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

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

Diana V. Do, MD

Professor of Ophthalmology

Byers Eye Institute

Stanford University School of Medicine

Palo Alto, CA

Angiogenesis, Exudation, and Degeneration 2020

February 8, 2020

Disclosures

- **Financial:**

  Research grants: Aerie, Boehringer Ingelheim, Genentech, Novartis, Regeneron, Santen

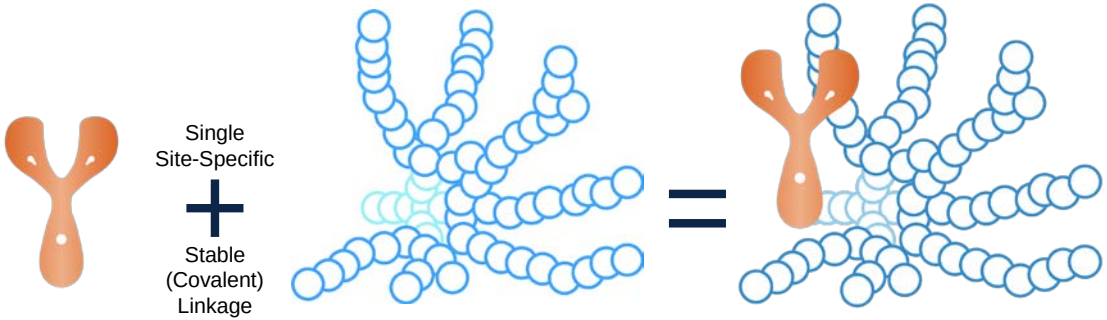
  Scientific advisor: Aerie, Boehringer Ingelheim, Kodiak, Novartis, Regeneron, Santen

- **Study Disclosures:**

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

Antibody Biopolymer Conjugates (ABC)

biologics engineered for increased durability and efficacy



ANTIBODY

IgG1 Antibody

Inert Immune
Effector function

BIOPOLYMER

Branched
High Molecular Weight
Optically Clear
Phosphorylcholine Polymer

CONJUGATE

Antibody and biopolymer covalently bound via single site-specific linkage

KSI-301 is an anti-VEGF ABC designed to block all VEGF-A isoforms

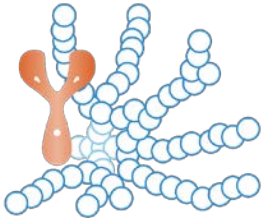
SAME WHERE IT MATTERS

- 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
- Improved stability

Next-Generation anti-VEGF:
larger size and higher dose for longer treatment duration

	Brolucizumab	Ranibizumab	Bevacizumab	Aflibercept	KSI-301
Molecule type	Single-chain antibody fragment	Antibody fragment	Antibody	Recombinant fusion protein	**Antibody Biopolymer Conjugate (ABC)**
Molecular structure					
Molecular weight	26 kDa	48 kDa	149 kDa	115 kDa	**950 kDa**
Clinical dose	6 mg	0.3-0.5 mg	1.25 mg	2 mg	**5 mg** (by weight of antibody)
Equivalent molar dose	11	0.5	0.9	1	**3.5**
Equivalent ocular PK	< 0.7	0.7	1	1	**3**
Equivalent ocular concentration at 3 months	< 0.1	0.001	NA[1]	1	**1,000**

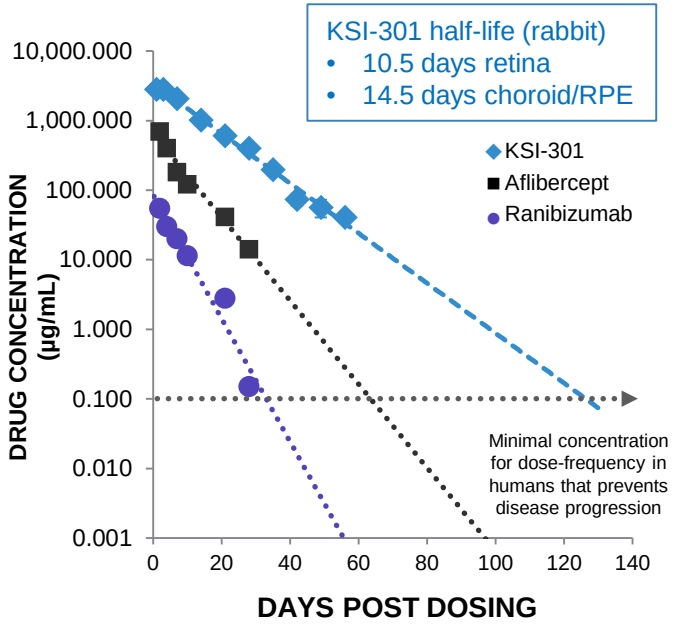
Equivalent values are shown as (approximate) fold difference relative to aflibercept. kDa= kilodalton

