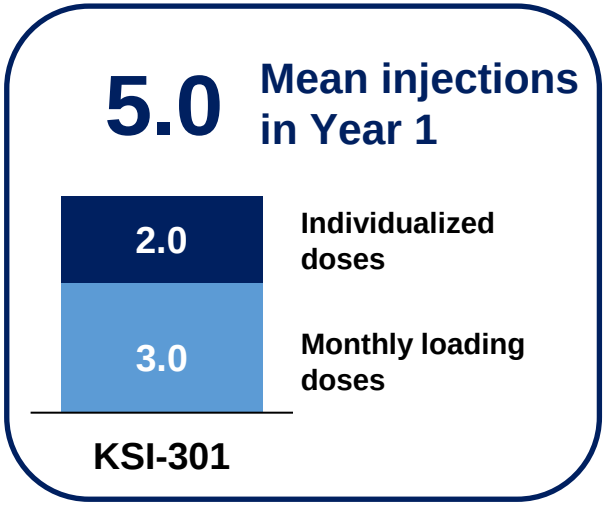


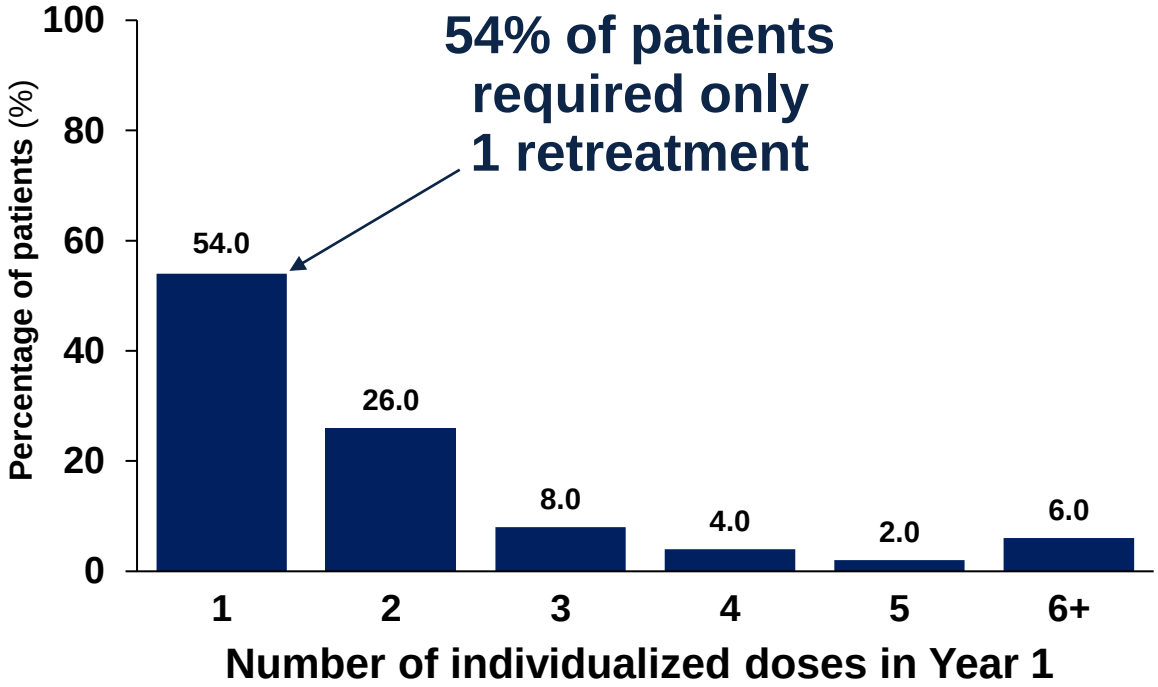
5.0 mean injections in Year 1

Interim data; 2.5 & 5 mg doses pooled. Observed data, includes only patients that received all (3) loading doses and reached Week 12 or later. Error bars represent standard error of the mean. Individualized doses reflect the number of injections received per patient between Week 12 and 48 inclusive. OCT CST site reported and includes the PED height. CST= central subfield thickness.

