One Year and Beyond: Long-Term Multiple-Dose Study of KSI-301, an Anti-VEGF Antibody Biopolymer Conjugate with Extended Durability, in wAMD, DME, and RVO

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Disclosures

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- Grant support: Adverum, Allergan, Chengdu Kanghong, Genentech, Graybug, Gyroscope, Gemini Therapeutics, Kodiak Sciences, Novartis, Iveric Bio, Opthea, Oxurion, Recens Medical, Roche, Regenxbio

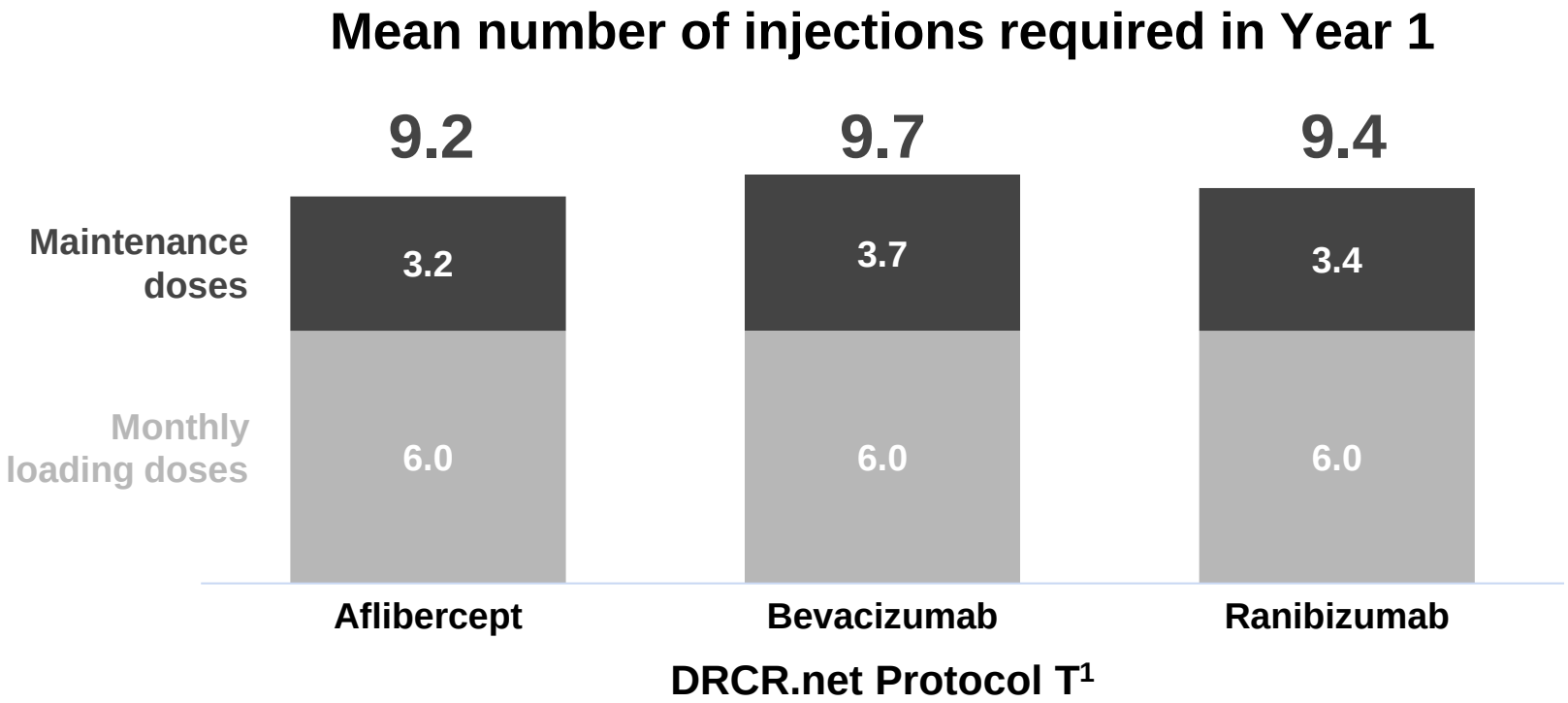
- Consultant: Adverum, Allergan, Bausch and Lomb, Chengdu Kanghong, DORC, Eyepoint Pharmaceuticals, Genentech, Graybug, Gyroscope, Gemini Therapeutics, Kodiak Sciences, Novartis, Opthea, Oxurion, Recens Medical, Regenxbio

- Speaker: Allergan, Novartis

- **Study Disclosures:**

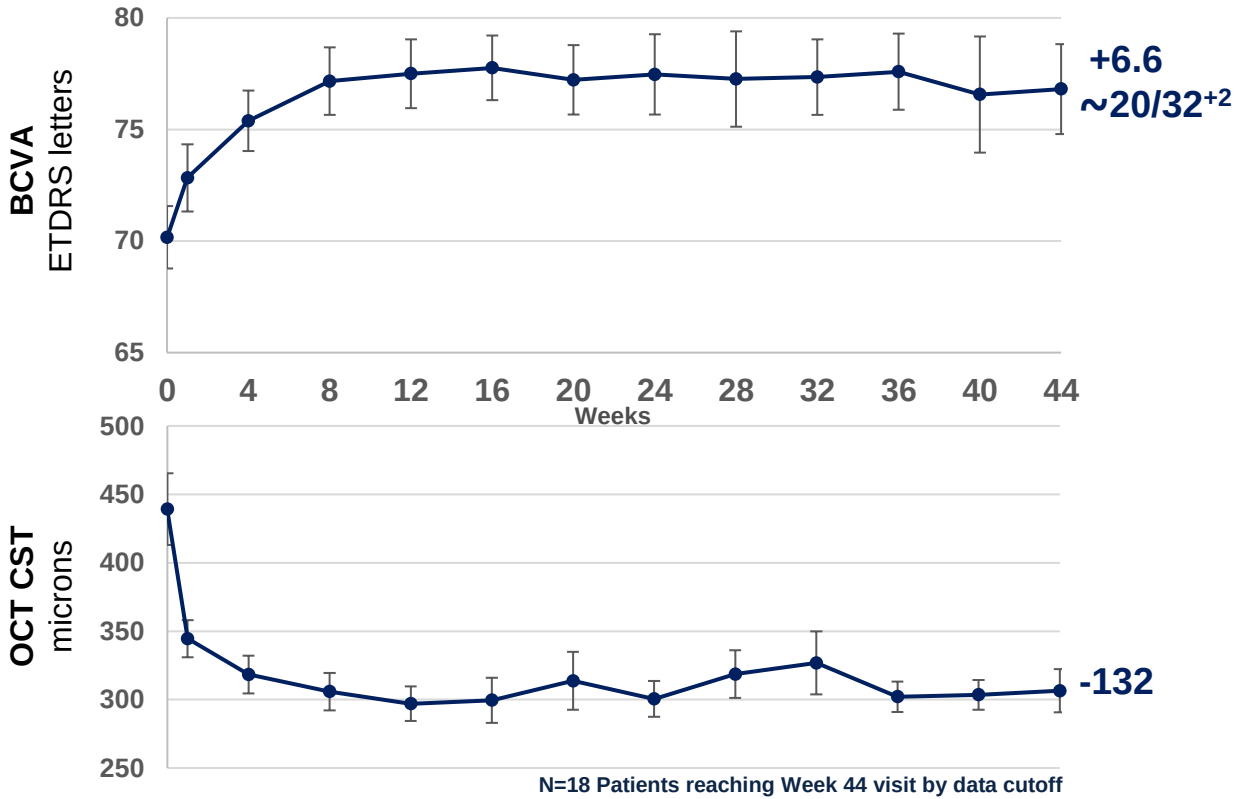
  This study includes research conducted on human subjects. Institutional Review Board (IRB) approval was obtained prior to study initiation.