1. Lower affinity of bevacizumab precludes a useful comparison

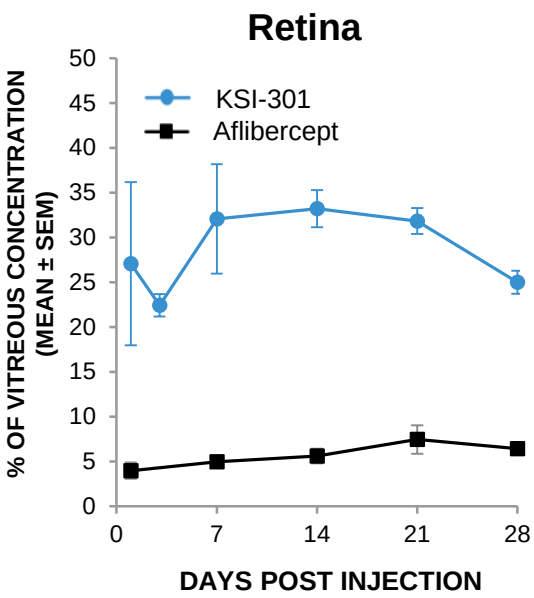
KSI-301 Properties: Preclinical Data

Special features from the ultra-hydrophilic phosphorylcholine biopolymer

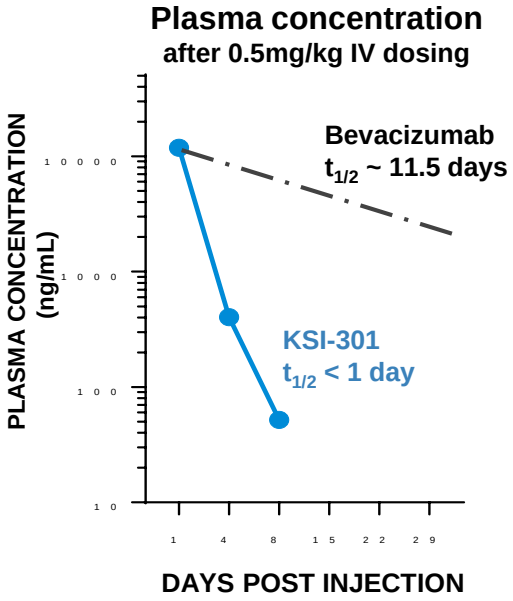
Remarkable Intraocular Half-life[1]



Excellent Retinal Bioavailability[2]



Fast Systemic Clearance[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: Non-human primate toxicology study, data on file; Bevacizumab data: Yeung et al 2010 Cancer Research.

KSI-301

Clinical Data

130 patients dosed in Phase 1 Program

KSI-301 Phase 1b

insight into durability among treatment naïve subjects

Randomized, open label study to evaluate multidose safety, efficacy & durability (n=120)

wAMD (n=50) | **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
Weeks	0	4	8	12 to 72 (months 3 to 18)
Treatment Schedule	■	■	■	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
prespecified by disease state

- **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

KSI-301 Phase 1b Baseline Characteristics

All cohorts fully enrolled

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
BCVA, Snellen 20/40 or better, n (%)	20 (39.2)	16 (45.7)	6 (17.1)
OCT CST, mean (SD), microns	430 (162)	453 (110)	675 (237)

Includes all patients randomized as of 21 January 2020. SD= standard deviation; BCVA= best corrected visual acuity; OCT= optical coherence tomography; CST= central subfield thickness