Durability of KSI-301 in Wet AMD

80% of patients received 2 or fewer retreatments in Year 1

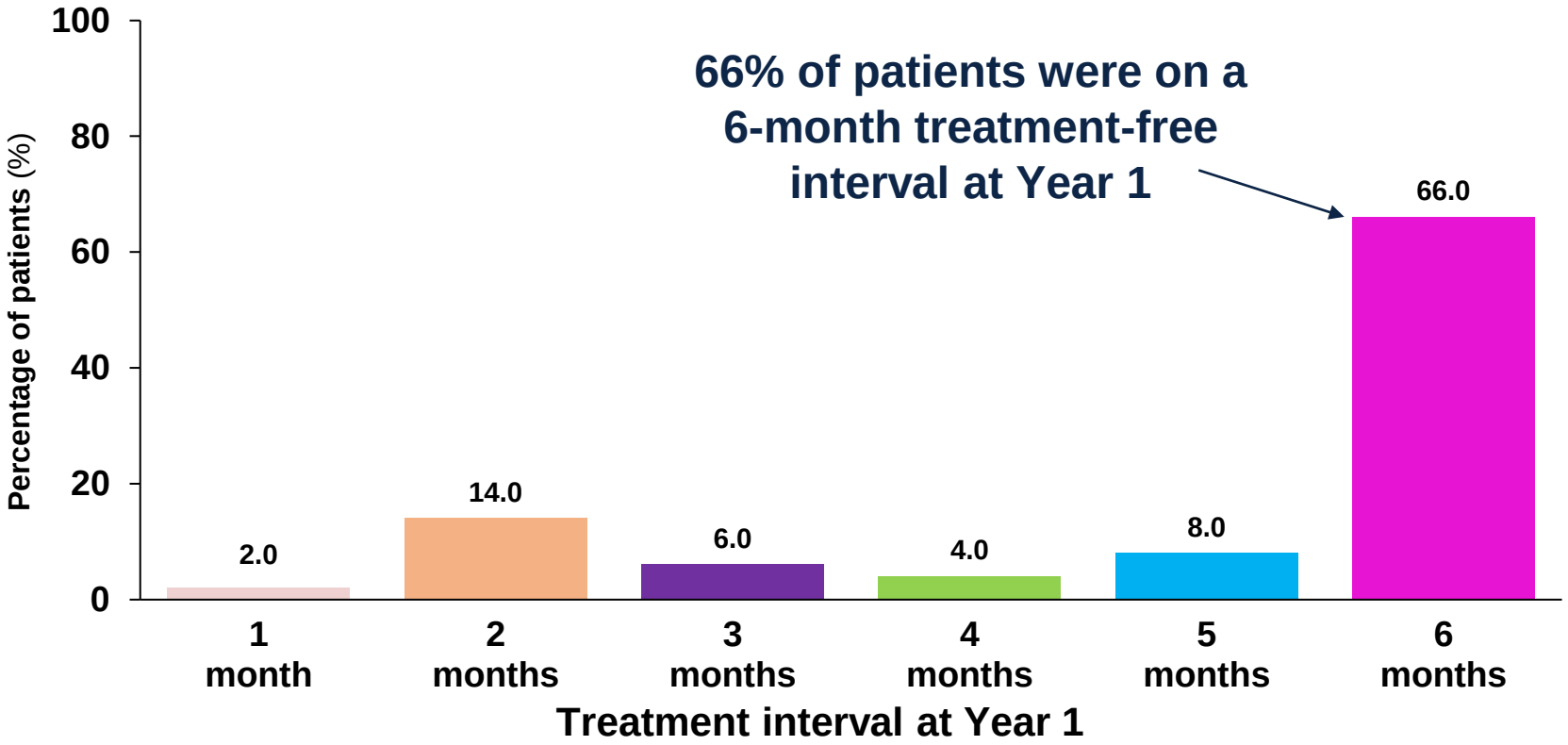




Interim data; 2.5 & 5 mg doses pooled. Includes only patients that received all (3) loading doses and received a dose before Week 52. Individualized doses reflect the number of injections received per patient between Week 12 and 48 inclusive. N=50

Durability of KSI-301 in Wet AMD

Distribution of retreatment intervals at Year 1



Interim data. 2.5 & 5 mg doses pooled. Includes only patients that received all (3) loading doses and either a) received a dose before Week 52 or b) did not receive a dose and were followed for at least six months after the last loading dose (Week 32 visit). Treatment interval at Year 1 reflects the treatment interval ongoing at the Week 52 visit (where available) or the last interval before Week 52. N=50

KSI-301 in wAMD: *the majority of patients can achieve 6-month durability*

Interval at Year 1*	n=50
1 month	2%
2 months	14%
3 months or longer	84%
4 months or longer	78%
5 months or longer	74%
6 months	66%

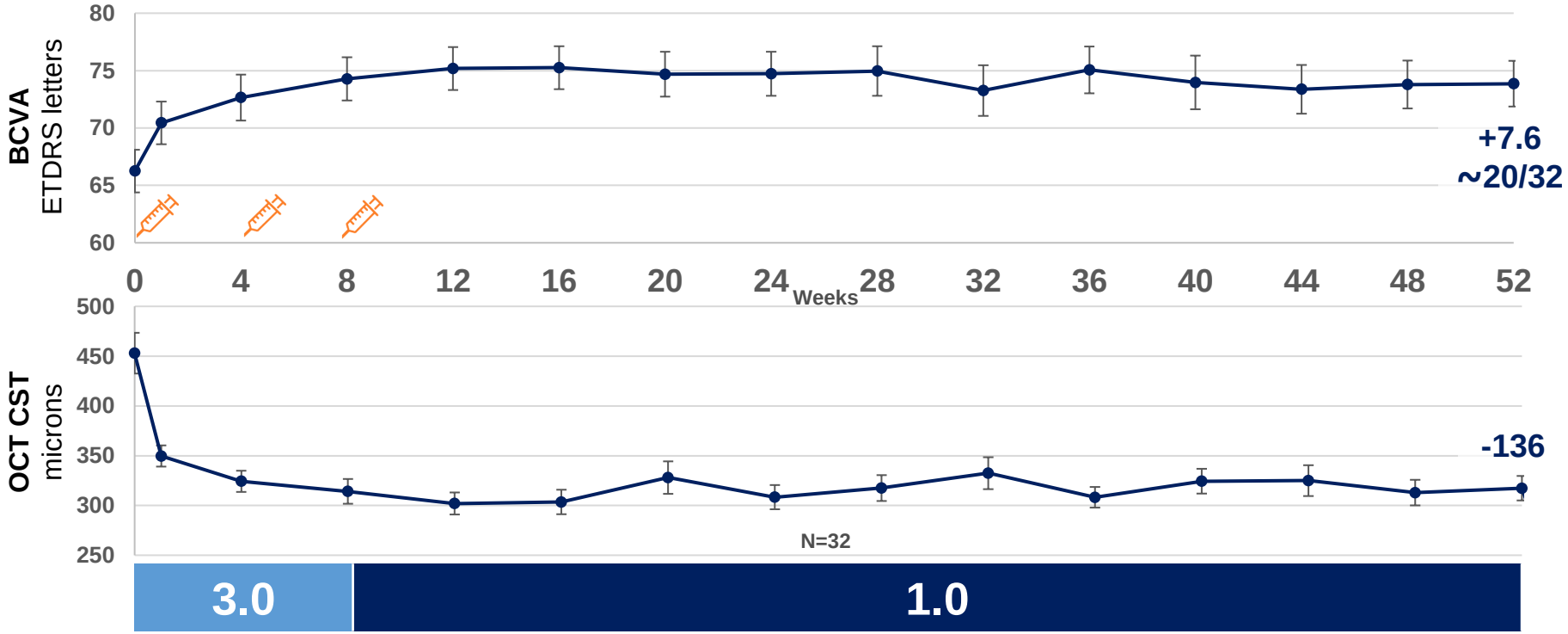
80% have achieved a 6-month treatment-free interval at least once during follow-up

Interim data. Includes only randomized patients that reached the first retreatment opportunity (Week 12 visit). Each bar represents an individual patient.
*Treatment intervals include only patients that received all (3) loading doses and received a dose before Week 52. Interval at Year 1 reflects the treatment interval ongoing at the Week 52 visit (where available) or the last interval before Week 52.

