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

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Disclosures

- **Financial:**

Alcon[C]
Allegro[C]
Allergan[C]
Alimera[C]
Bausch and Lomb[C]
Clearside Biomedical[C]
EyePoint Pharmaceuticals[C]
Kodiak Sciences[C]
Genentech[BC]
Novartis[BC]
NeuBase[S]
Ocular Therapeutix[C]
Oxurion[S]
RegenxBio[C]

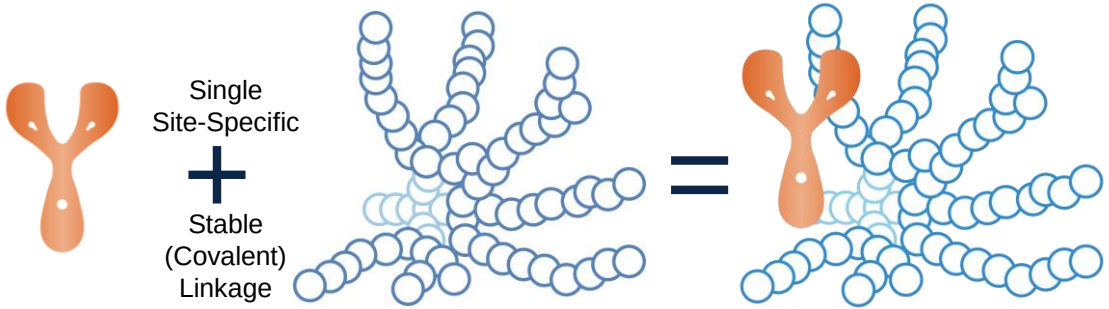
- **Study Disclosures:**

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

B = Speakers' Bureau; C = Consultant; S = Minor Shareholder

Antibody Biopolymer Conjugates (ABC)

biologics engineered for increased durability and efficacy



ANTIBODY

lgG1 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

The biopolymer conjugate improves durability while structuring water at critical binding interfaces for improved specificity, affinity and tissue access

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

SAME WHERE IT MATTERS

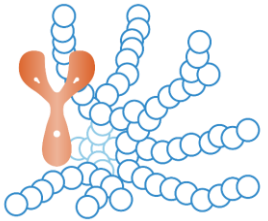
- Clinically proven targets
- Antibody-based biologic
- Intravitreal: safest method of administration
- Optically clear, no residues
- Fast and potent clinical responses

DIFFERENT WHERE IT COUNTS

- Designed-in ocular durability
- Designed-in rapid systemic clearance
- Improved bioavailability
- Improved biocompatibility
- Improved stability

Next-Generation anti-VEGF:

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**

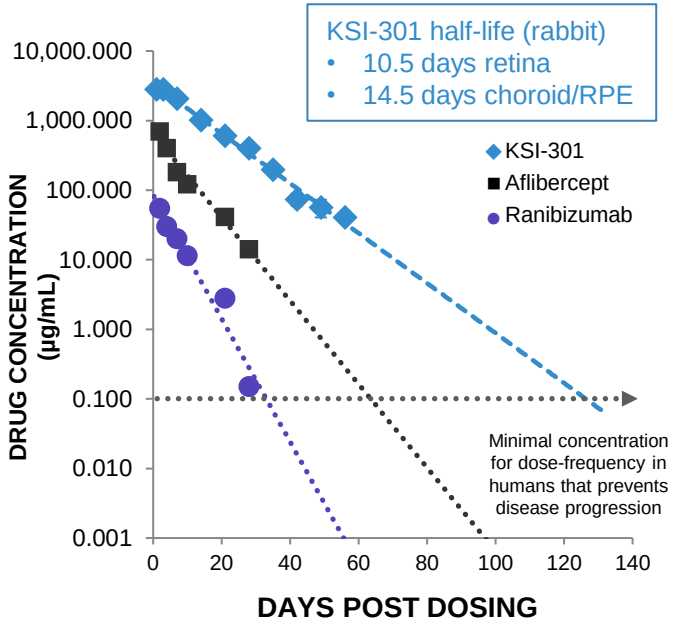
Equivalent values are shown as (approximate) fold difference relative to aflibercept. kDa= kilodalton