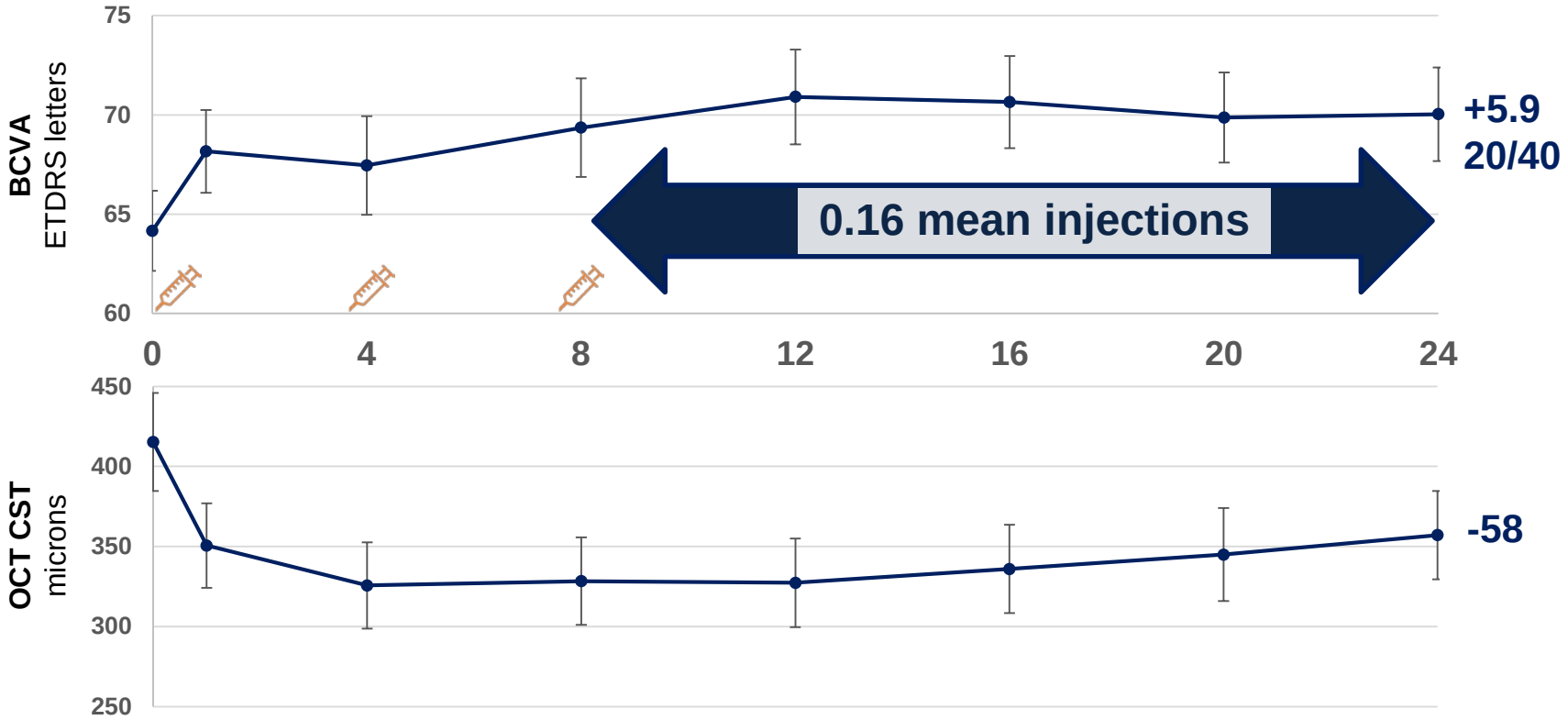
KSI-301 Phase 1b

wAMD

6 month data

Efficacy of KSI-301 in Wet AMD

change from baseline to week 24 in mean BCVA & OCT

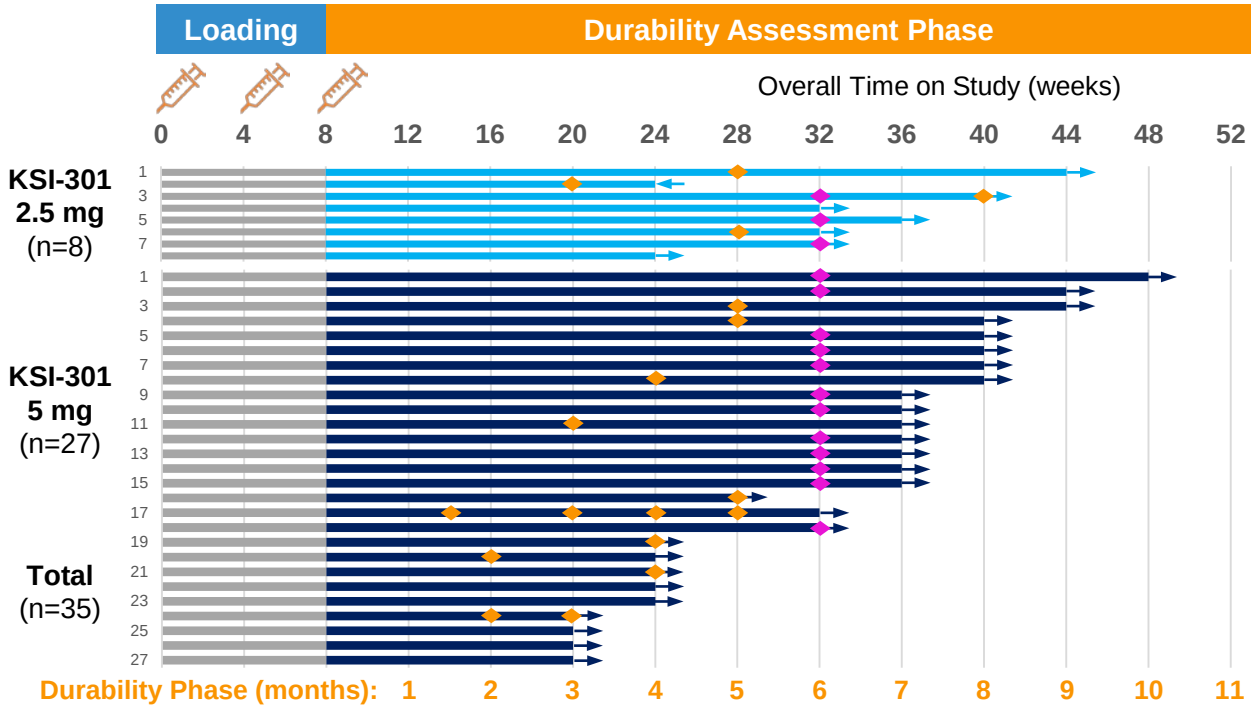


Interim data. Includes only randomized patients that reached Week 24 visit by the data cutoff date of 21 Jan 2020; 2.5 & 5 mg doses pooled. Error bars represent standard error of the mean. OCT CST values are site reported and include PED height. BCVA= best corrected visual acuity; OCT= optical coherence tomography; CST= central subfield thickness. Mean injections reflect the average number of injections received per patient between Week 8 and 24 (aflibercept and brolucizumab per label mean number of injections 1.0).

n= 31 **Patients reaching Week 24 visit by data cutoff**

KSI-301 in wAMD: Durability Assessment

Emerging data support 3 to 6 month durability



First Retreatment	Percentage
At or before 3 months	14% (5/35)
4 months or longer	84% (27/32)
5 months or longer	72% (21/29)
6 months	55% (16/29)

55% (16/29) have achieved a 6-month interval before a mandated first retreatment

- Retreatment
- Capped retreatment at 6 months
- Continuing follow-up
- Discontinuation

Interim data. Includes only randomized patients that reached the first retreatment opportunity (Week 12 visit) by the data cutoff date of 21 Jan 2020. Each bar represents an individual patient.