KSI-301 Phase 1b
DME
Year 1 Data

Efficacy of KSI-301 in DME

Change from baseline to Week 52 in mean BCVA & OCT

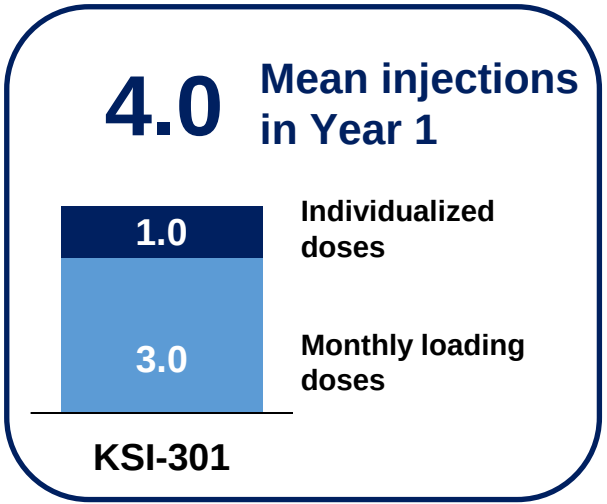


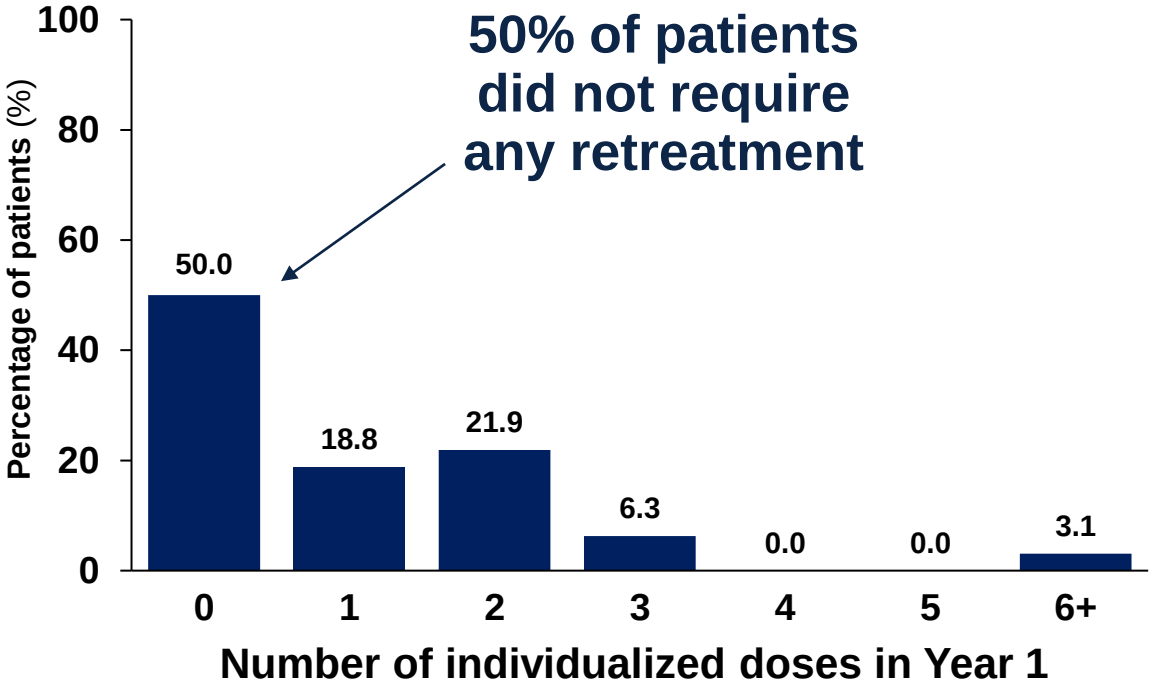
4.0 mean injections in Year 1

Interim data; 2.5 & 5 mg doses pooled. Observed data, includes only patients that received all (3) loading doses and reached Week 12 or later. Error bars represent standard error of the mean. Individualized doses reflect the number of injections received per patient between Week 12 and 48 inclusive. OCT CST site reported. CST= central subfield thickness.

Durability of KSI-301 in DME

90% of patients received 2 or fewer retreatments in Year 1





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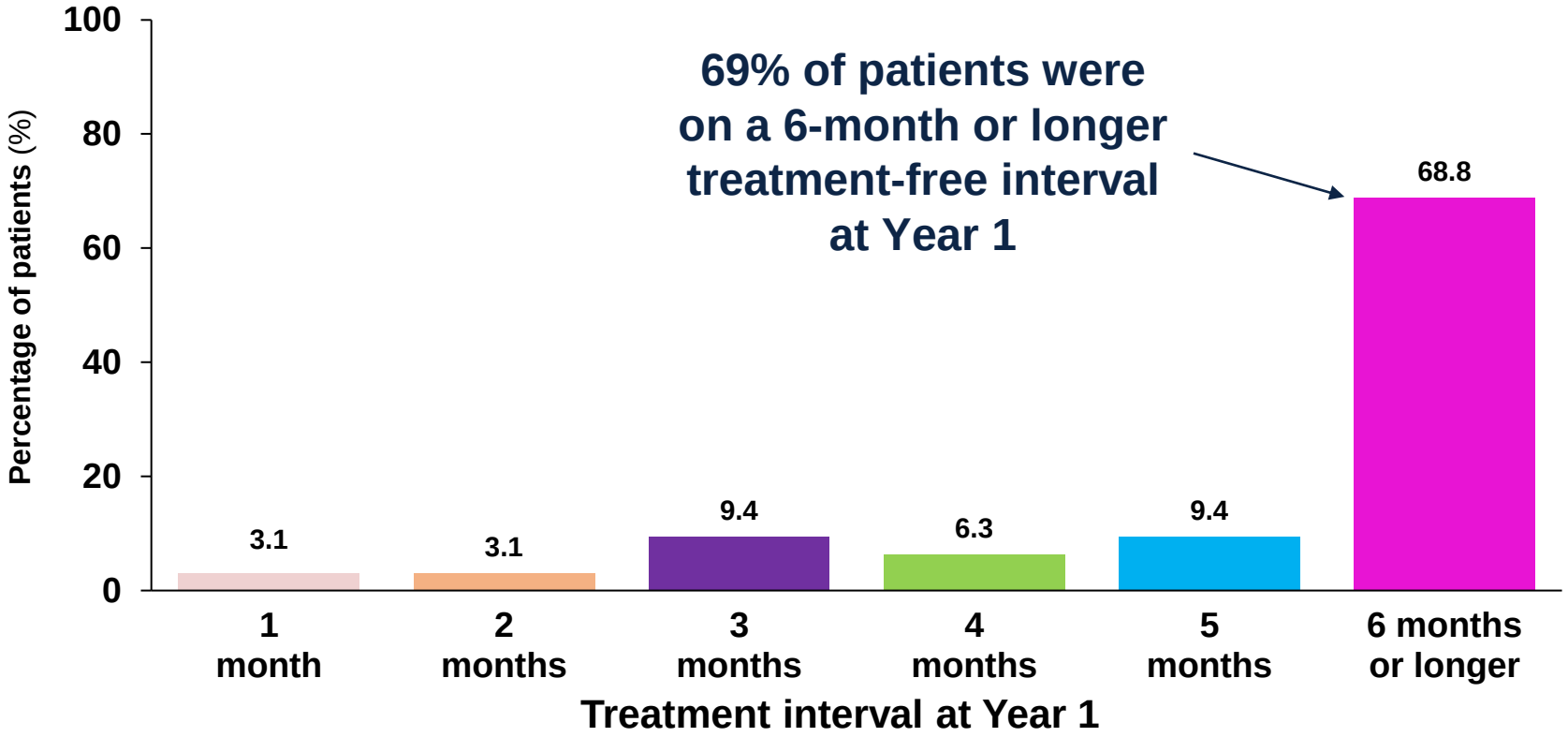
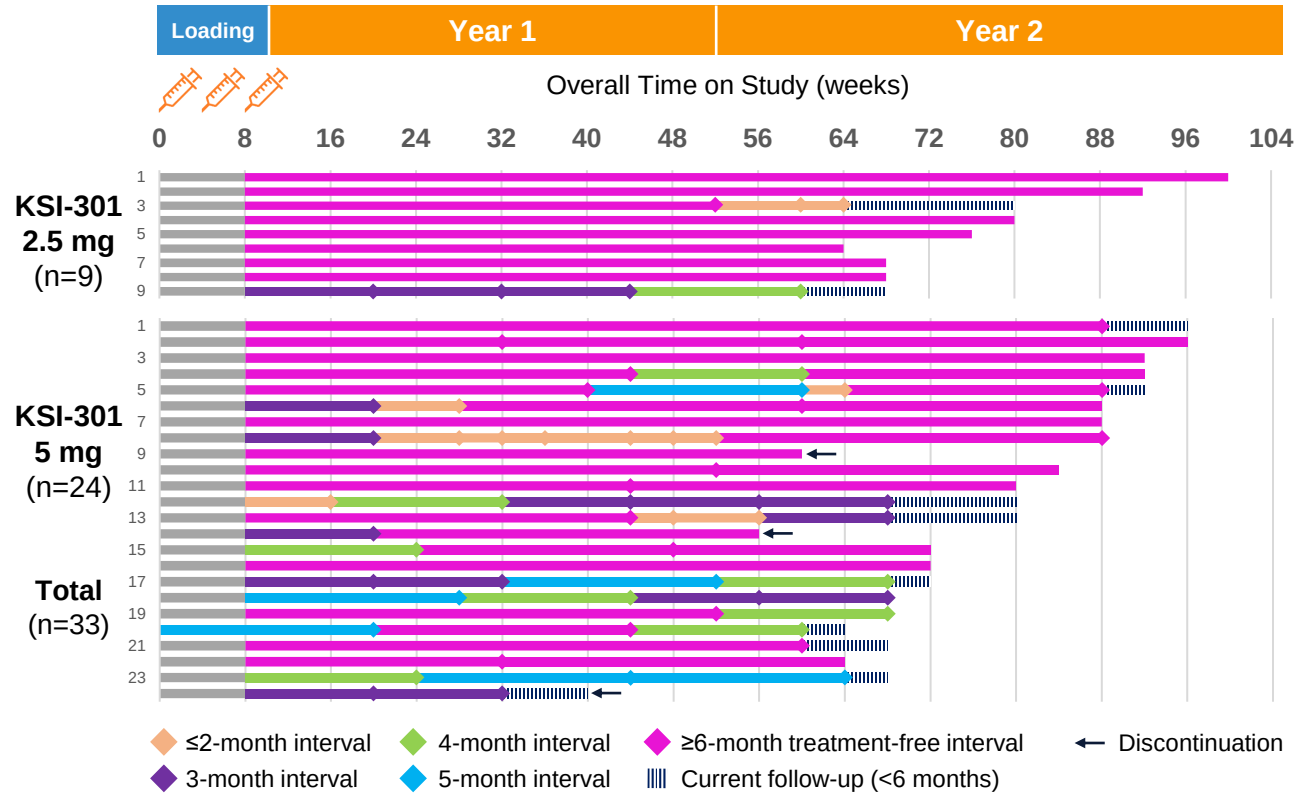
Durability of KSI-301 in DME