1. Lower affinity of bevacizumab precludes a useful comparison

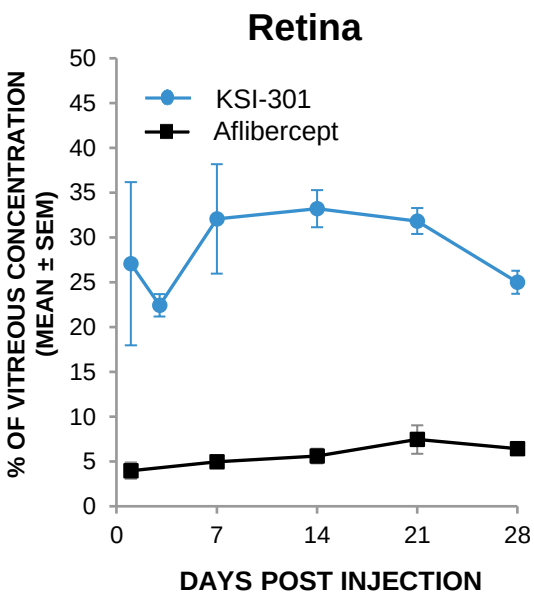
KSI-301 Properties: Preclinical Data

Special features from the ultra-hydrophilic phosphorylcholine biopolymer

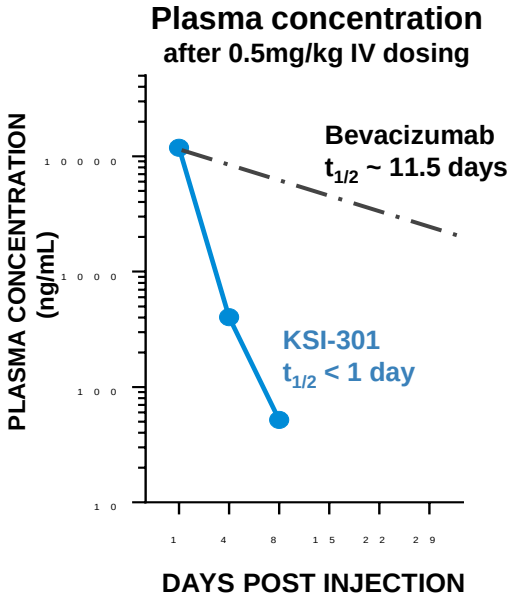
Remarkable Intraocular Half-life[1]



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 Phase 1b Study

Clinical Data

121 treatment-naïve patients dosed

101+ patient-years of clinical experience

KSI-301 Phase 1b

insight into durability among treatment naïve subjects

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
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