Current anti-VEGF agents require high-frequency treatment to be most efficacious in DME



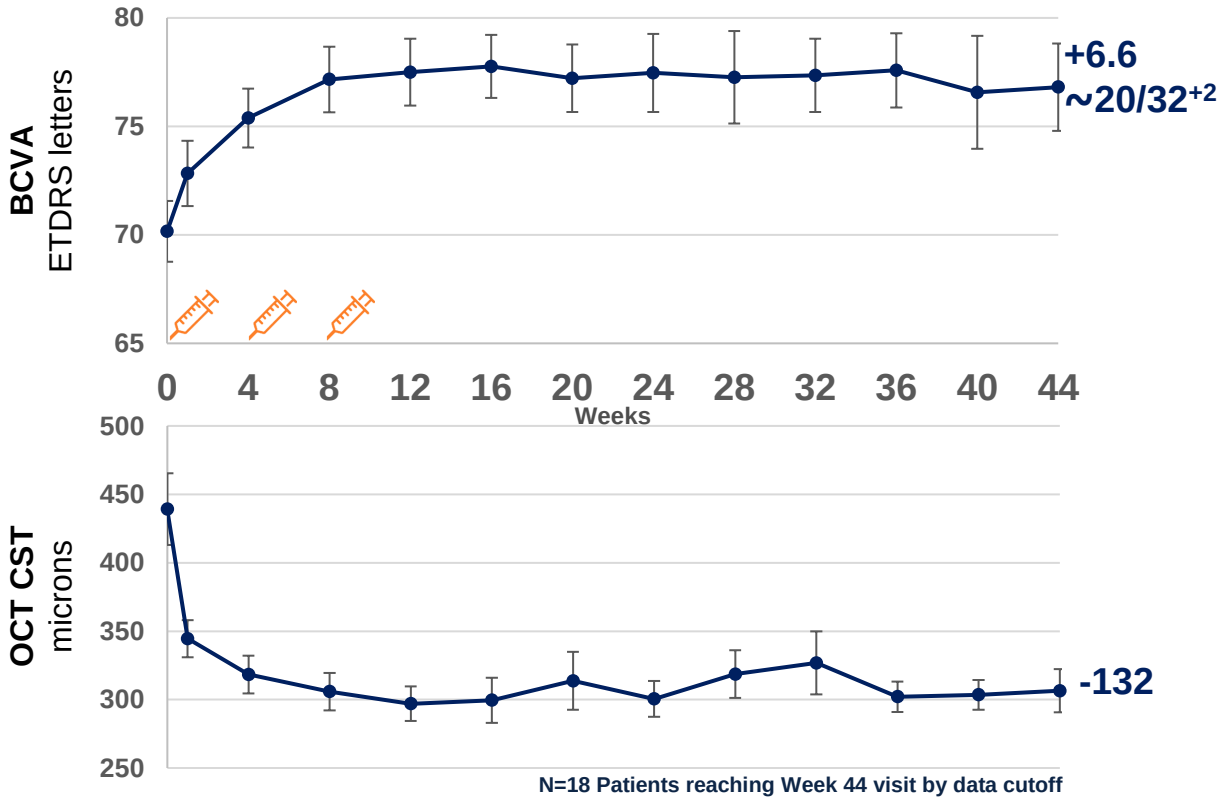
1. Wells JA. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema (DRCR Protocol T). N Engl J Med. 2015 Mar 26;372(13):1193-203 (supplemental data).

How many KSI-301 injections are needed to achieve these results in DME?



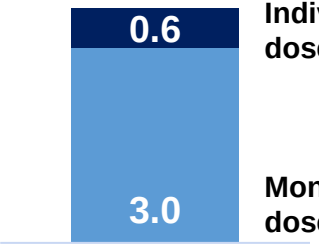
Interim data. Includes only randomized patients that reached Week 44 visit by the data cutoff date of 09 Jun 2020; 2.5 & 5 mg doses pooled. Observed data. Error bars represent standard error of the mean. OCT CST values are site reported. BCVA= best corrected visual acuity; OCT= optical coherence tomography; CST= central subfield thickness. Mean injections reflect the average number of injections received per patient between Week 12 and 40 (aflibercept per label mean number of injections 5.0).

Only 3 loading doses and 0.6 mean individualized doses of KSI-301 demonstrate strong efficacy