Distribution of retreatment intervals at Year 1



Interim data. 2.5 & 5 mg doses pooled. Includes only patients that received all (3) loading doses and either a) received a dose before Week 52 or b) did not receive a dose and were followed for at least six months after the last loading dose (Week 32 visit). Treatment interval at Year 1 reflects the treatment interval ongoing at the Week 52 visit (where available) or the last interval before Week 52. N=32

KSI-301 in DME: *3 loading doses can provide sustained disease control of 3 to 6+ months*



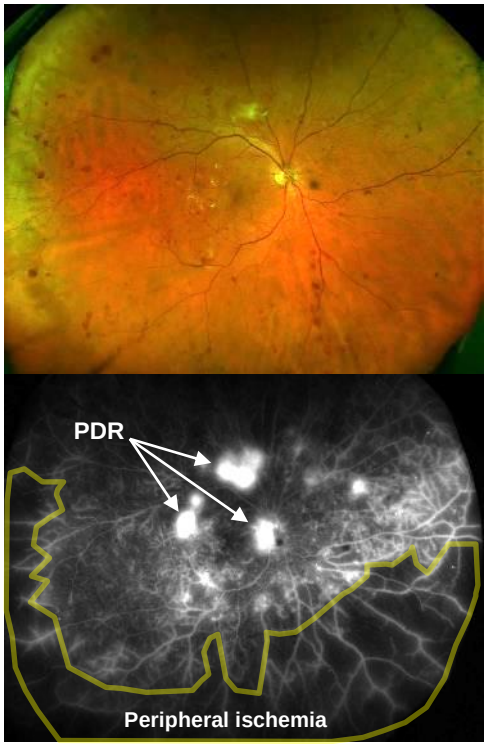
Interval at Year 1*	n=32
1 month	3%
2 months	3%
3 months or longer	94%
4 months or longer	84%
5 months or longer	78%
6 months or longer	69%

81% have achieved a 6-month or longer treatment-free interval at least once during follow-up

Interim data. Includes only randomized patients that reached the first retreatment opportunity (Week 12 visit). Each bar represents an individual patient. *Treatment intervals include only patients that received all (3) loading doses and either a) received a dose before Week 52 or b) did not receive a dose and were followed for at least six months after the last loading dose (Week 32 visit). Interval at Year 1 reflects the treatment interval ongoing at the Week 52 visit (where available) or the last interval before Week 52. One patient only received one loading dose and was excluded from the calculation

6-month disease control after only 3 loading doses is also seen in proliferative diabetic retinopathy

DAY 1
Proliferative DR (DRSS 71)

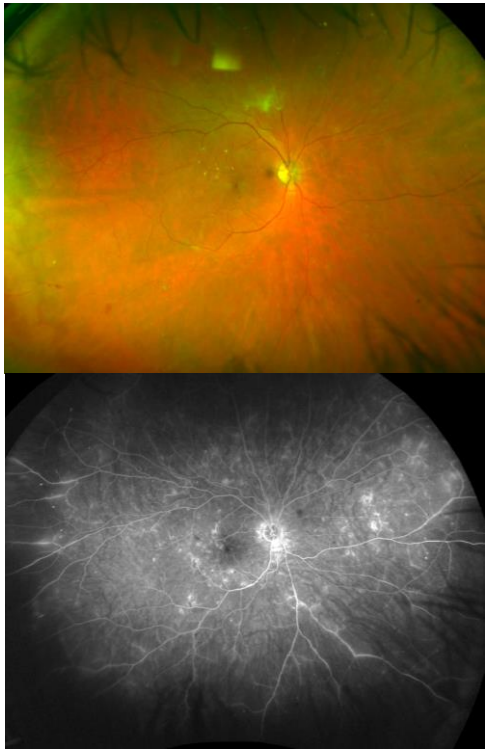


KSI-301 5 mg
3 loading doses

WEEK 12
Non-Proliferative DR (DRSS 53)

Two additional doses

WEEK 72
Non-Proliferative DR (DRSS 53)