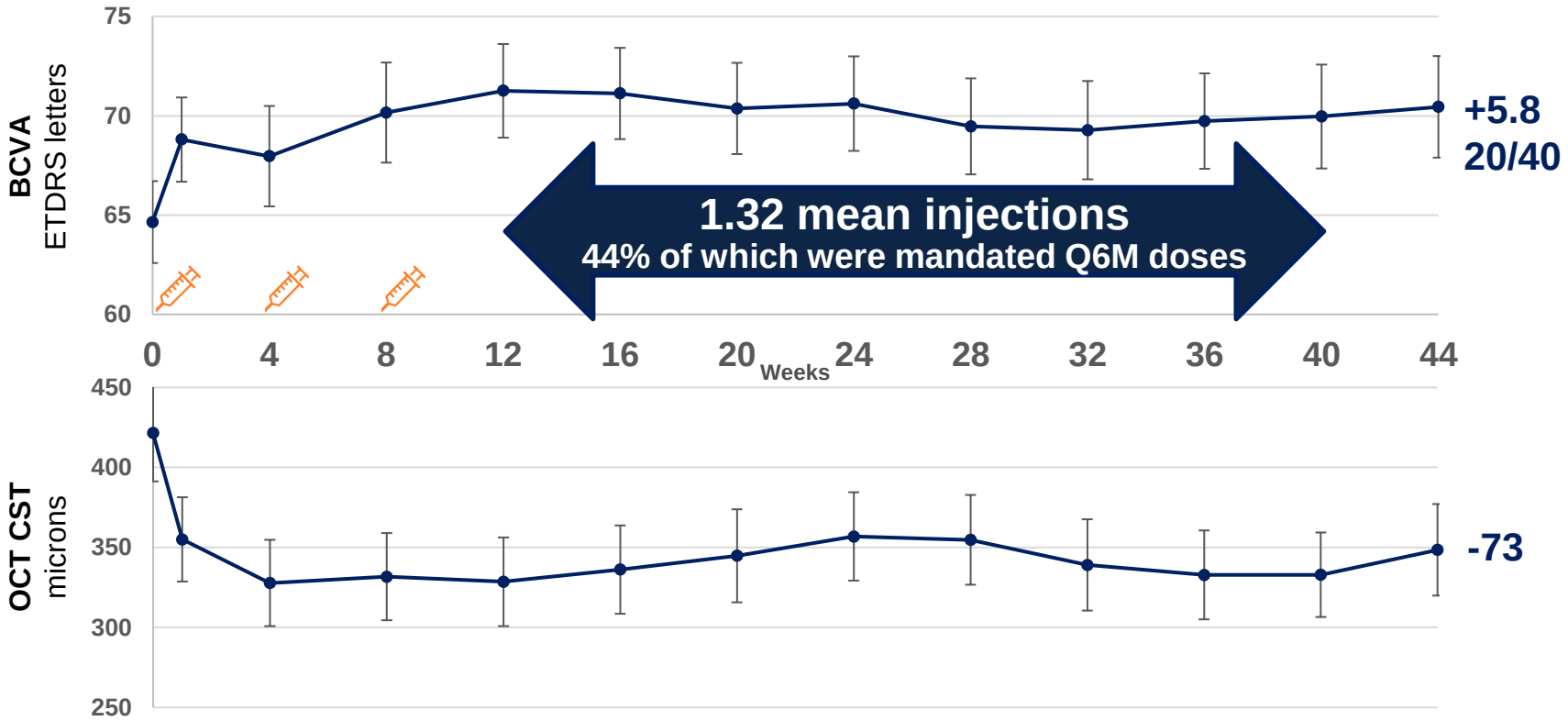
Variable	wAMD Cohort (n=51)	DME Cohort (n=35)	RVO Cohort (n=35)
Age, mean (SD), years	77.9 (10.5)	59.7 (11.7)	63.6 (12.6)
Gender, n (%), female	32 (62.7)	14 (40.0)	13 (37.1)
Race, n (%), White	48 (94.1)	28 (80.0)	31 (88.6)
BCVA, mean (SD), ETDRS letters	63.3 (13.3)	66.8 (10.2)	54.9 (15.4)
Snellen equivalent	~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 09 June 2020. SD= standard deviation; BCVA= best corrected visual acuity; OCT= optical coherence tomography; CST= central subfield thickness