N=18 Patients reaching Week 44 visit by data cutoff

3.6 Injections over 44 weeks



Individualized doses

Monthly loading doses

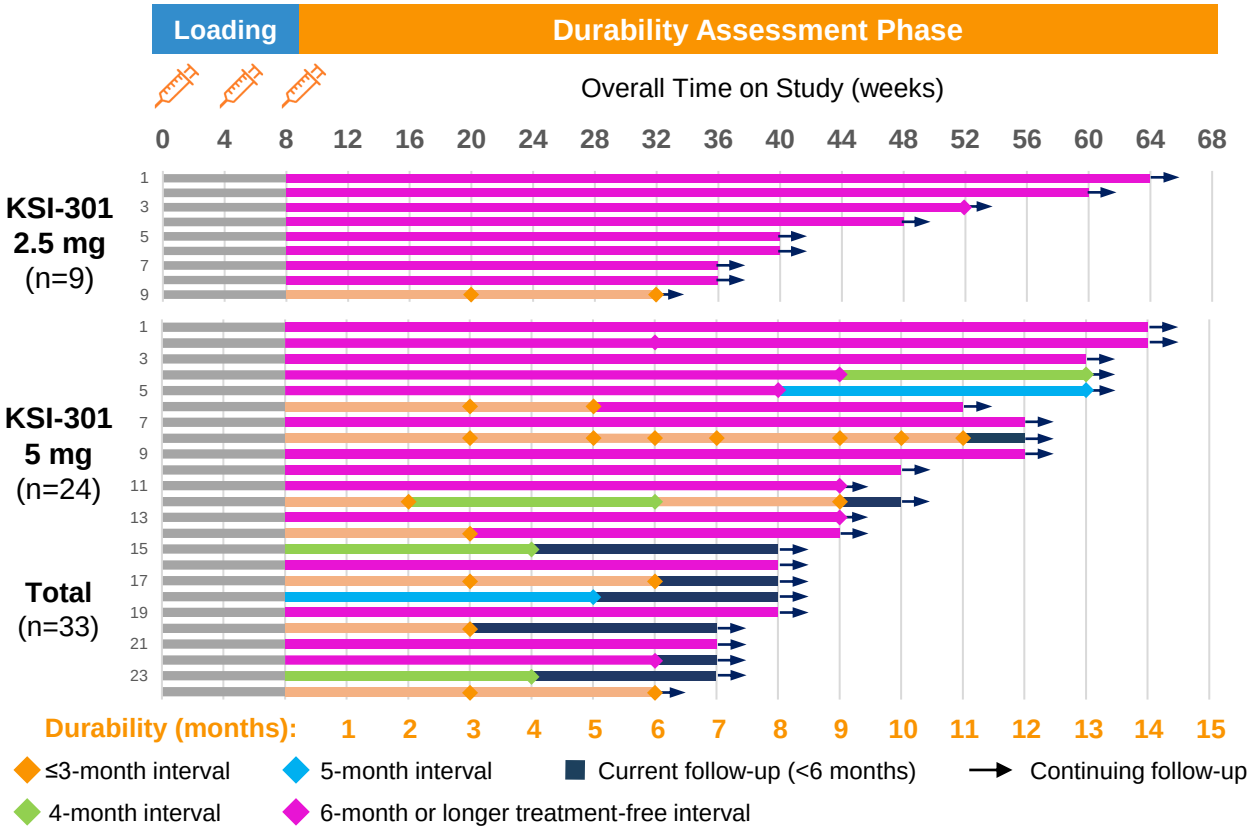
KSI-301

67% of patients did not require retreatment

Interim data. Includes only randomized patients that reached Week 44 visit by the data cutoff date of 09 Jun 2020; 2.5 & 5 mg doses pooled. Observed data. Error bars represent standard error of the mean. OCT CST values are site reported. BCVA= best corrected visual acuity; OCT= optical coherence tomography; CST= central subfield thickness. Mean injections reflect the average number of injections received per patient between Week 12 and 40 (aflibercept per label mean number of injections 5.0).

With only 3 loading doses, what is the durability profile of KSI-301 in DME?

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



First Retreatment	Percentage n=33
At 2 months	3%
3 months or longer	97%
4 months or longer	76%
5 months or longer	70%
6 months or longer	67%

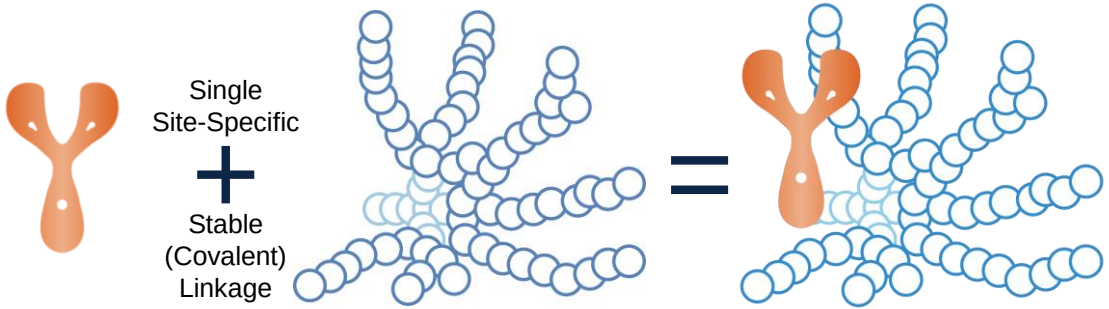
73% (24/33) have achieved a 6-month or longer treatment-free interval at least once during follow-up

Interim data. Includes only randomized patients that reached the first retreatment opportunity (Week 12 visit) by the data cutoff date of 09 Jun 2020.
Each bar represents an individual patient. All depicted patients continue to be followed (no discontinuations)

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

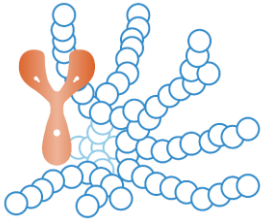
- Clinically proven targets
- Antibody-based biologic
- Intravitreal: safest method of administration
- Optically clear, no residues
- Fast and potent clinical responses

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**

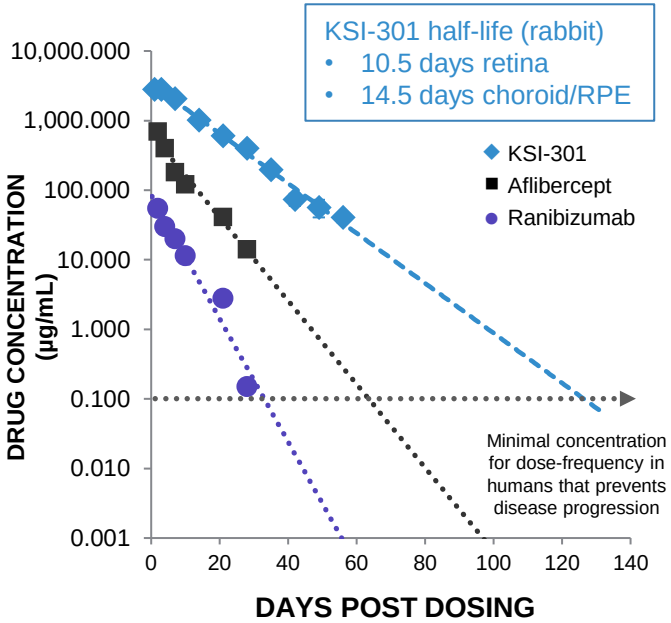
Equivalent values are shown as (approximate) fold difference relative to aflibercept. kDa= kilodalton