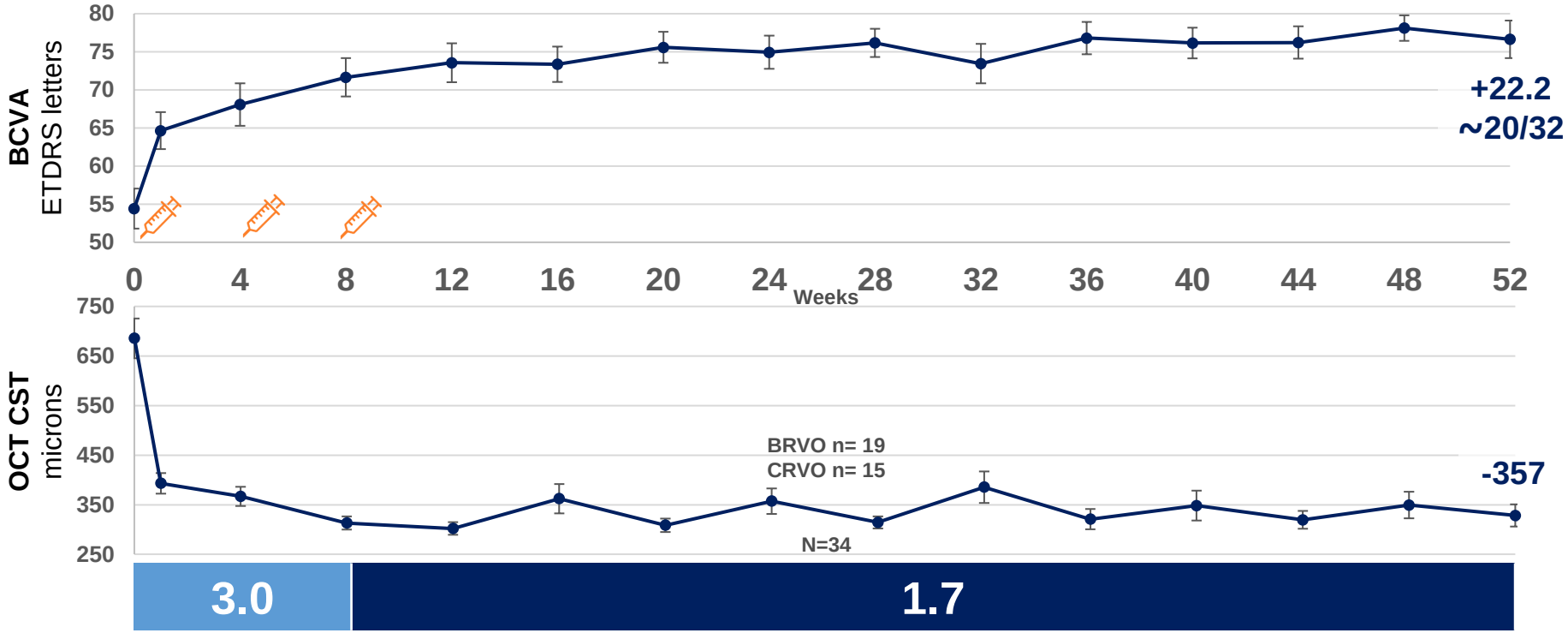
Regression from PDR to NPDR
Fast and substantial (3-step) improvement, sustained for 18 months with only 2 additional doses (26-week mean retreatment interval)

DR= Diabetic Retinopathy; PDR= Proliferative DR; NPDR= Non-Proliferative DR; DRSS = DR Severity Scale; DRSS 53 = Severe NPDR; DRSS 71 = High-risk PDR

KSI-301 Phase 1b
RVO
Year 1 Data

Efficacy of KSI-301 in RVO

Change from baseline to Week 52 in mean BCVA & OCT

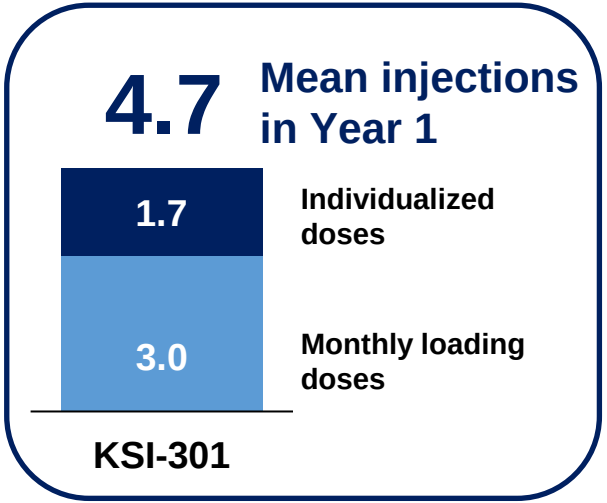


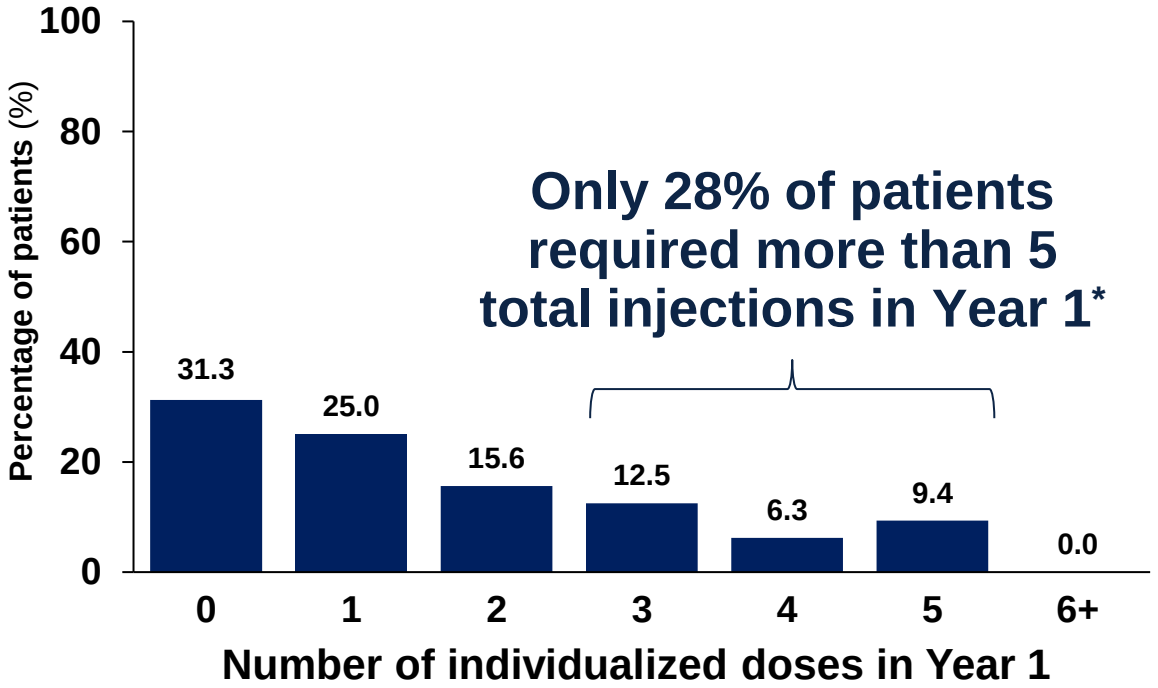
4.7 mean injections in Year 1

Interim data; 2.5 & 5 mg doses pooled. Observed data, includes only patients that received all (3) loading doses and reached Week 12 or later. Error bars represent standard error of the mean. Individualized doses reflect the number of injections received per patient between Week 12 and 48 inclusive. OCT CST site reported. CST= central subfield thickness.