KSI-301 Phase 1b
wAMD
10-month data

Efficacy of KSI-301 in Wet AMD

change from baseline to week 44 in mean BCVA & OCT

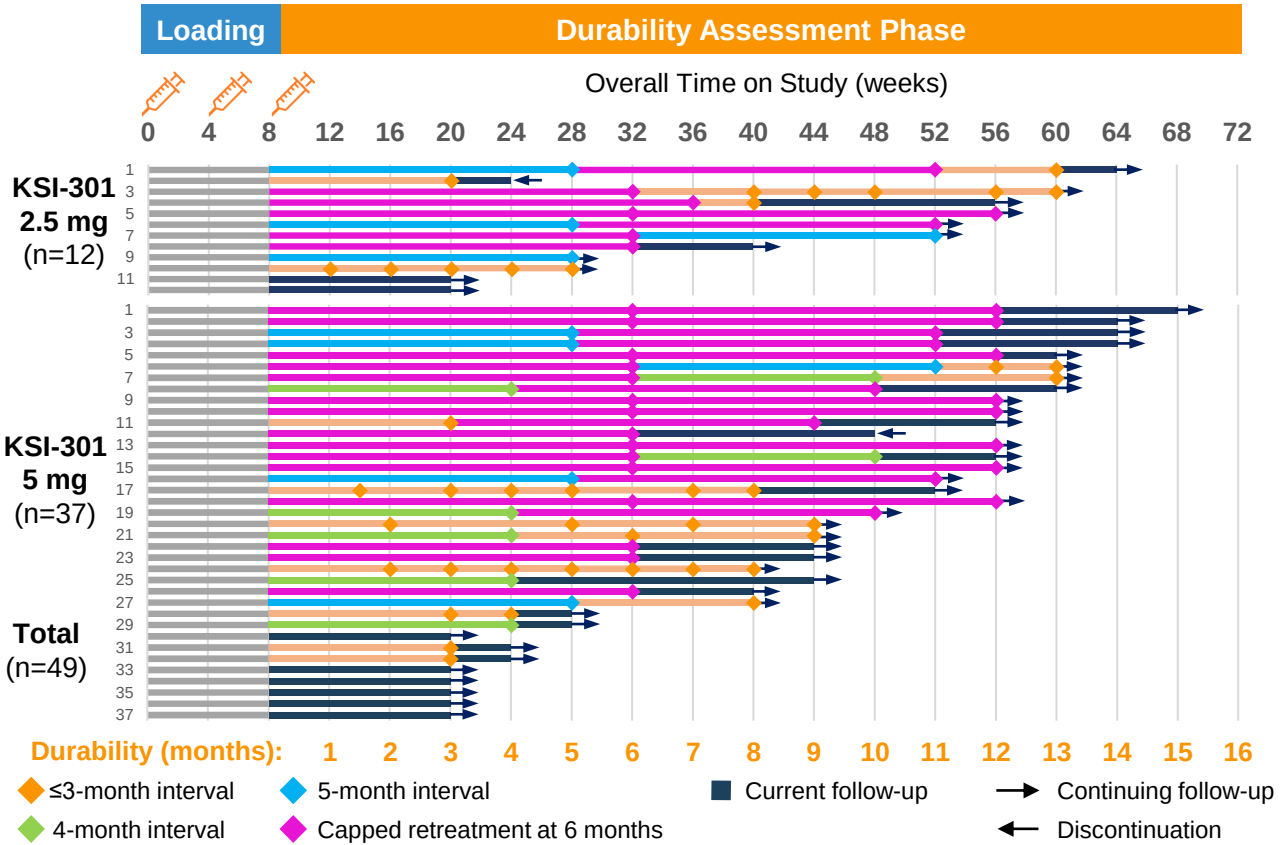


Interim data. Includes only randomized patients that reached Week 44 visit by the data cutoff date of 09 Jun 2020; 2.5 & 5 mg doses pooled. Observed data. Error bars represent standard error of the mean. OCT CST values are site reported and include PED height. BCVA= best corrected visual acuity; OCT= 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 in wAMD: Durability Assessment

Data continue to support 3- to 6-month durability



First Retreatment	Percentage
At or before 3 months	18% (9/49)
4 months or longer	82% (40/49)
5 months or longer	66% (27/41)
6 months	49% (20/41)