1. Lower affinity of bevacizumab precludes a useful comparison

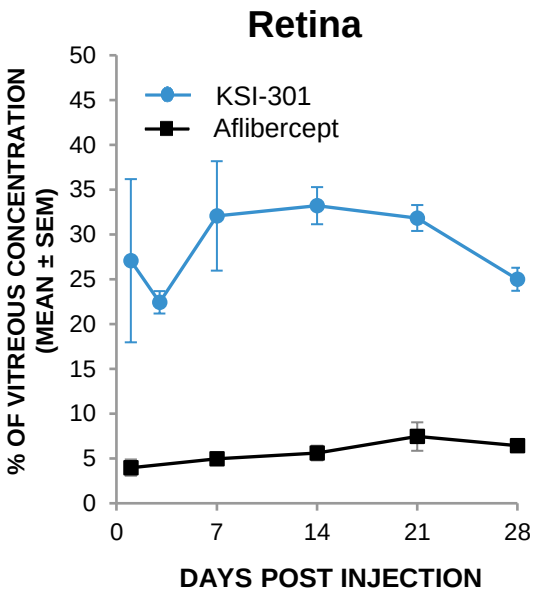
A new set of integrated properties

More than the sum of its parts

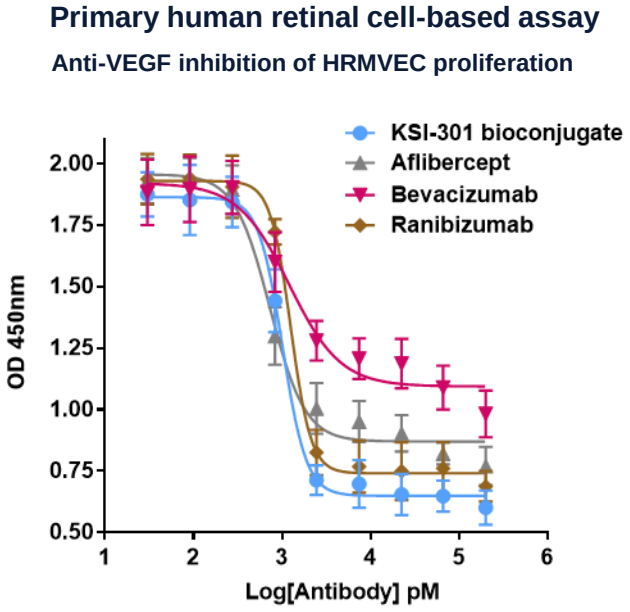
Remarkable Intraocular Half-life[1]



Excellent Retinal Bioavailability[2]



Deeper Inhibitory Potency[3]



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.

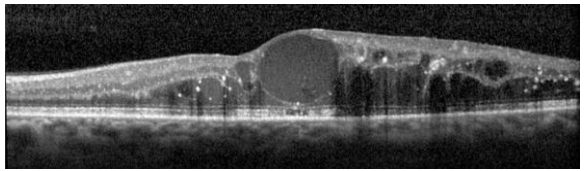
Are there any additional features of KSI-301 in DME seen on imaging?

Sustained DME control for 12 Months with only 3 loading doses can be achieved with KSI-301

OCT Images
From Phase 1b Study

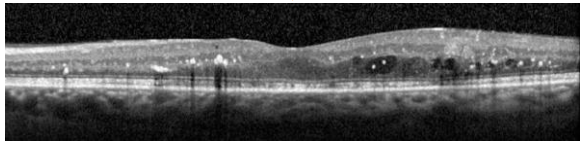
3 total injections in Year 1

Day 1
(Pre-Treatment)



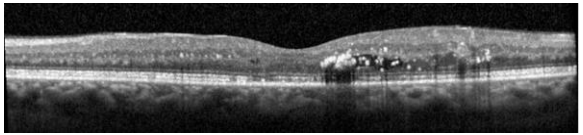
3 Loading doses
Day 1
Week 4
Week 8

Week 12
+3 letters



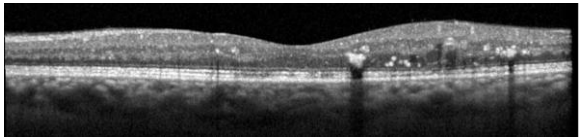
1 month after 3 loading doses

Week 32
+7 letters



6 months after 3 loading doses

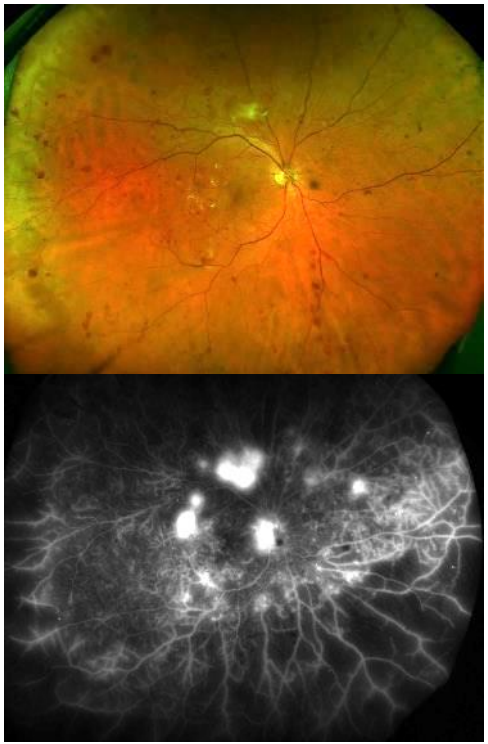
Week 56
+8 letters (20/20)



12 months after 3 loading doses

The sustained disease control of only 3 loading doses of KSI-301 is also seen in proliferative diabetic retinopathy

DAY 1
Proliferative DR (DRSS 65)

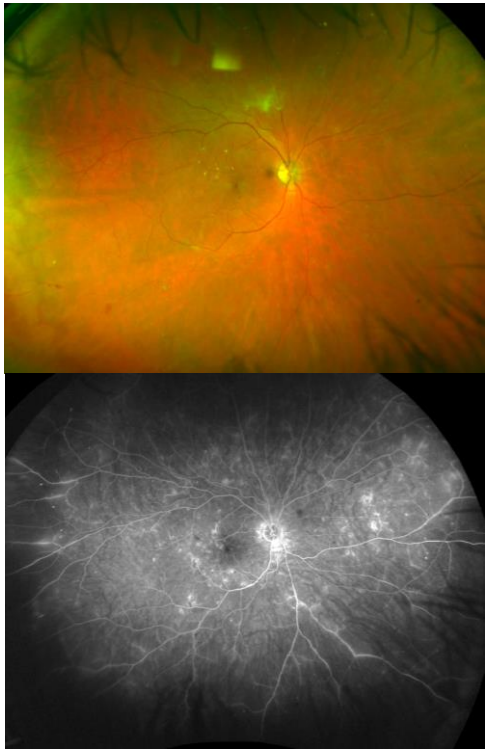


KSI-301 5 mg
3 loading doses

WEEK 12
Non-Proliferative DR (DRSS 53)