Durability of KSI-301 in RVO

72% of patients received 2 or fewer retreatments in Year 1





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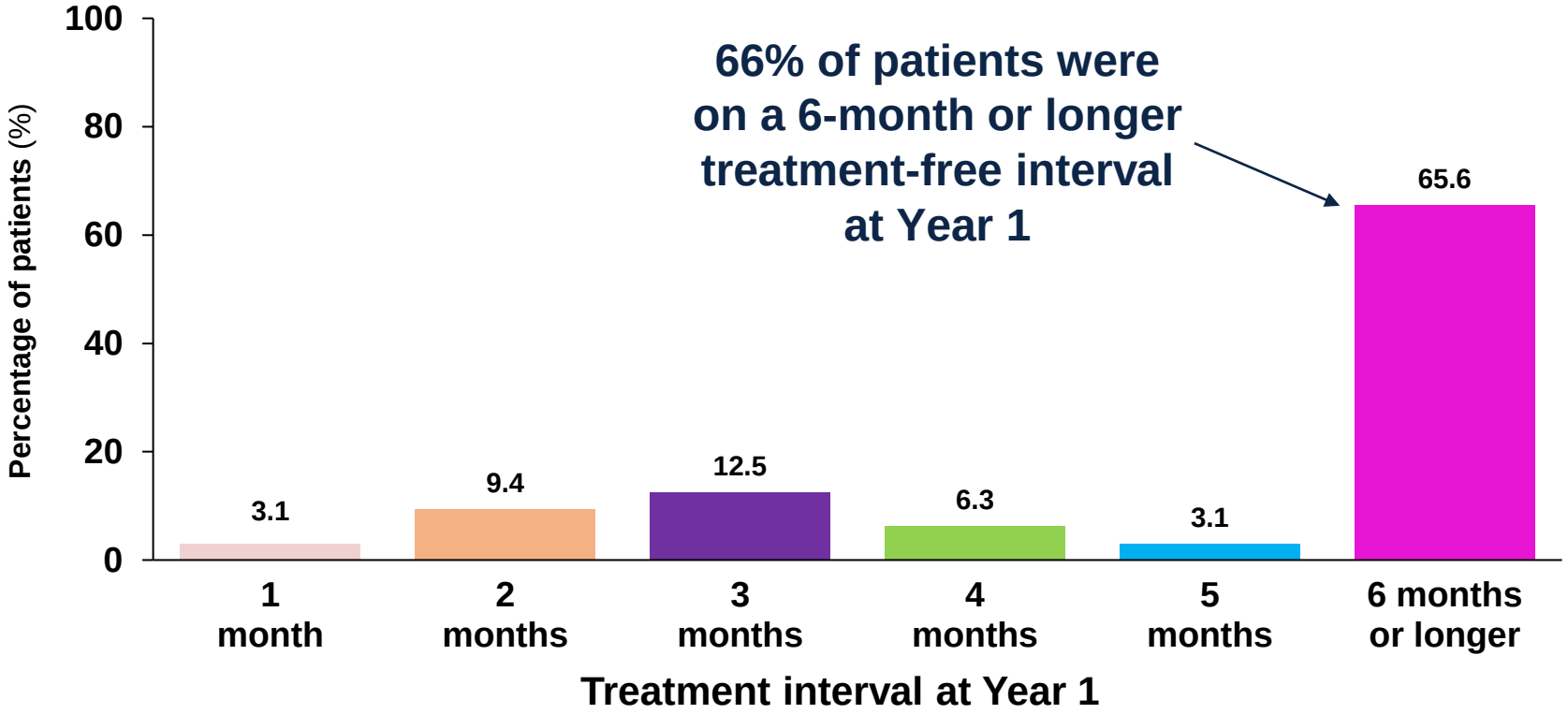
* 3 loading doses plus more than 2 individualized doses

Durability of KSI-301 in RVO

Distribution of retreatment intervals at Year 1



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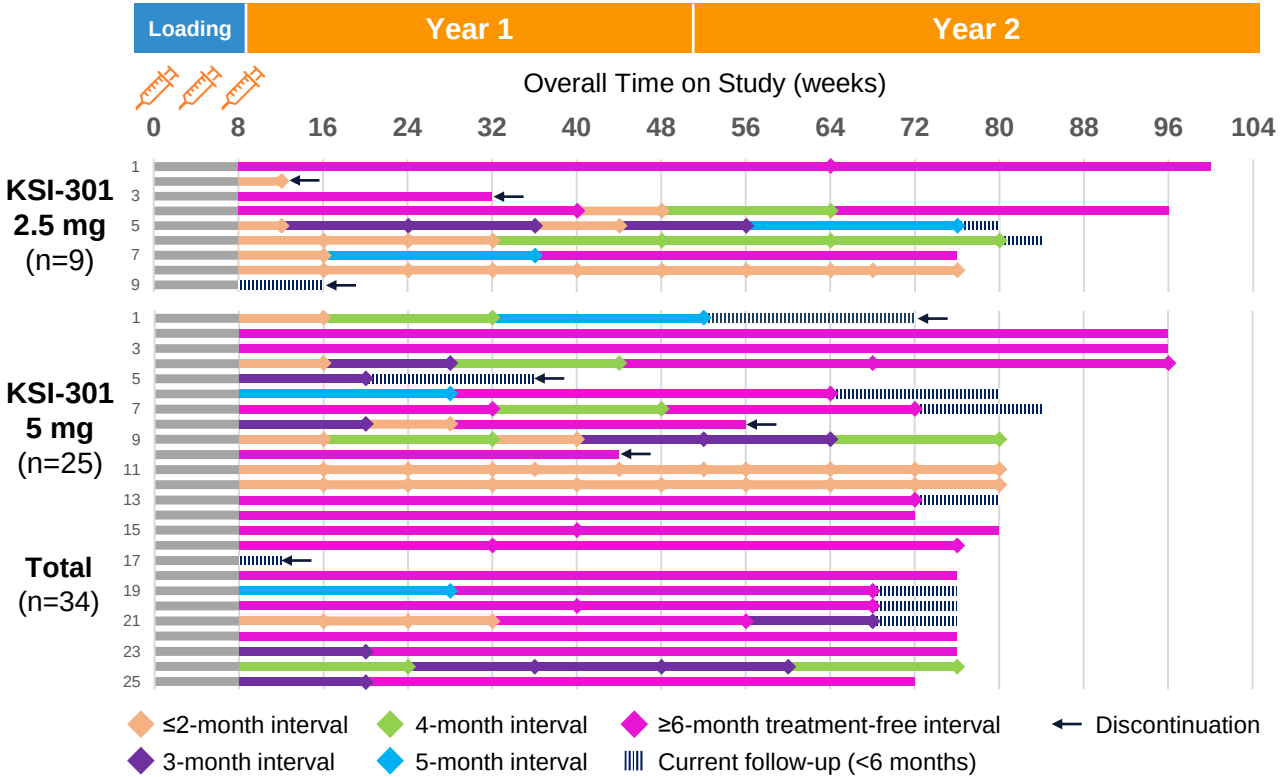
KSI-301 in RVO: *3 loading doses can provide sustained disease control of 2 to 6+ months*