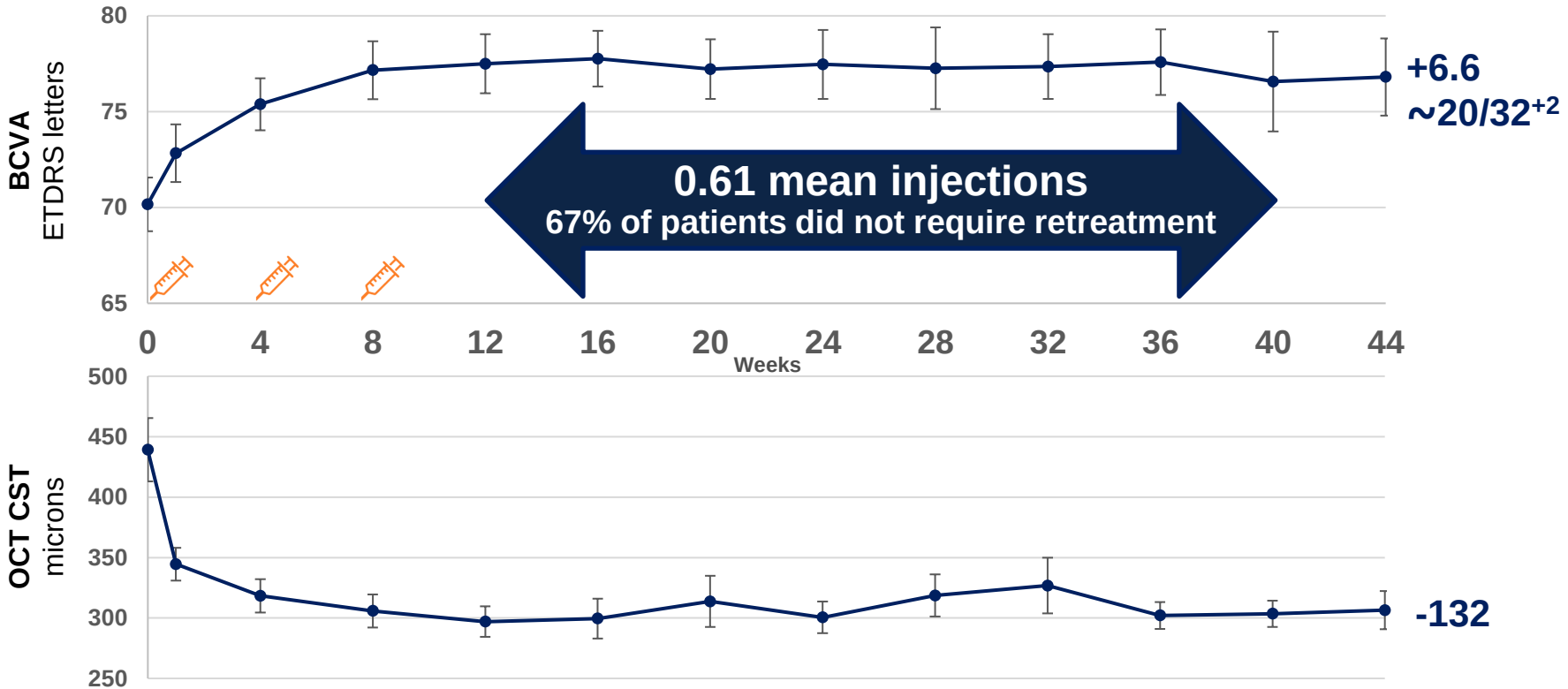
68% (28/41) have achieved a 6-month treatment interval at least once during follow-up

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.

