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

First-time Results from a Phase 1b Study in Patients with wAMD, DME and RVO

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Disclosures

- **Financial:**

  Adverum (C, R); Aerpio (C, R); Alimera Sciences (C); Allegro (C); Allergan (C, R); Apellis (C, R); Bayer (C); Clearside Biomedical (C, R); Chengdu Kanghong (R); DORC (C); EyePoint (C); Fosun (C); Genentech/Roche (C, R); Iveric Bio (formerly Ophthotech) (C, R); Kodiak Sciences (C, R); Neurotech (R), Novartis (C, R); ONL Therapeutics (C); Opthea (R); PolyPhotonix (C); Recens Medical (C, R); Regeneron (C, R, S); Regenxbio (C, R); Samsung (R), Santen (C, R), Takeda (C).

- **Study Disclosures:**

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

Investigational Treatments for Exudative Retinal Diseases
aimed at improving efficacy & durability

Aflibercept

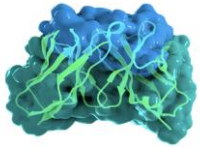
Bevacizumab

Ranibizumab

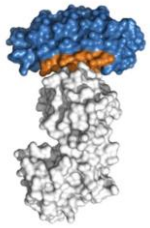
Dexamethasone

Triamcinolone

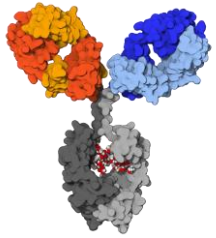
Fluocinolone acetonide



Brolucizumab

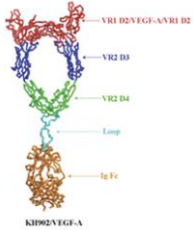


Abicipar

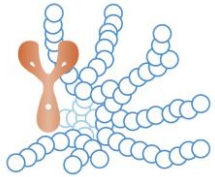


Faricimab

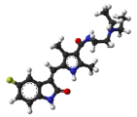
PDS



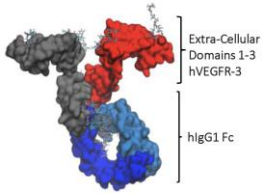
Conbercept



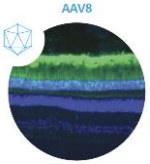
KSI-301



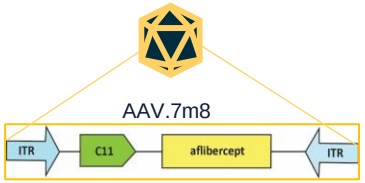
Sunitinib



OPT-302



RGX-314

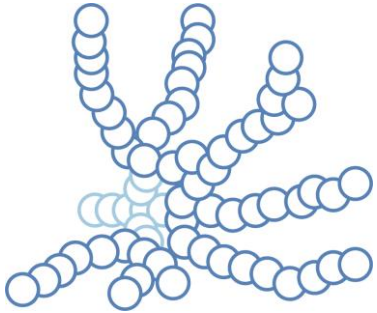


ADVM-022

Antibody Biopolymer Conjugates (ABC)

biologics engineered for increased durability and efficacy

Single
Site-Specific
+
Stable
(Covalent)
Linkage



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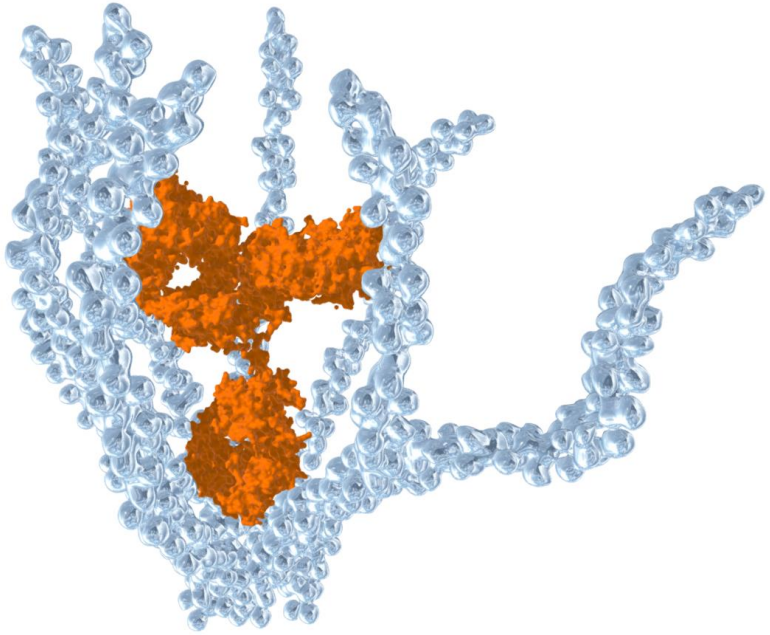