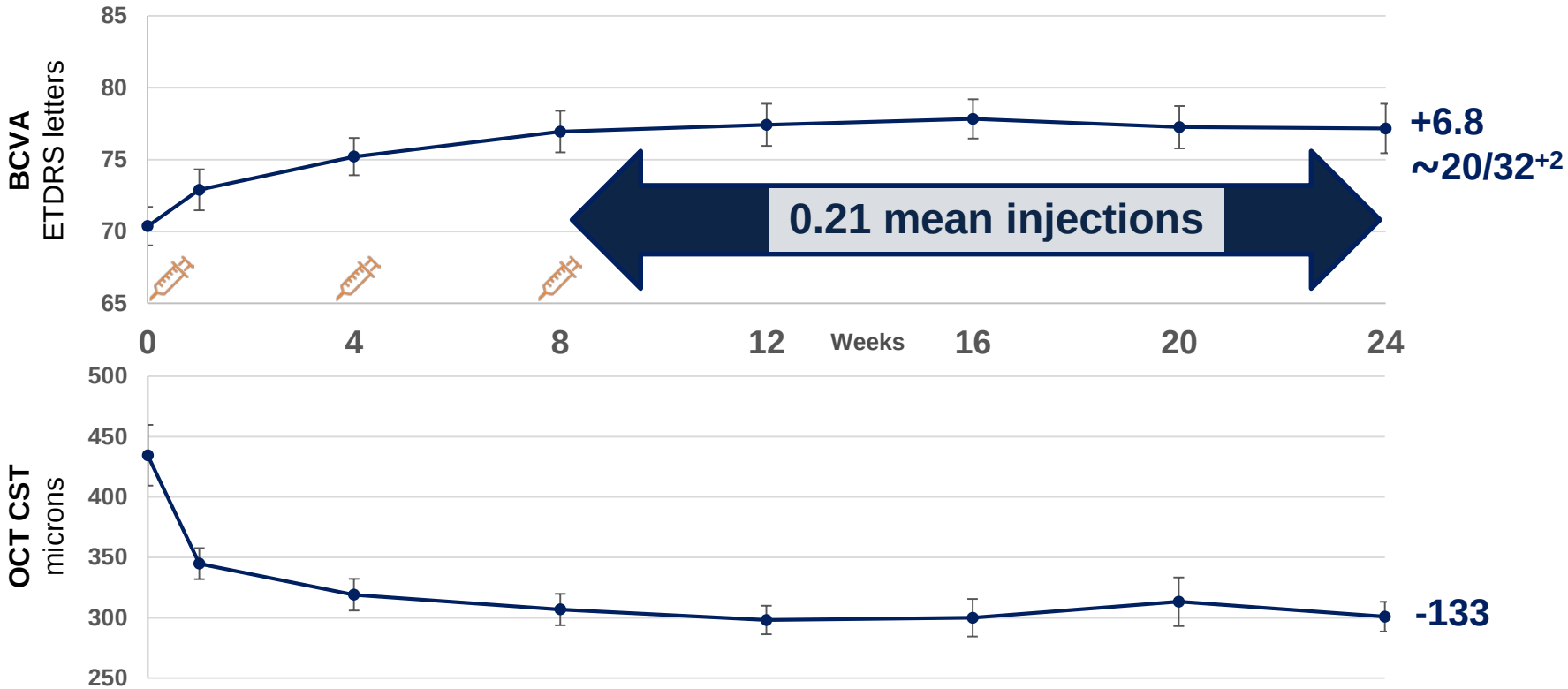
KSI-301 Phase 1b

DME

6 month data

Efficacy of KSI-301 in DME

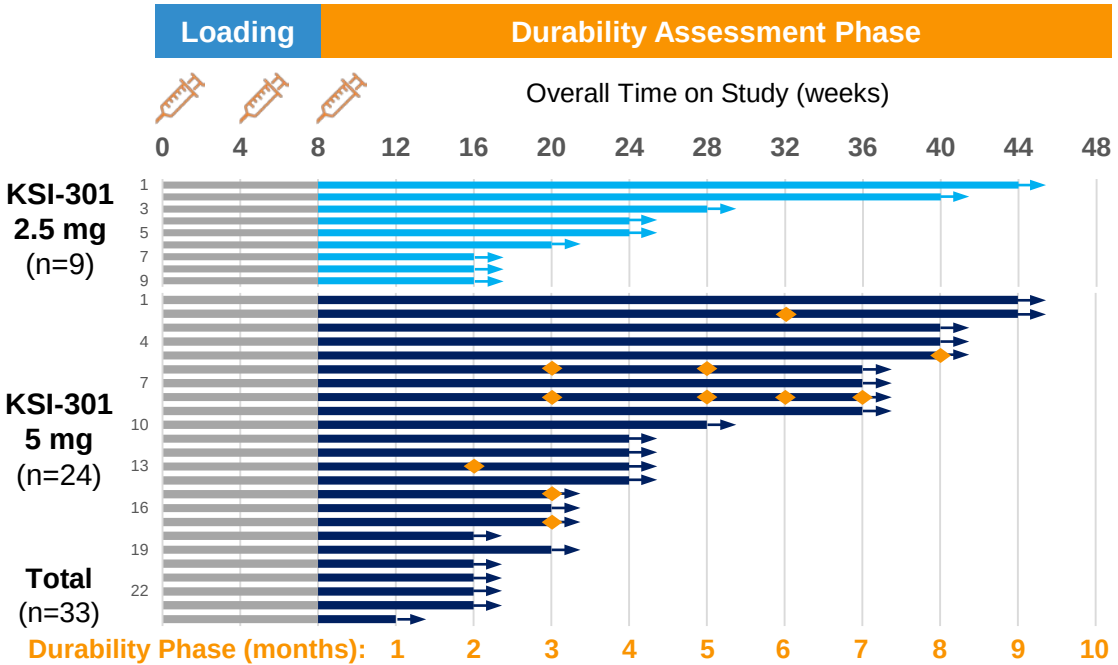
change from baseline to week 24 in mean BCVA & OCT