Interval at Year 1*	n=32
1 month	3%
2 months	9%
3 months or longer	87%
4 months or longer	75%
5 months or longer	69%
6 months or longer	66%

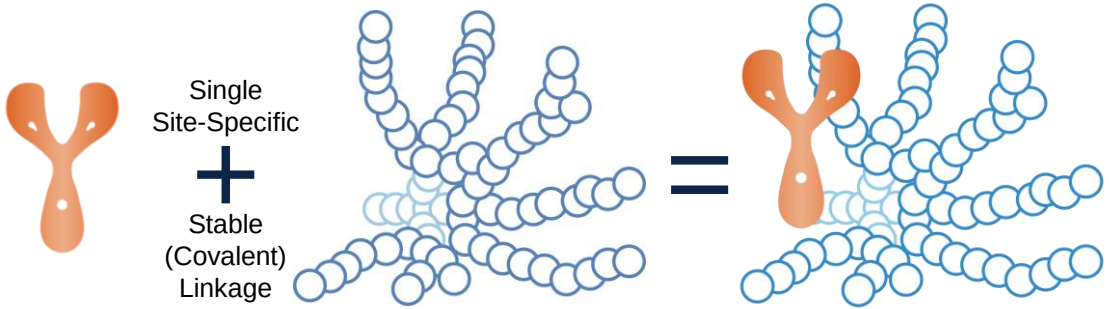
69% have achieved a 6-month or longer treatment-free interval at least once during follow-up

Interim data. Includes only randomized patients that reached the first retreatment opportunity (Week 12 visit). Each bar represents an individual patient. *Treatment intervals include only patients that received all (3) loading doses and either a) received a dose before Week 52 or b) did not receive a dose and were followed for at least six months after the last loading dose (Week 32 visit). Interval at Year 1 reflects the treatment interval ongoing at the Week 52 visit (where available) or the last interval before Week 52. Two patients discontinued before receiving their first retreatment and less than 6 months of follow-up after the loading phase.

How can KSI-301 achieve strong efficacy ***and*** remarkable durability?

Antibody Biopolymer Conjugates (ABC)

Biologics precision-engineered for increased durability and efficacy



ANTIBODY

lgG1 Antibody
Immunologically inert

BIOPOLYMER

Branched, High Molecular Weight, Optically Clear Phosphorylcholine Polymer

CONJUGATE

A new set of integrated properties
– more than the sum of its parts –

Nature's zwitterion

Structured water micro-environment

Non-adsorption

Zero-friction

Stereospecific docking

SAME WHERE IT MATTERS

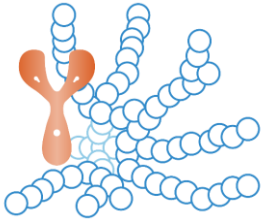
- Clinically proven targets
- Antibody-based biologic
- Intravitreal: safest method of administration
- Optically clear, no residues
- Fast and potent clinical responses

DIFFERENT WHERE IT COUNTS

- Designed-in ocular durability
- Designed-in rapid systemic clearance
- Improved bioavailability
- Improved biocompatibility
- Deeper potency

KSI-301: Next-Generation anti-VEGF

ABC Platform and higher dose for longer treatment duration

	Ranibizumab	Bevacizumab	Aflibercept	KSI-301
Molecule type	Antibody fragment	Antibody	Recombinant fusion protein	**Antibody Biopolymer Conjugate (ABC)**
Molecular structure				
Molecular weight	48 kDa	149 kDa	115 kDa	**950 kDa**
Clinical dose	0.3-0.5 mg	1.25 mg	2 mg	**5 mg** (by weight of antibody)
Equivalent molar dose	0.5	0.9	1	**3.5**
Equivalent ocular PK	0.7	1	1	**3**
Equivalent ocular concentration at 3 months	0.001	NA[1]	1	**1,000**

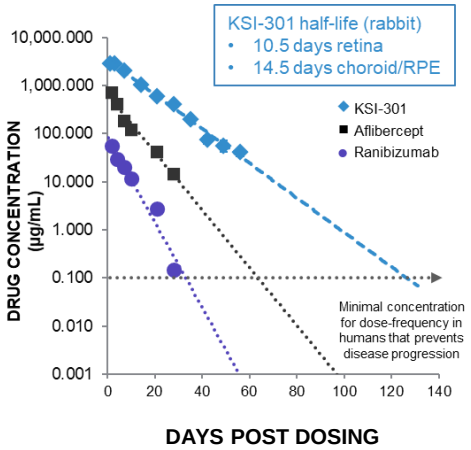
Equivalent values are shown as (approximate) fold difference relative to aflibercept. kDa= kilodalton

1. Lower affinity of bevacizumab precludes a useful comparison

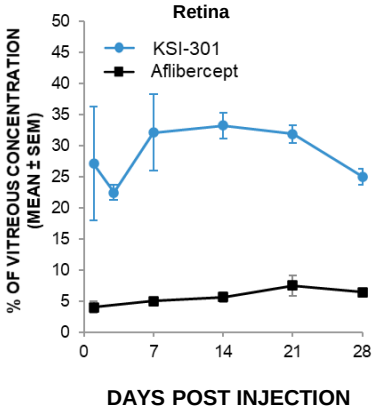
Integrated properties of ABC Platform are ideal for a long-acting intravitreal therapeutic

More than the sum of its parts

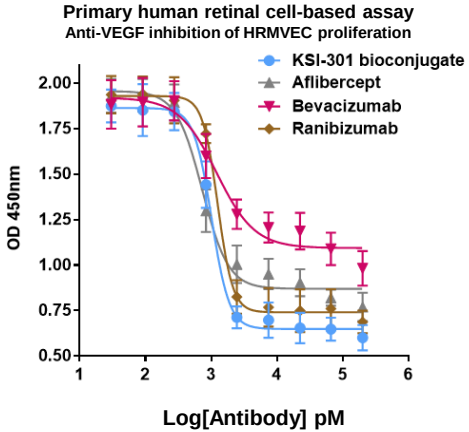
Remarkable Intraocular Half-life[1]



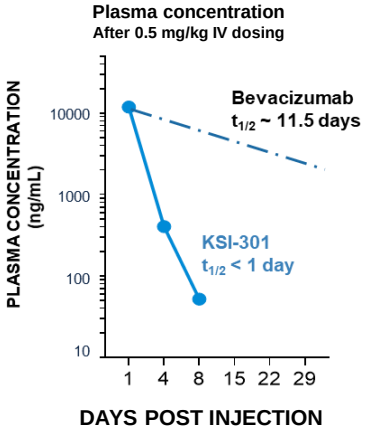
Excellent Retinal Bioavailability[2]