KSI-301 Phase 1b
DME
10-month data

Efficacy of KSI-301 in DME

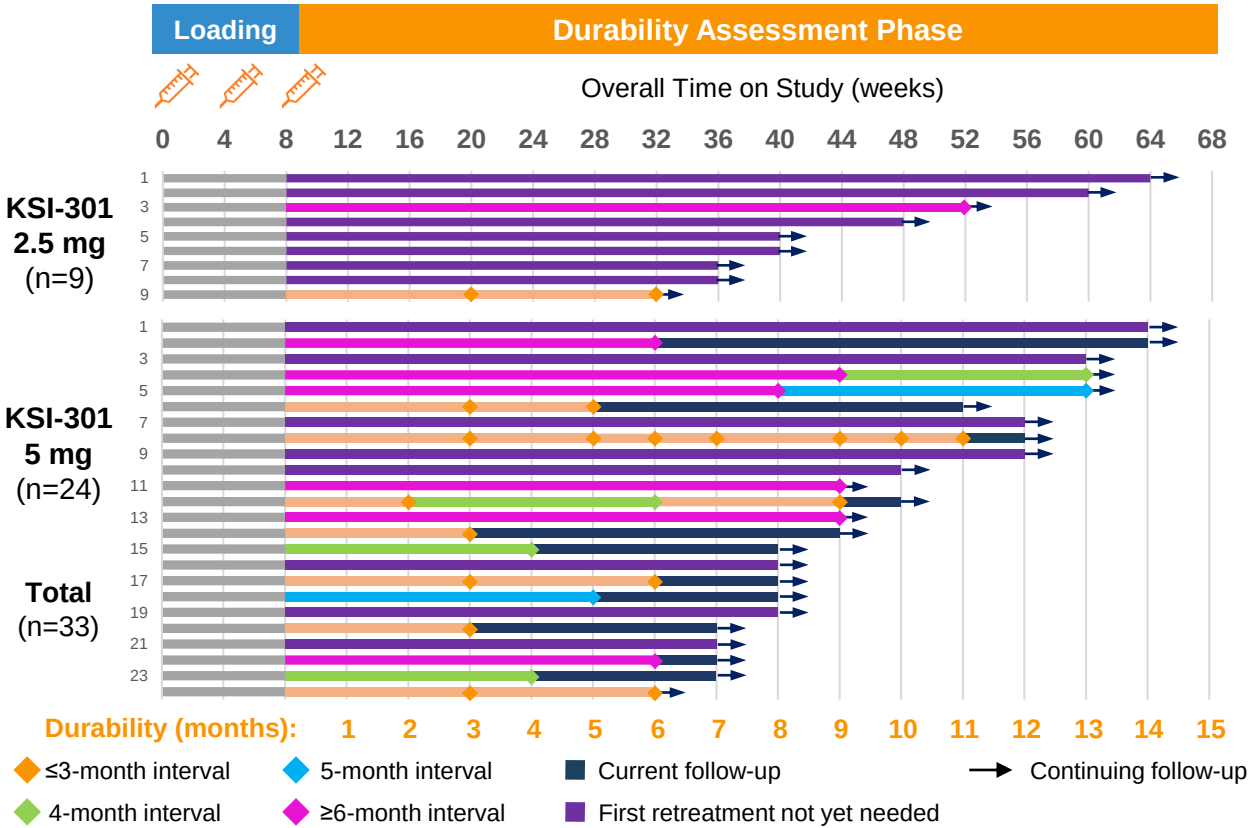
change from baseline to week 44 in mean BCVA & OCT



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 5.0).