ANTIBODY

IgG1 Antibody
Inert Immune
Effector Function

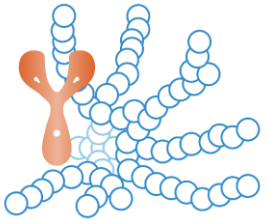
BIOPOLYMER

Branched
High Molecular Weight
Optically Clear
Phosphorylcholine Polymer

ANTIBODY BIOPOLYMER CONJUGATE
KSI-301 is an intravitreally injected anti-VEGF ABC

Go Bigger to Last Longer

KSI-301: ABC designed to block all VEGF-A Isoforms

	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**

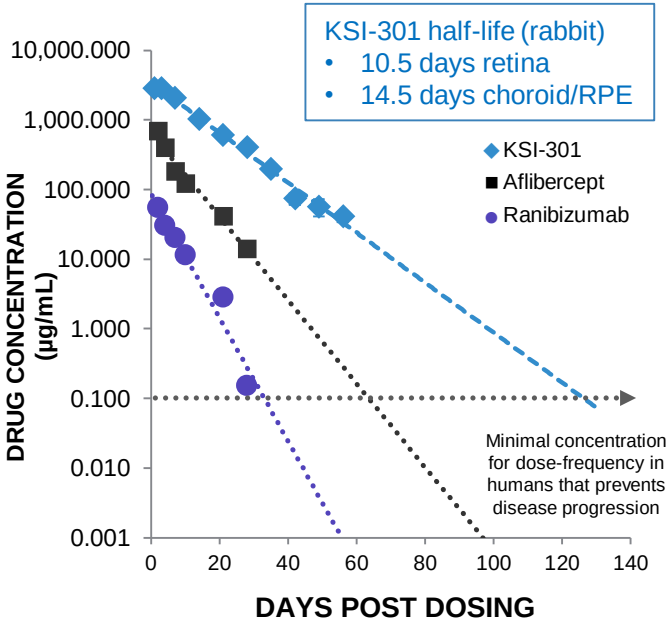
Equivalent values are shown as (approximate) fold difference relative to aflibercept. kDa= kilodalton