Interim data. Includes only randomized patients that reached Week 24 visit by the data cutoff date of 21 Jan 2020; 2.5 & 5 mg doses pooled. 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 8 and 24 (aflibercept per label mean number of injections 2.0).

n= 19 **Patients reaching Week 24 visit by data cutoff**

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



First Retreatment	Percentage
At or before 3 months	20% (5/24)
4 months or longer	76% (16/21)
5 months or longer	68% (11/16)
6 months or longer	64% (9/14)

64% (9/14) have reached 6 months or longer without retreatment

◆ Retreatment with KSI-301
→ Continuing follow-up

Interim data. Includes only randomized patients that reached the first retreatment opportunity (Week 12 visit) by the data cutoff date of 21 Jan 2020.
Each bar represents an individual patient. All depicted patients continue to be followed (no discontinuations)

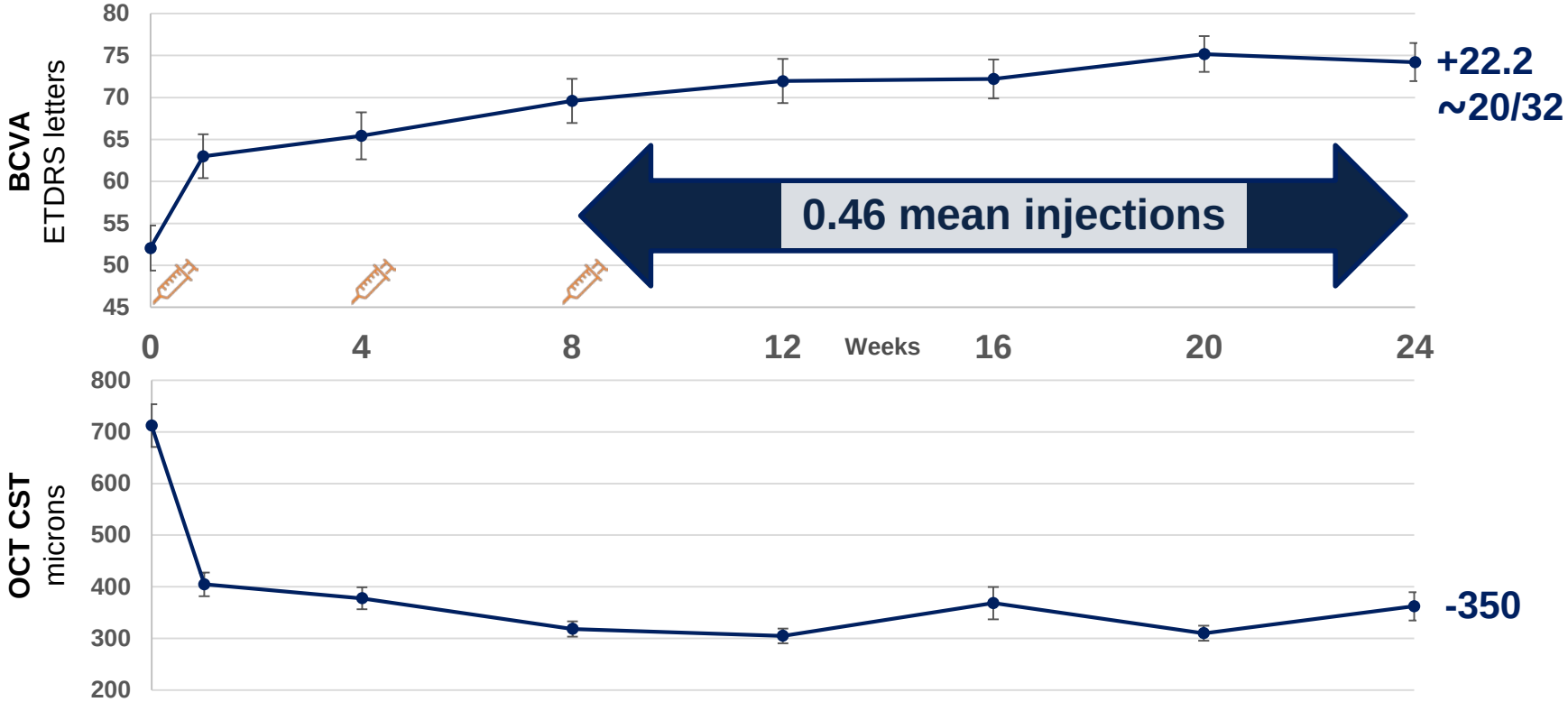
KSI-301 Phase 1b

RVO

6 month data

Efficacy of KSI-301 in RVO

change from baseline to week 24 in mean BCVA & OCT

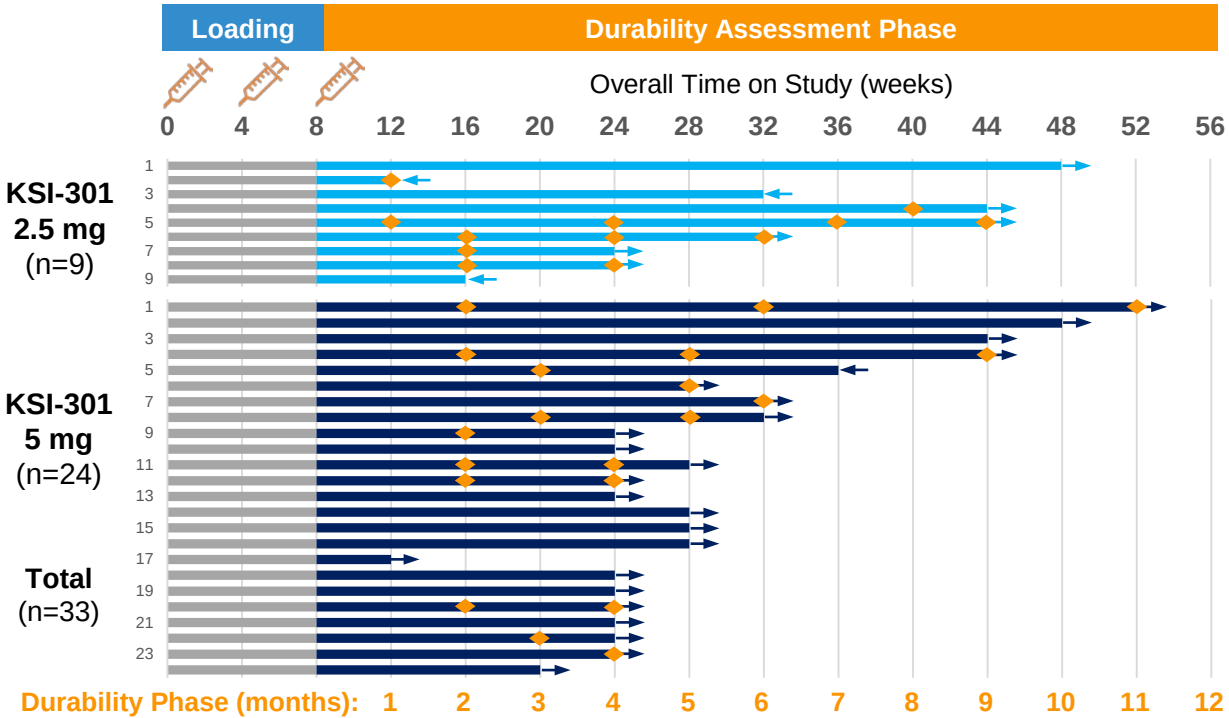


Interim data. Includes only randomized patients that reached Week 24 visit by the data cutoff date of 21 Jan 2020; 2.5 & 5 mg doses pooled. Observed data; datapoints include two subjects that discontinued after Week 12. Error bars represent standard error of the mean. OCT CST values are site reported. 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 8 and 24 (aflibercept per label mean number of injections 3.0).

n= 30 Patients reaching Week 24 visit by data cutoff

BRVO n= 17
CRVO n= 13

KSI-301 in RVO: *3 loading doses show potential for 2 to 4 month or longer dosing*



First Retreatment	Percentage
At or before 2 months	34% (11/32)
At or before 3 months	45% (14/31)
4 months or longer	53% (16/30)

53% (16/30) have reached 4 months or longer without retreatment

◆ Retreatment
→ Continuing follow-up
← Discontinuation

Interim data. Includes only randomized patients that reached the first retreatment opportunity (Week 12 visit) by the data cutoff date of 21 Jan 2020. Each bar represents an individual patient.

KSI-301 Phase 1b

Safety

Safety of KSI-301: *multiple-dose exposure is well-tolerated with no intraocular inflammation*