Two additional doses

WEEK 72
Non-Proliferative DR (DRSS 53)



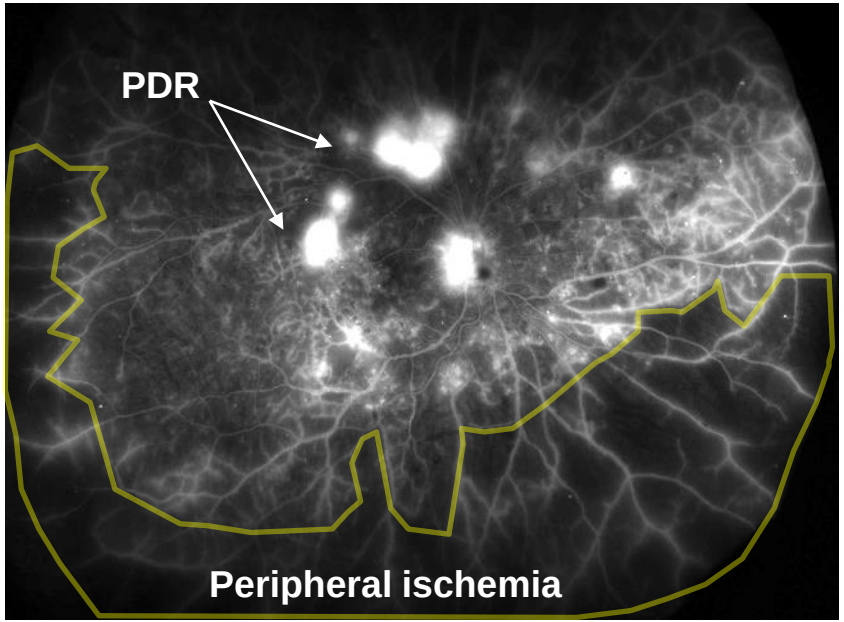
Regression from PDR to NPDR
Fast and substantial (2-step) improvement, sustained for 18 months with only 2 additional doses (26-week mean retreatment interval)

DR= Diabetic Retinopathy; PDR= Proliferative DR; NPDR= Non-Proliferative DR; DRSS = DR Severity Scale; DRSS 53 = Severe NPDR; DRSS 65 = Moderate PDR

In addition to the regression from PDR to NPDR, this patient exhibits signs of peripheral vascular reperfusion

DAY 1

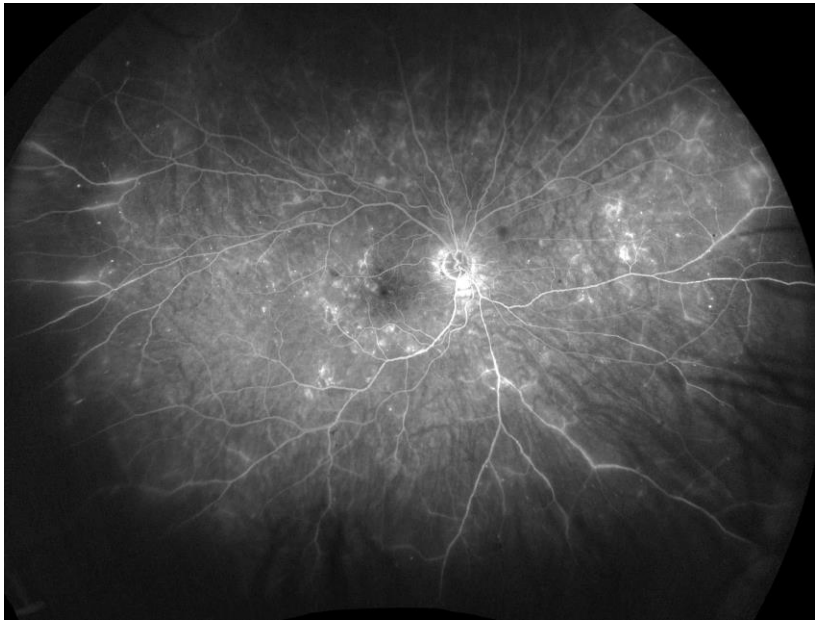
Proliferative DR (DRSS 65)



KSI-301
5 mg

WEEK 72

Non-Proliferative DR (DRSS 53)



Sustained signs of disease modification for 18 months with only 2 additional doses (26-week mean treatment interval)

PDR= Proliferative DR; NPDR= Non-Proliferative DR; DRSS = DR Severity Scale; DRSS 53 = Severe NPDR; DRSS 65 = Moderate PDR

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

KSI-301 Phase 3 DME GLEAM and GLIMMER Studies

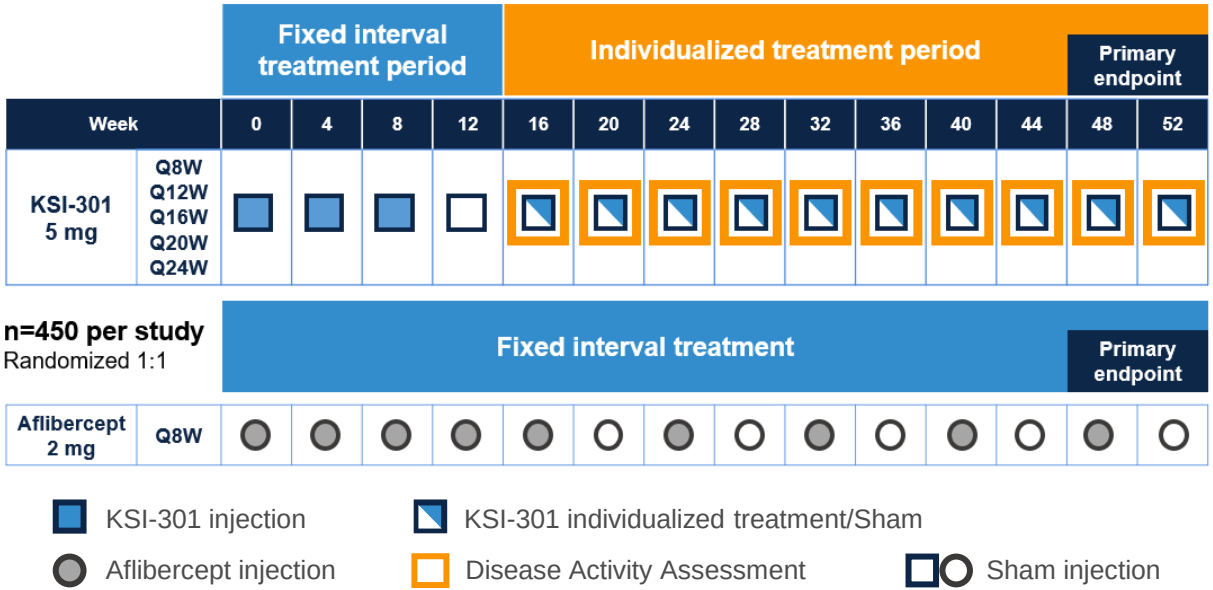
*Dosing with KSI-301 as infrequently as every 24 weeks**