1. Lower affinity of bevacizumab precludes a useful comparison

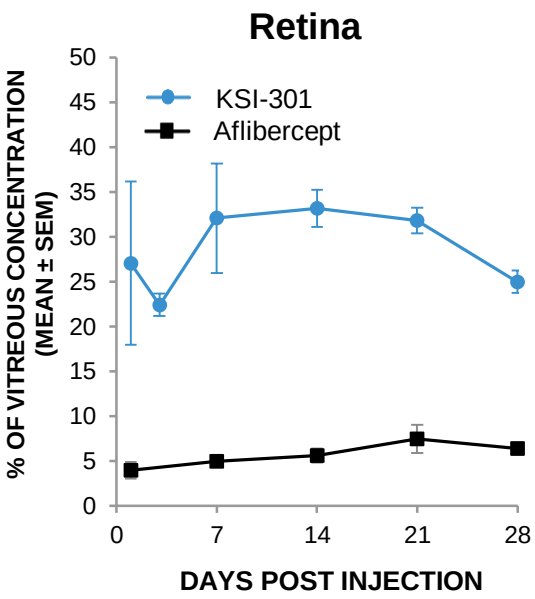
KSI-301 Properties: Preclinical Data

Special features from the ultra-hydrophilic phosphorylcholine biopolymer

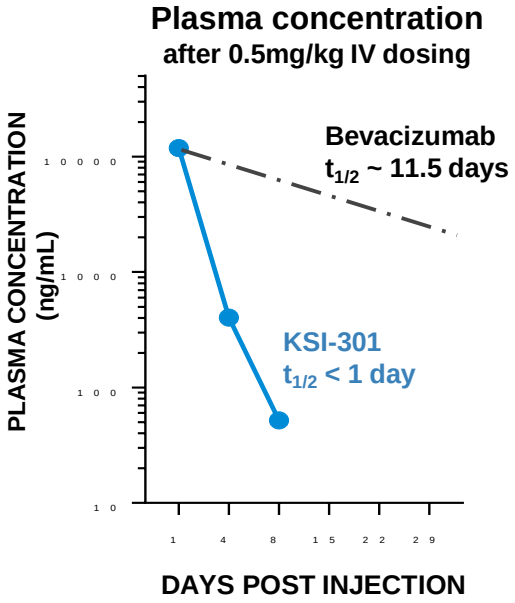
Remarkable Intraocular Durability[1]



Excellent Retinal Bioavailability[2]



Fast Systemic Clearance[3]



1. Data from rabbit model. Ranibizumab data: Gaudrealt et al (2007) IOVS 46(2) 726 Gaudrealt 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

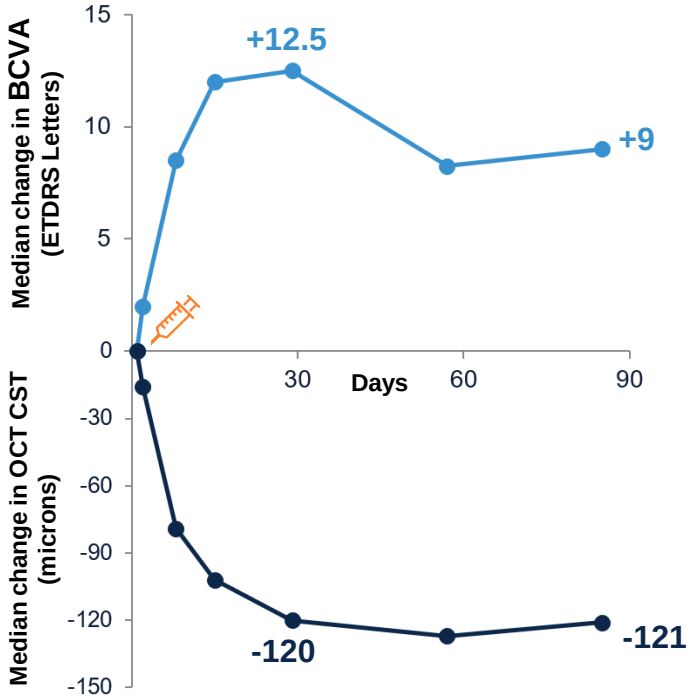
Clinical Data

113 patients dosed to date

KSI-301 Phase 1a

well-tolerated with rapid anatomic & visual response

- Diabetic macular edema (DME) patients with severe disease (n=9)
- Incompletely responsive to previous anti-VEGF treatment (8/9 previously treated) (median 3, range 0-7 in the year prior)
- A single injection of KSI-301 resulted in rapid, high-magnitude responses durable to 12 weeks
  - n=3 patients per dose level (1.25mg, 2.5mg, 5mg)
- No intraocular inflammation and no drug-related adverse events



Median changes from baseline to week 12 pooled across 3 dose groups (n=9 patients total)