n= 18 Patients reaching Week 44 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	24% (8/33)
4 months or longer	76% (25/33)
5 months or longer	70% (23/33)
6 months or longer	67% (22/33)

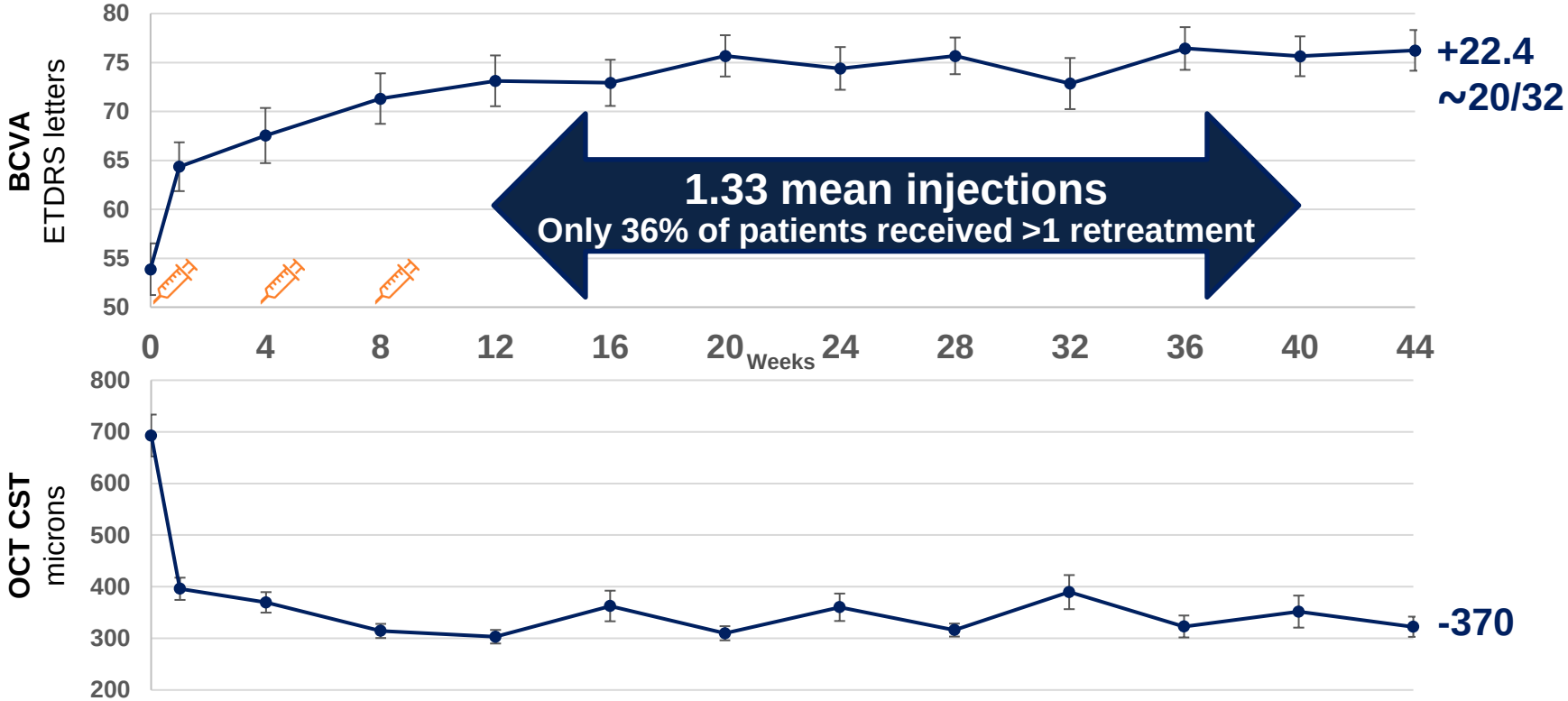
45% (15/33) have not yet required a single retreatment