DME – Phase 1b

First Retreatment	Percentage (n= 33)
At 2 months	3%
3 months or longer	97%
4 months or longer	76%
5 months or longer	70%
6 months or longer	67%

79% have now achieved a ≥6-month treatment interval at least once during follow-up[1]

Now recruiting: GLEAM-GLIMMER pivotal studies evaluate individualized dosing of every 8, 12, 16, 20 or 24 weeks, after only 3 loading doses

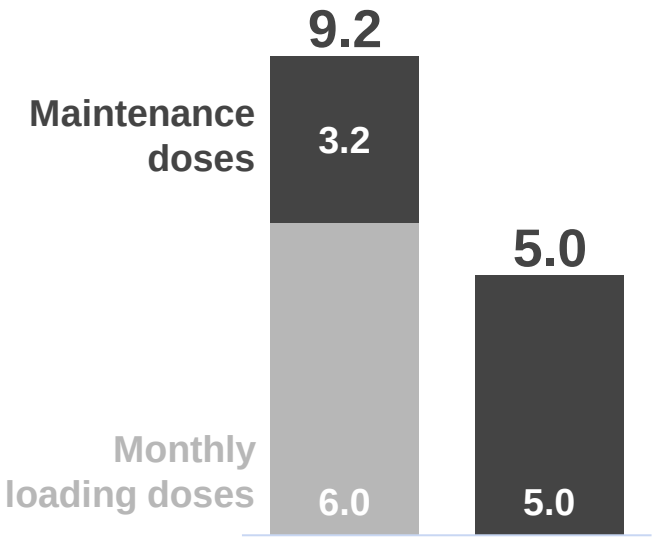


*After the loading phase. 1. As of 15 Sep 2020

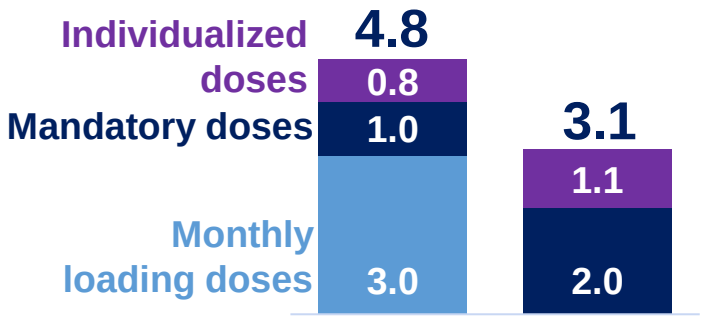
Projecting Phase 1b data into GLEAM and GLIMMER

Potential for dramatic treatment burden reduction in DME

Mean number of injections required



DRCR.net Protocol T
Aflibercept doses[1,2]



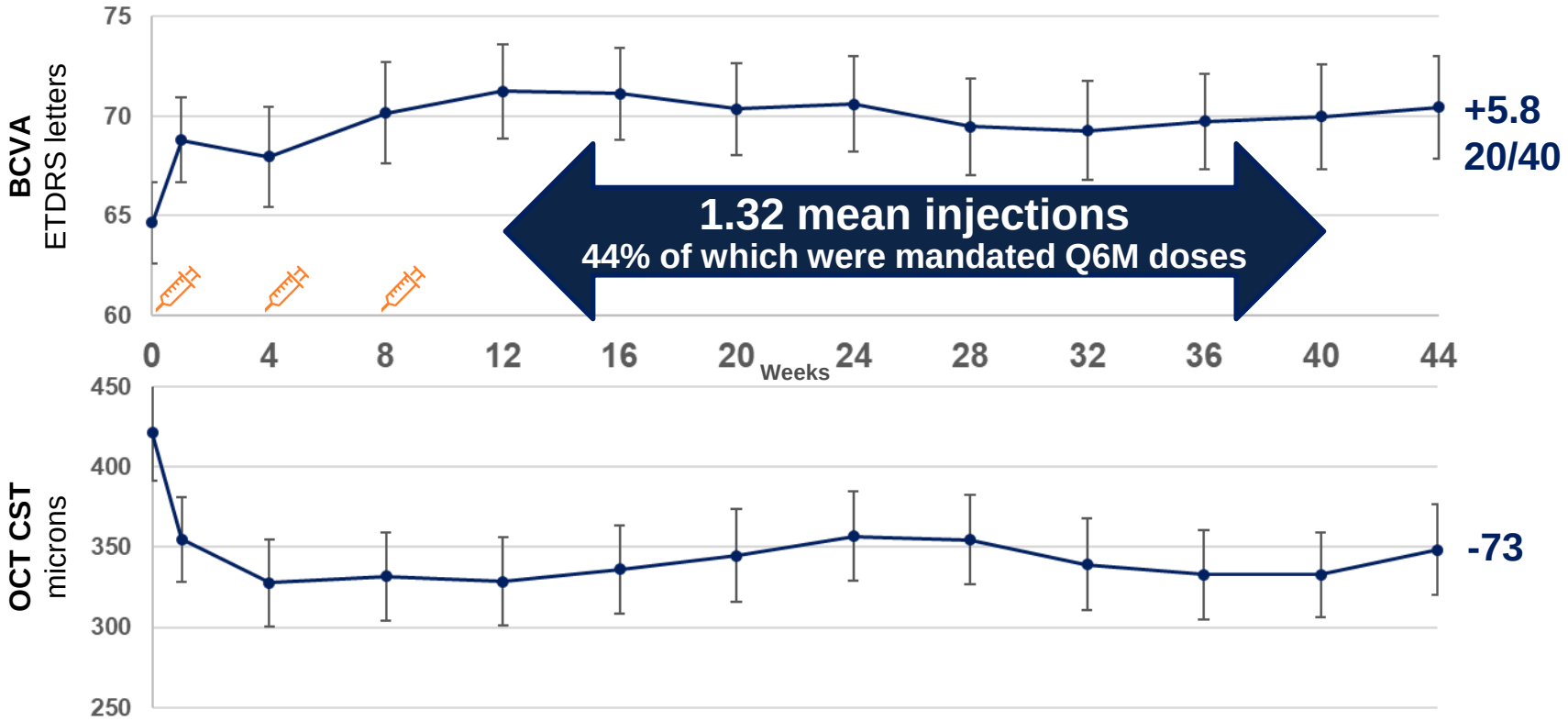
GLEAM/GLIMMER
KSI-301 projected doses[3]

Treatment burden could be reduced by almost half over 2 years (14.2 vs 7.9 injections)

1. Wells JA. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema (DRCR Protocol T). N Engl J Med. 2015 Mar 26;372(13):1193-203 (supplemental data). N= 221
2. Wells JA. Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema: two-year results. Ophthalmology. 2016 Jun;123(6):1351-9. (supplemental data). N=201
3. Interim data. Annualized injections based on GLEAM and GLIMMER's study design and the current monthly injection rate in Phase 1b DME patients as of 09 Jun 2020. n= 33

Are there supportive data for KSI-301’s efficacy and durability in other retinal diseases?