Do DV, Angiogenesis 2019; Patel et al., ARVO 2019

KSI-301 Phase 1b

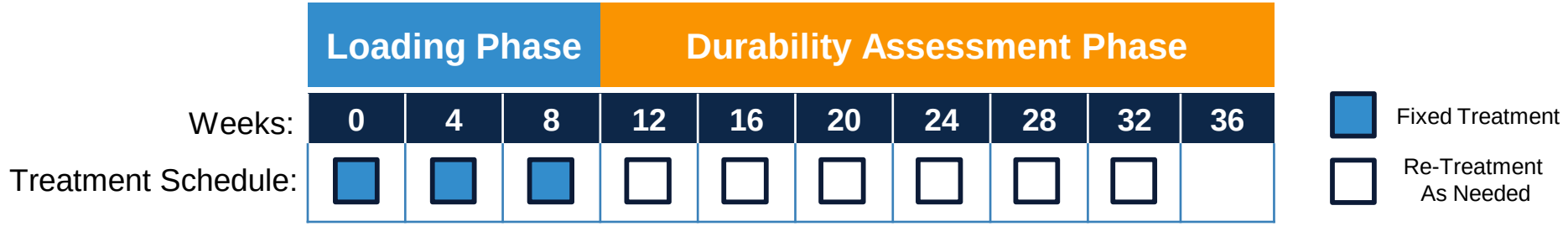
insight into durability among treatment naïve subjects

Randomized, open label study to evaluate multidose safety, efficacy & durability (n=105)

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

Randomized 1:3

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



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

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
- **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=35)	DME Cohort (n=34)	RVO Cohort (n=35)
Age, mean (SD), years	77.2 (11.0)	60.7 (10.4)	63.6 (12.6)
Gender, n (%), female	25 (71.4)	13 (38.2)	13 (37.1)
Race, n (%), White	32 (91.4)	28 (82.4)	31 (88.6)
BCVA, mean (SD), ETDRS letters	64.5 (11.1)	66.8 (10.3)	54.9 (15.4)
BCVA, Snellen 20/40 or better, n (%)	14 (40.0)	16 (47.1)	6 (17.1)
OCT CST, mean (SD), microns	426 (176)	449 (109)	675 (237)

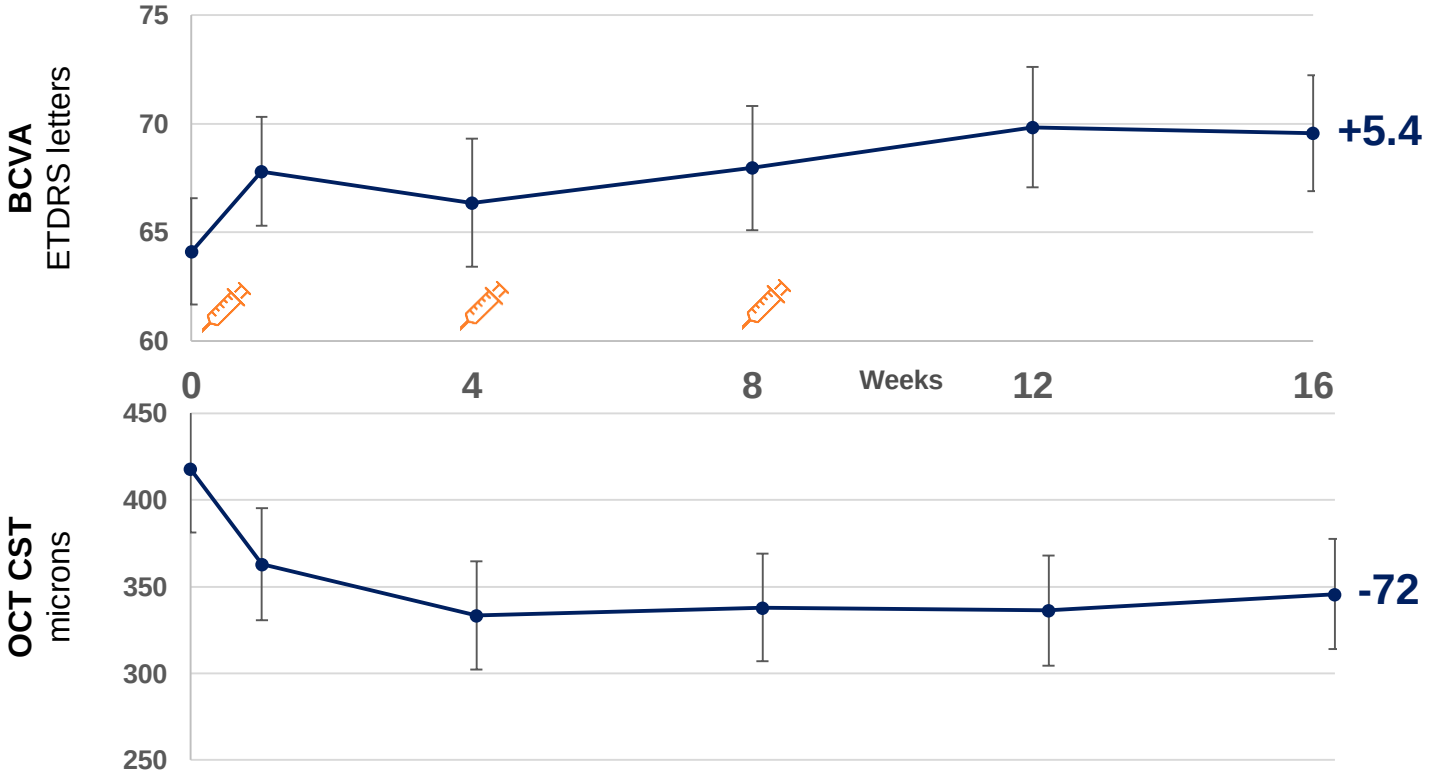
Includes all patients randomized as of 10 October 2019. SD= standard deviation; BCVA= best corrected visual acuity; OCT= optical coherence tomography; CST= central subfield thickness