130
Subjects dosed in Phase 1a+1b

420
Total doses given in Phase 1a+1b

121 At Day 1 | **112** At Week 4 | **105** At Week 8

Phase 1b subjects with # of loading doses received

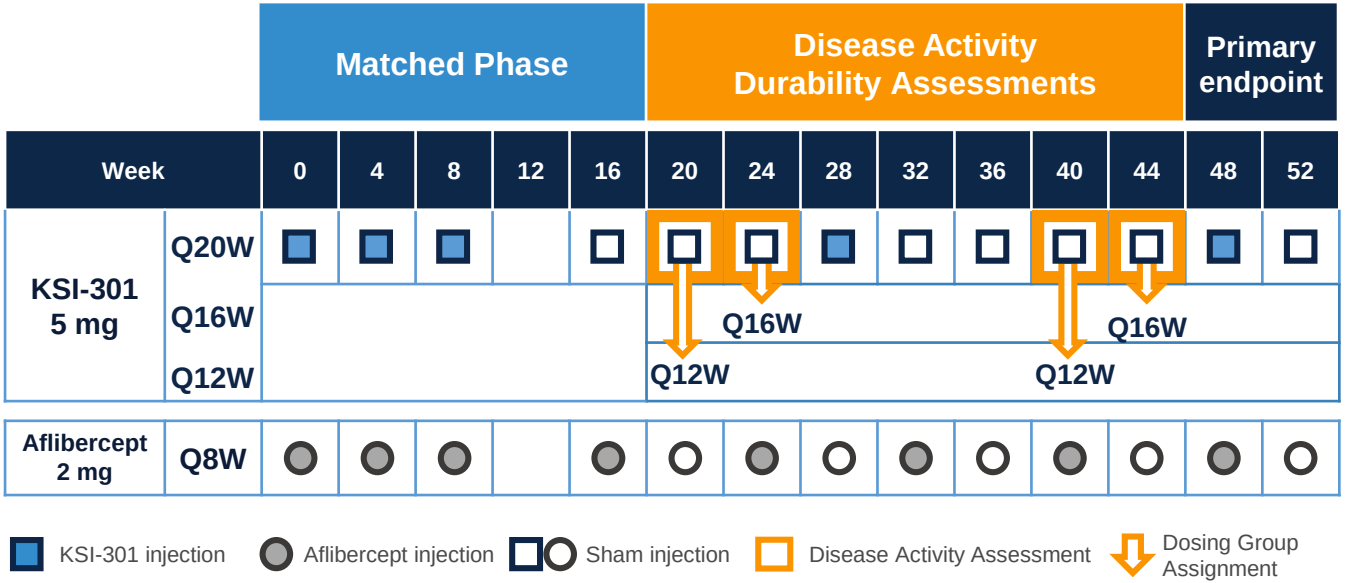
- No intraocular inflammation or ocular SAEs in the study eye reported to date
- No drug-related AEs or drug-related SAEs reported to date
- Most AEs were assessed as mild and are consistent with profile of intravitreal anti-VEGFs
- 16 non-ocular SAEs that were not drug-related have been reported in 10 subjects:
  - One 92 y/o RVO subject with hospitalization related to a pre-existing condition that resulted in death
  - Six (43, 56, 62, 66, 70 and 72 y/o, respectively) DME subjects with hospitalization related to a pre-existing condition
  - One 66 y/o RVO subject with hospitalization related to dizziness
  - One 43 y/o RVO subject with a broken leg related to a motorcycle accident
  - One 85 y/o RVO subject with hospitalization related to a pre-existing condition

Includes all patients randomized as of 21 Jan 2020, all doses administered across cohorts. Interim safety data as of 21 Jan 2020; AE: adverse event; SAE: serious adverse event

Now Recruiting: Pivotal DAZZLE wAMD Study

Dosing with KSI-301 as infrequently as every 20 weeks

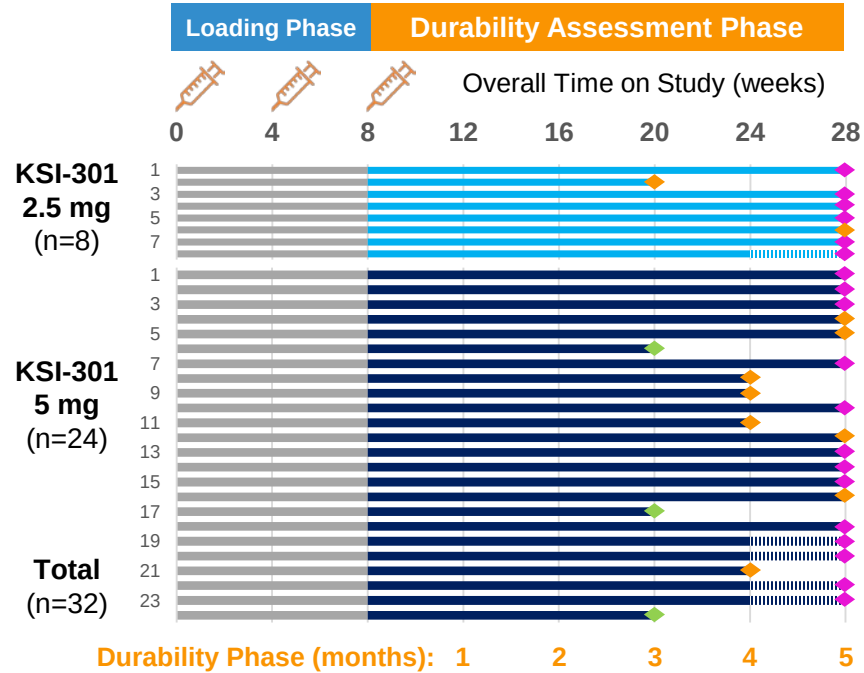
- ~550 treatment naïve wAMD patients
- Randomized study vs aflibercept
- US & EU study sites
- KSI-301 dosing: every 12, 16, or 20 weeks depending on pre-specified disease activity assessments*