The strong efficacy and remarkable durability of KSI-301 is consistently seen in wAMD



Interim data. Includes only randomized patients that reached Week 44 visit by the data cutoff date of 09 Jun 2020; 2.5 & 5 mg doses pooled. Observed data. Error bars represent standard error of the mean. OCT CST values are site reported and include PED height. BCVA= best corrected visual acuity; OCT= optical coherence tomography; CST= central subfield thickness. Mean injections reflect the average number of injections received per patient between Week 12 and 40 (aflibercept per label mean number of injections 4.0).

n= 31 Patients reaching Week 44 visit by data cutoff

KSI-301 Phase 2b/3 wAMD DAZZLE Study

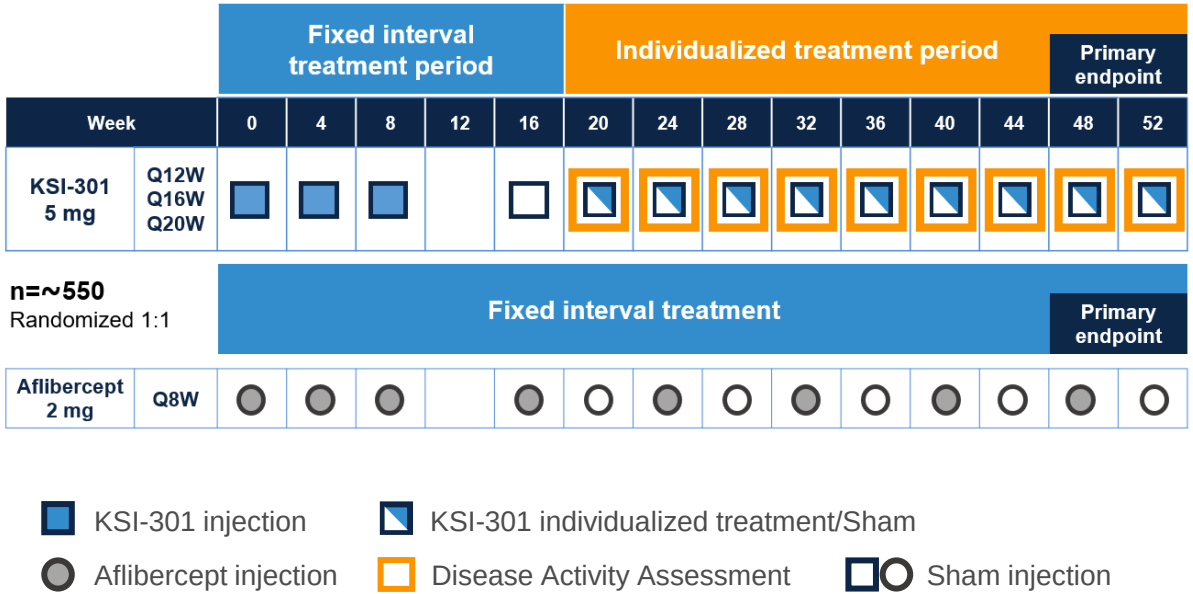
*Dosing with KSI-301 as infrequently as every 20 weeks**

Wet AMD – Phase 1b

First Retreatment	Percentage (n=49)
At or before 2 months	8%
3 months or longer	92%
4 months or longer	82%
5 months or longer	66%
6 months	49%

72% have achieved a 6-month treatment interval at least once during follow-up[1]