KSI-301 Phase 1b

First Time Results

Efficacy of KSI-301 in Wet AMD

change from baseline to week 16 in mean BCVA & OCT

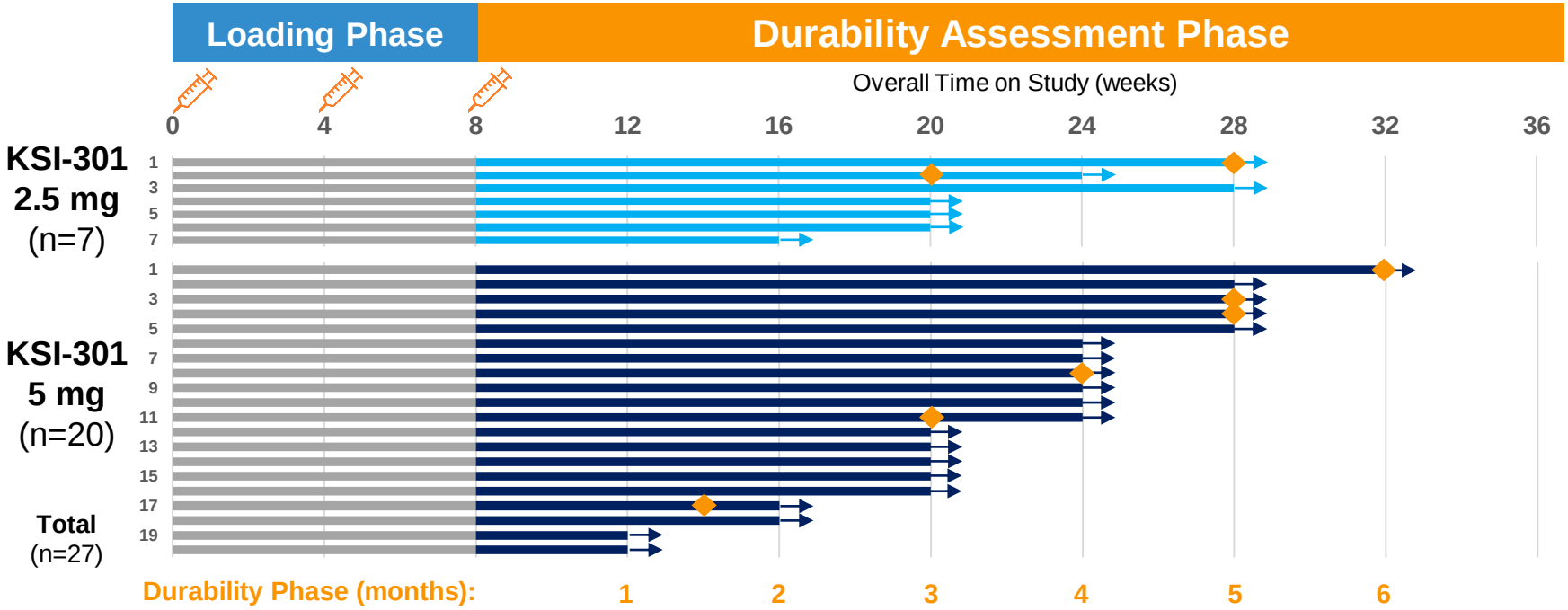


Interim data. Includes only randomized patients that reached Week 16 visit by the data cutoff date of 10 Oct 2019; 2.5 & 5 mg doses pooled. Error bars represent standard error of the mean. OCT CST values are site reported.
BCVA= best corrected visual acuity; OCT= optical coherence tomography; CST= central subfield thickness