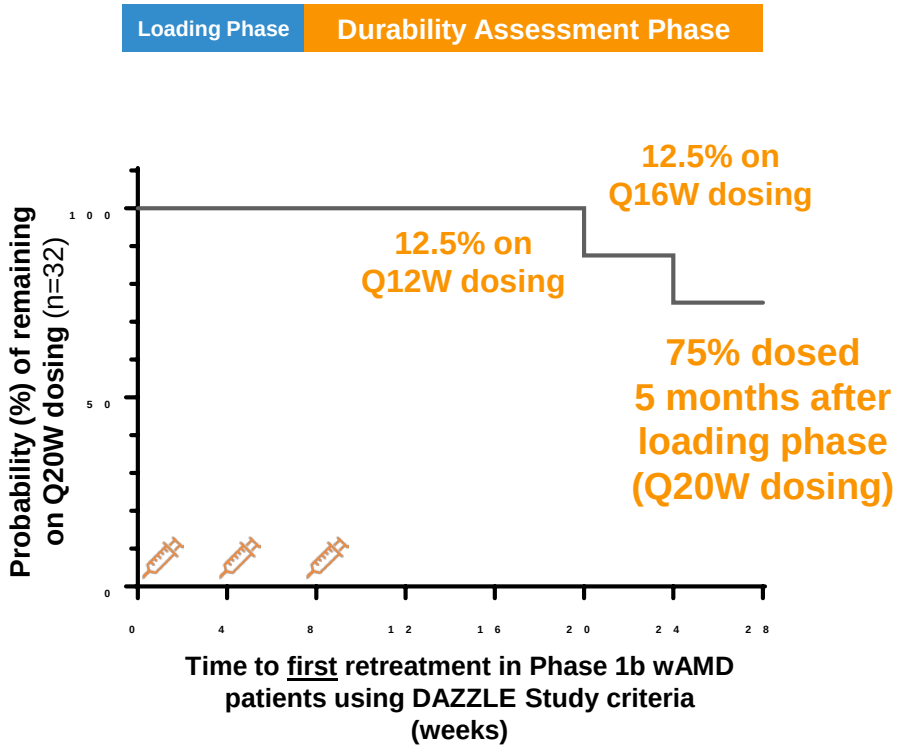


*After the loading phase
Clinicaltrials.gov ID NCT04049266

KSI-301 in wAMD: Time to first retreatment

Ph1b patient projected retreatments based on DAZZLE criteria





- Retreatment criteria met
- Minimum 3 month interval
- Capped retreatment at 5 months

Interim data. Includes only randomized patients that would have met retreatment criteria before or at Week 28 by the data cutoff date of 21 Jan 2020. Each bar represents an individual patient.

Conclusion: KSI-301 showing promising safety, efficacy and durability - Development program accelerating

- Antibody Biopolymer Conjugates (ABCs) are a new design platform for long durability intravitreal medicines
- Phase 1b exploratory study informs pivotal study designs
  - **Excellent Safety:** zero cases of intraocular inflammation after 400+ doses
  - **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 clinical program is accelerating
  - Pivotal 'DAZZLE' study of KSI-301 vs aflibercept in treatment-naïve wet AMD now recruiting
  - Pivotal Studies in RVO, DME, and NPDR expected to begin recruiting in 2020

Acknowledgements

Principal Investigators

- Mark Barakat, MD
- Brian Berger, MD
- David Boyer, MD
- David Brown, MD
- Pravin Dugel, MD
- David Eichenbaum, MD
- Arshad Khanani, MD
- Ted Leng, MD
- Sunil Patel, MD, PhD
- Carl Regillo, MD
- Mark Wieland, MD
- Charles Wykoff, MD, PhD

Kodiak Sciences

- Pablo Velazquez-Martin, MD
- Daniel Janer, MD
- Amy Duguay, BS
- Frances Faurot
- Pam Henderson, RN
- Hong Liang, PhD
- Bryce Miller, MPA
- Joel Naor, MD, MSc
- Almas Qudrat, MSc
- Jason Ehrlich, MD, PhD
- Victor Perlroth, MD

Ocular Imaging Research & Reading Center

Appendix

The DAZZLE Study Disease Activity Assessment Criteria allow for tighter disease control

Parameters	Phase 1b Study	DAZZLE study	Change
Visual *and* anatomical	Increase in CST ≥75 µm with a decrease in BCVA of ≥ 5 letters compared to Week 12, *OR*	Increase in CST ≥50 µm with a decrease in BCVA of ≥ 5 letters compared to Week 12, *OR*	Tighter CST control (25 microns)
Visual only	Decrease in BCVA of ≥ 10 letters compared to the best prior BCVA, due to worsening wAMD activity, *OR*	Decrease in BCVA of ≥ 10 letters compared to the best prior BCVA, due to worsening wAMD activity, *OR*	No change
	Decrease in BCVA of > 5 letters compared to Day 1, due to worsening wAMD activity	N/A	Eliminated for simplicity
Anatomical only	N/A	Increase of ≥ 75 microns compared to Week 12, *OR*	Added two anatomical-only criteria
	N/A	New Macular Hemorrhage	

CST = central subfield retinal thickness; BCVA = best corrected visual acuity.