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)

KSI-301 Phase 1b
RVO
10-month data

Efficacy of KSI-301 in RVO

change from baseline to week 44 in mean BCVA & OCT

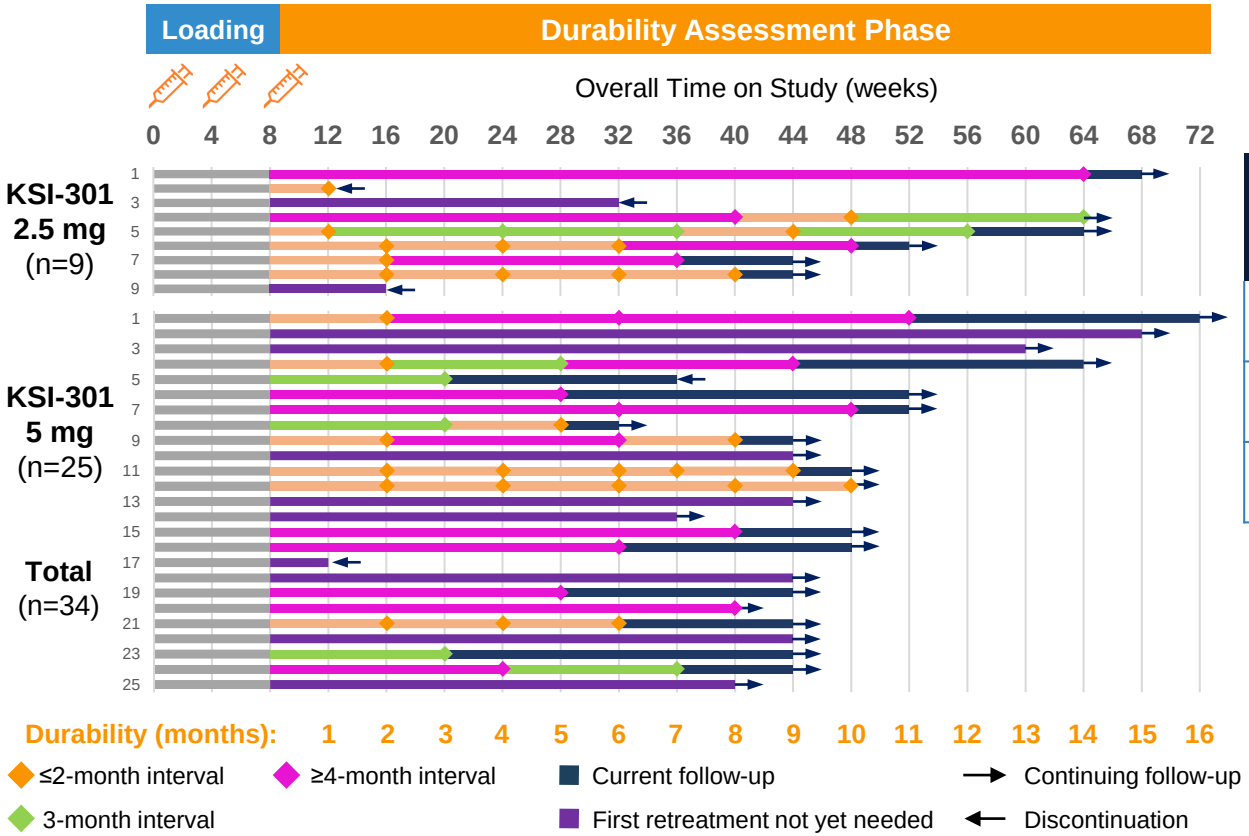


Interim data. Includes only randomized patients that reached Week 44 visit by the data cutoff date of 09 Jun 2020; 2.5 & 5 mg doses pooled. Observed data. Error bars represent standard error of the mean. OCT CST values are site reported. BCVA= best corrected visual acuity; OCT= optical coherence tomography; 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 in RVO: *3 loading doses show potential for 2 to 4 month or longer dosing*



First Retreatment	Percentage
At or before 2 months	33% (11/33)
At or before 3 months	44% (14/32)
4 months or longer	56% (18/32)

71% (24/34) have achieved ≥4-month treatment 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.

KSI-301 Phase 1b

Safety

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

130
Subjects dosed in Phase 1a+1b

546
Total doses given in Phase 1a+1b

121
Completed the loading phase in Phase 1b

81
Phase 1b subjects at Week 12 or later that have received all three loading doses plus at least one additional retreatment

- To date, 29 SAEs have been reported in 16 subjects – none drug related
- One ocular SAE in the study eye (worsening DME secondary to systemic fluid overload, not drug related)
- Two AEs of intraocular inflammation, both trace to 1+ vitreous cells, with complete resolution
  - Rate of 0.37% (2/546 injections)
  - No vasculitis or retinitis in either patient
- Most AEs were assessed as mild and are consistent with profile of intravitreal anti-VEGFs
- Immunogenicity and Anti-Drug-Antibody (ADA)[1]
  - No pre-existing ADA in any patient
  - Very low treatment-emergent ADA & transient and/or mild in all cases

Includes all Phase 1a+1b patients randomized as of 09 Jun 2020, all doses administered across cohorts. Interim safety data as of 09 Jun 2020; AE: adverse event; SAE: serious adverse event
1. As of 117 patients with at least one sample analyzed for ADA from phase 1a+1b

KSI-301 - Next Steps in Development

KSI-301 Phase 1b durability informs the design of pivotal studies testing clinically differentiated treatment regimens

Now Recruiting
~300 patients randomized[1]

Wet AMD

DAZZLE Study
(n~550)

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

Comparator

Aflibercept
once every 2 months
after 3 monthly doses

Planned to Start in 2020

Diabetic Macular Edema

GLEAM and
GLIMMER Studies
(n~450 each)

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

Comparator

Aflibercept
once every 2 months
after 5 monthly doses

Retinal Vein Occlusion

BEACON Study
(n~550)

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

Comparator

Aflibercept
once every month

Non-Proliferative Diabetic Retinopathy

GLOW Study
(n~400)

KSI-301
once every 4 or 6 months
after 2 bimonthly doses

Comparator

Sham

1. As of 19 Jun 2020

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
  - 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 clinical program is accelerating
  - Pivotal ‘DAZZLE’ study of KSI-301 vs aflibercept in treatment-naïve wet AMD now recruiting
  - Pivotal Studies in DME, RVO and NPDR expected to begin recruiting in 2020
  - Objective of a single regulatory filing (BLA) in wAMD, DME and RVO in 2022

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