n= 25 **Patients reaching Week 16 visit by data cutoff**

KSI-301 in wAMD: Durability Assessment

Emerging data support 3 to 5+ month durability



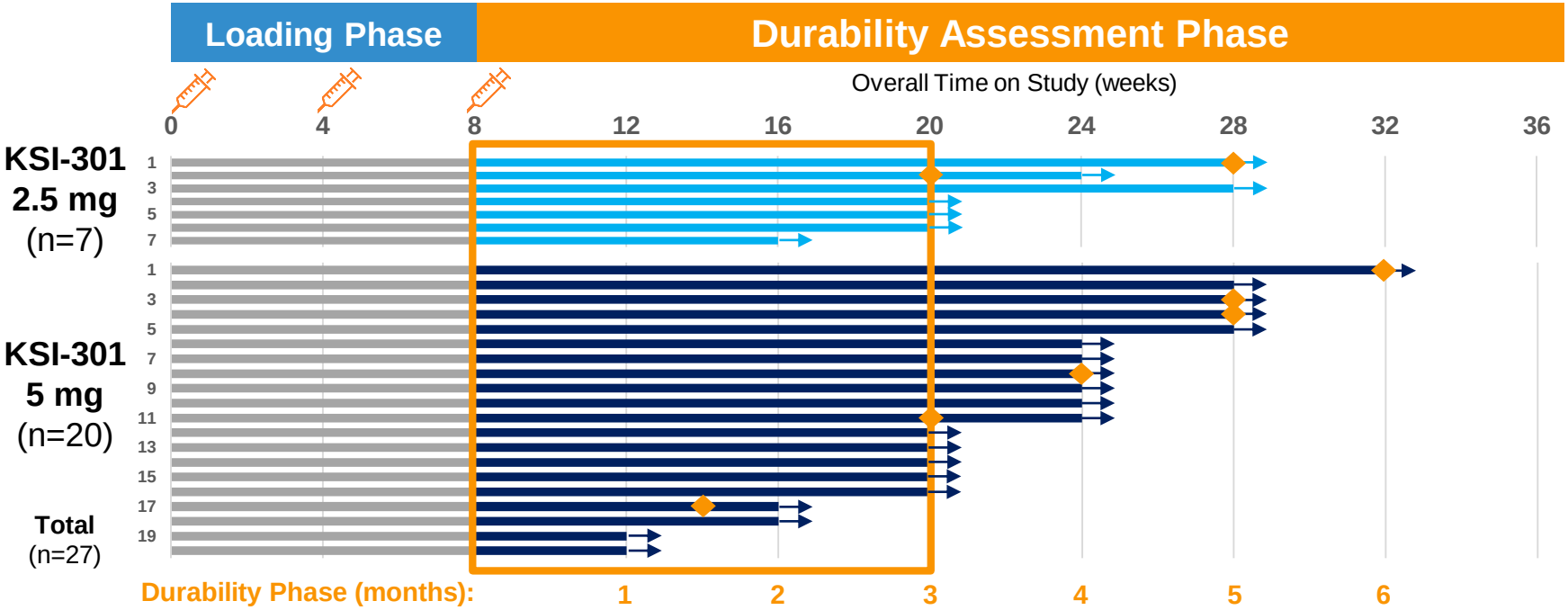
◆ Retreatment with KSI-301

→ Continuing follow-up

Interim data. Includes patients that reached the first retreatment opportunity (Week 12 visit) by the data cutoff date of 10 Oct 2019.
Each bar represents an individual patient. All depicted patients continue to be followed (no discontinuations)