DAZZLE pivotal study evaluates individualized dosing of every 12, 16 or 20 weeks

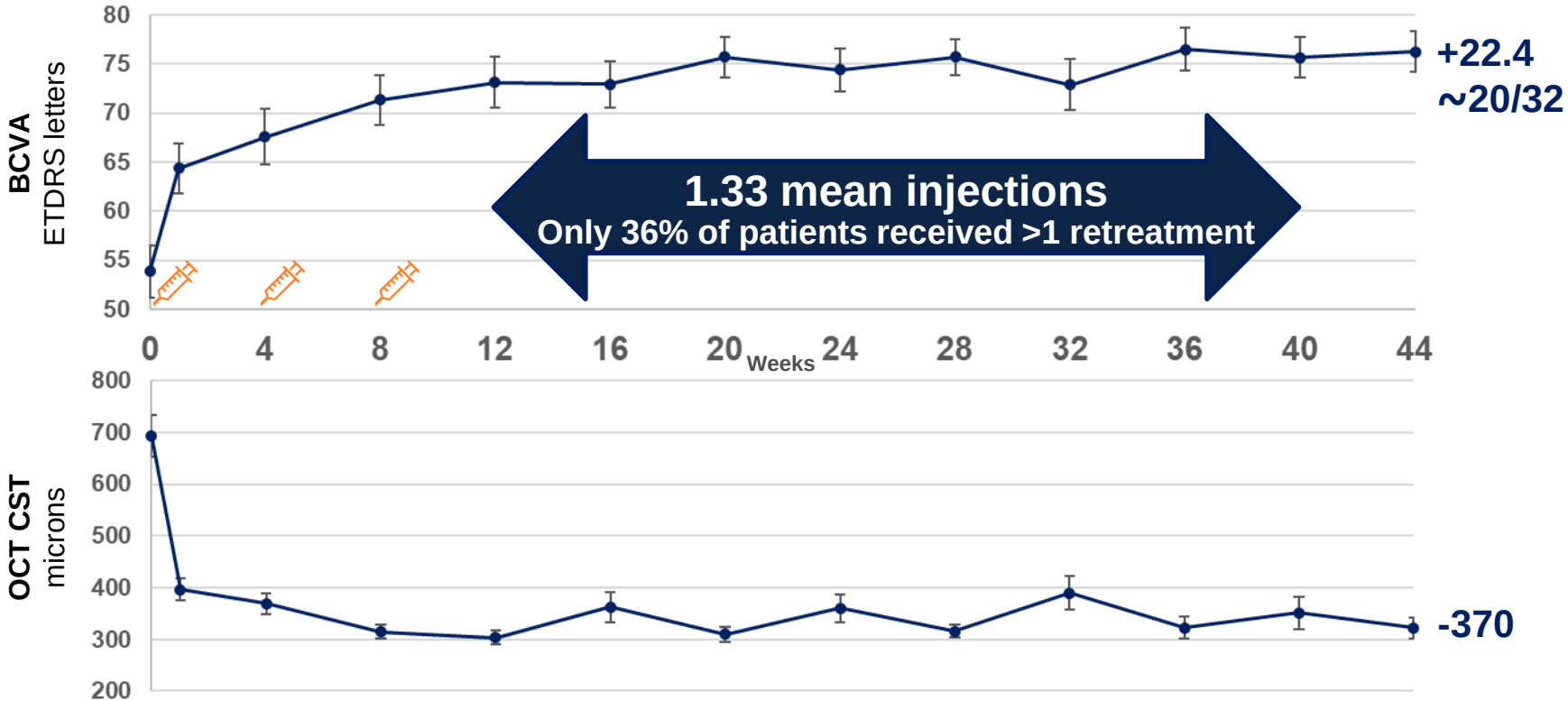


*After the loading phase. Clinicaltrials.gov ID NCT04049266, currently in late stages of recruitment

1. As of 15 Sep 2020

Efficacy of KSI-301 in RVO

change from baseline to week 44 in mean BCVA & OCT



Interim data. Includes only randomized patients that reached Week 44 visit by the data cutoff date of 09 Jun 2020; 2.5 & 5 mg doses pooled. Observed data. Error bars represent standard error of the mean. OCT CST values are site reported. BCVA= best corrected visual acuity; OCT= optical coherence tomography; CST= central subfield thickness. Mean injections reflect the average number of injections received per patient between Week 12 and 40 (aflibercept per label mean number of injections 8.0).

n= 33 Patients reaching Week 44 visit by data cutoff

BRVO n= 19
CRVO n= 14

KSI-301 Phase 3 RVO BEACON Study

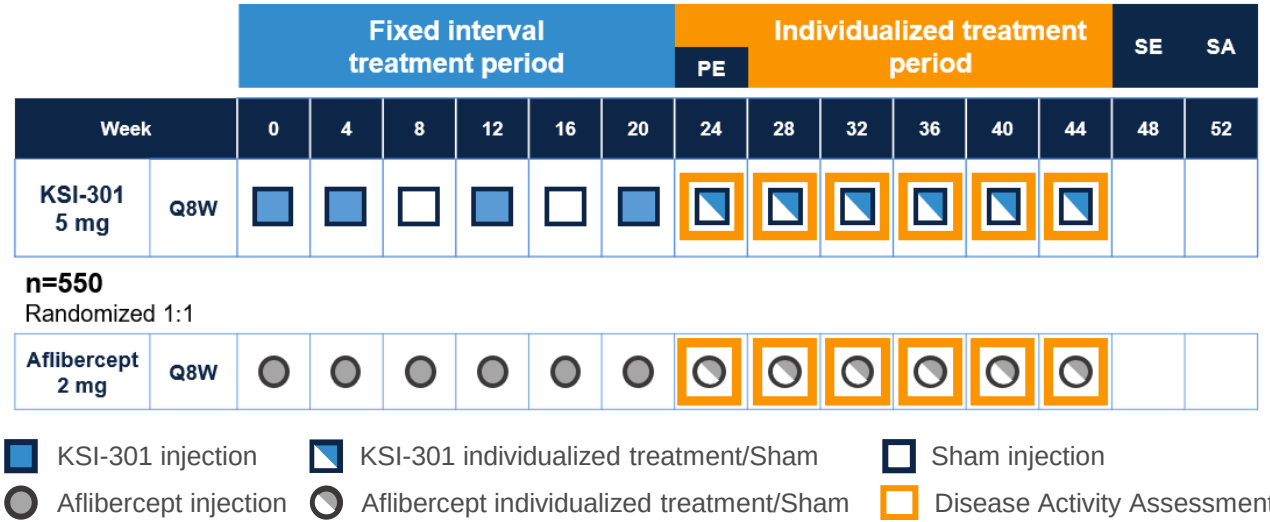
Two loading doses with KSI-301 + every 8 weeks

RVO – Phase 1b

First Retreatment	Percentage (n= 34)
At 1 month	6%
2 months or longer	94%
3 months or longer	66%
4 months or longer	56%

81% have achieved a 4-month or longer treatment interval at least once during follow-up[1]

BEACON pivotal study evaluates two loading doses and every 8-week dosing, followed by individualized dosing



Clinicaltrials.gov ID NCT04592419, currently recruiting

1. As of 15 Sep 2020

PE= Primary endpoint. SE= Secondary endpoints. SA= Safety assessment

KSI-301 Phase 1b

Safety

Safety of KSI-301:
multiple-dose exposure is well-tolerated

130
Subjects dosed

622
Total doses

130
Patient-years

Across the Phase 1a/1b program

121
Completed the loading phase in Phase 1b

92
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, 29 SAEs have been reported in 19 subjects – none drug related
- Two ocular SAEs in the study eye, not drug related
  - Worsening DME secondary to systemic fluid overload
  - Worsening cataract in a diabetic patient
- Only two AEs of intraocular inflammation, both trace to 1+ vitreous cells, with complete resolution
  - Rate of 0.32% (2/622 injections)
  - No vasculitis or retinitis in either patient

Includes all Phase 1a+1b patients randomized as of 15 Sep 2020, all doses administered across cohorts. Interim safety data as of 15 Sep 2020; AE: adverse event; SAE: serious adverse event
Inflammation scored based on the 0 – 4+ standardized vitreous grading scale (Foster 2002)

Conclusion

- Antibody Biopolymer Conjugates (ABCs) are a new design platform for long durability intravitreal medicines
  - KSI-301, KSI-501 (anti-VEGF/IL-6 dual inhibitor) and KSI-601 (novel “triplet” inhibitor for dry AMD)
- Phase 1b exploratory study informs pivotal study designs
  - **Excellent Safety**
  - **Strong Efficacy:** across 3 major phenotypically variable retinal diseases wet AMD, DME & RVO
  - **Remarkable Biological Durability:**
    - 3 to 6-month interval in wAMD
    - 3 to 6+ month interval in DME
    - 2 to 4+ month interval in RVO
- KSI-301 is in late-stage clinical development
  - Pivotal DAZZLE study of KSI-301 vs aflibercept in treatment-naïve wAMD: U.S. recruitment complete
  - GLEAM, GLIMMER, and BEACON pivotal Studies in DME, RVO now recruiting
  - GLOW pivotal study in NPDR expected to begin early 2021

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- Jason Ehrlich, MD, PhD
- Victor Perlroth, MD

Ocular Imaging Research & Reading Center

KSI-301 Phase 1b

Appendix

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