Deeper Inhibitory Potency[3]



Fast Systemic Clearance[4]



1. Data from rabbit model. Ranibizumab data: Gaudreault et al (2007) IOVS 46(2) 726 Gaudreault et al (2007) Retina 27(9) 1260 Bakri et al (2007) Ophthalmol 114(12) 2179 || Aflibercept data: EVER Congress Portoroz Slovenia (2008) Struble (Covance) Koehler-Stec (Regeneron). Aflibercept data adjusted arithmetically to reflect 2,000µg dose administered (based on rabbit in vivo dosing of 500 µg) || KSI-301 data on file, adjusted arithmetically to reflect 5,000 µg dose administered (based on rabbit in vivo dosing of 725 µg). Error bars reflects standard error of the mean
2. Covance rabbit ADME (absorption, distribution, metabolism, elimination) model: Aflibercept data (2008): EVER Congress Portoroz Slovenia Struble (Covance), Koehler-Stec (Regeneron). KSI-301 data (2017): Covance study, data on file. Error bars reflects standard error of the mean
3. KSI-301 data: data on file; Bevacizumab data: Yeung et al 2010 Cancer Research.
4. KSI-301 data: Non-human primate toxicology study, data on file; Bevacizumab data: Yeung et al 2010 Cancer Research.

KSI-301 Phase 1b

Safety

Safety of KSI-301:
Excellent safety profile

130
Subjects dosed

710
Total doses

168
Patient-years

Across the Phase 1a/1b program

121
Completed the loading phase in Phase 1b

96
Phase 1b subjects at Week 12 or later that have received all three loading doses plus at least one additional retreatment

- Most AEs were assessed as mild and are consistent with profile of intravitreal anti-VEGFs
- To date, 43 SAEs have been reported in 24 subjects – none drug related
- Three ocular SAEs in the study eye, not drug related, all resolved
  - Worsening DME secondary to systemic fluid overload
  - Worsening cataract in a diabetic patient
  - Subretinal hemorrhage in a wAMD patient
- Only two AEs of intraocular inflammation, both trace to 1+ vitreous cells, with complete resolution
  - Rate of 0.28% (2/710 injections)
  - No vasculitis or retinal artery occlusion in either patient

Includes all Phase 1a+1b patients randomized as of 26 Jan 2021, all doses administered across cohorts. Interim safety data as of 26 Jan 2021; AE: adverse event; SAE: serious adverse event
Inflammation scored based on the 0 – 4+ standardized vitreous grading scale (Foster 2002)

How do the Phase 1b Study data inform the design of KSI-301 pivotal studies?

KSI-301 Phase 1b data in treatment-naïve patients inform the design of Kodiak pivotal studies

Maintained

- Treatment-naïve patients
- 3 loading doses in wAMD and DME
- Monthly visits

Optimized

- Only high dose (5 mg) advanced
- Tighter disease activity criteria
- Proactive dosing
- Tighter dosing intervals
- 2 loading doses in RVO
- Decreased subjectivity (treatment based strictly on IRT)
- High statistical power for non-inferiority

KSI-301 pivotal program: long-interval dosing to meaningfully change the treatment paradigm

Wet AMD

Comparator

Aflibercept
once every 2 months
after 3 monthly loading doses

DAZZLE Study[1]

KSI-301
once every 3, 4 or 5 months
after 3 monthly loading doses

5	2
Minimum doses in Year 1[4]	**Minimum doses in Year 2[4]**

Completed Recruitment

Diabetic Macular Edema

Comparator

Aflibercept
once every 2 months
after 5 monthly doses

GLEAM and GLIMMER Studies[2]

KSI-301
once every 2 to 6 months
after 3 monthly loading doses

4	2
Minimum doses in Year 1[4]	**Minimum doses in Year 2[4]**

Now Recruiting

Retinal Vein Occlusion

Comparator

Aflibercept
once every month

BEACON Study[3]

KSI-301
once every 2 months or longer
after 2 monthly loading doses

4
Minimum doses in Year 1[4]

Now Recruiting

Non-Proliferative Diabetic Retinopathy

Comparator

Sham

GLOW Study

KSI-301
once every 6 months
after 3 initiating doses

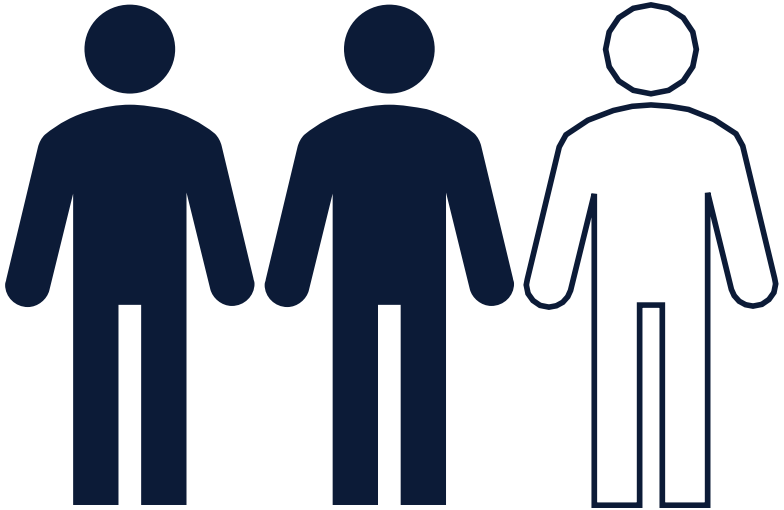
4	2
Doses in Year 1[4]	**Doses in Year 2[4]**

Starting in 1H2021

1. NCT04049266. 2. NCT04611152 and NCT04603937. 3. NCT04592419 4. Based on study design.

What is the potential impact of KSI-301 in clinical practice and patients' lives?

KSI-301 has the potential to be the longest-acting intravitreal biologic



2 in every 3 patients are on a ≥ 6-month treatment-free interval at Year 1 after only 3 loading doses

Interval at Year 1	wAMD n=50	DME n=32	RVO n=32
≥6 months	66%	69%	66%

Phase 1b interim data. 2.5 & 5 mg doses pooled. Includes only patients that received all (3) loading doses and either a) received a dose before Week 52 or b) did not receive a dose and were followed for at least six months after the last loading dose (Week 32 visit). Two RVO patients were not included as they discontinued at the Week 12 and 16 visits, respectively, without receiving a retreatment dose. Treatment interval reflects the treatment interval ongoing at the Week 52 visit (where available) or the last interval before Week 52.

KSI-301 Phase 1b Study – Year 1 Results
Key Questions

The data support the potential for KSI-301 to meaningfully advance the treatment paradigm for major retinal vascular diseases

Can KSI-301 provide the expected **efficacy gains in line with current anti-VEGF agents**?	**Yes**
Can KSI-301 achieve **clinical durability of 6-months or longer** in the majority of patients, and **with fewer loading doses**?	**Yes**
Does KSI-301 have the **excellent safety profile** expected for intravitreal anti-VEGF agents ranibizumab and aflibercept?	**Yes**

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