KSI-301 in wAMD: Durability Assessment

Emerging data support 3 to 5+ month durability



◆ Retreatment with KSI-301

→ Continuing follow-up

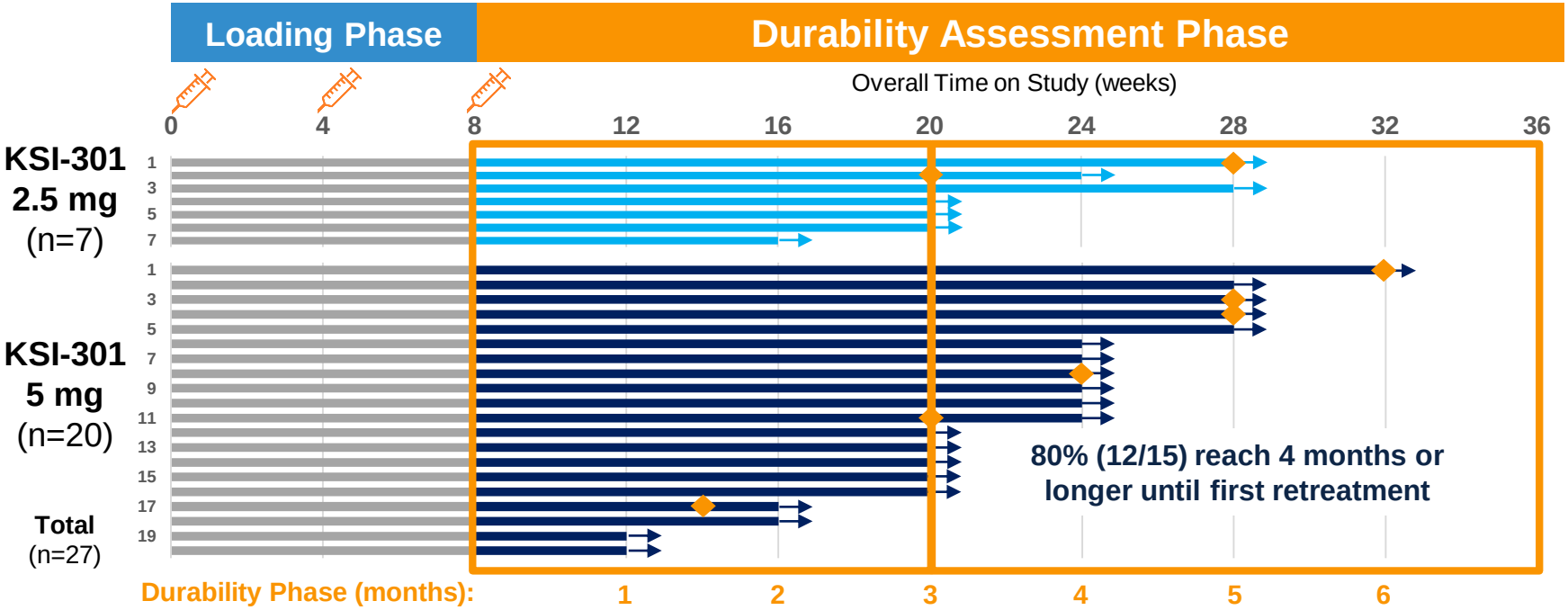
4% (1/25) retreated before 3 months

10% (2/20) retreated at 3 months

Interim data. Includes patients that reached the first retreatment opportunity (Week 12 visit) by the data cutoff date of 10 Oct 2019.
Each bar represents an individual patient. All depicted patients continue to be followed (no discontinuations)

KSI-301 in wAMD: Durability Assessment

Emerging data support 3 to 5+ month durability



Retreatment with KSI-301

Continuing follow-up

4% (1/25) retreated before 3 months

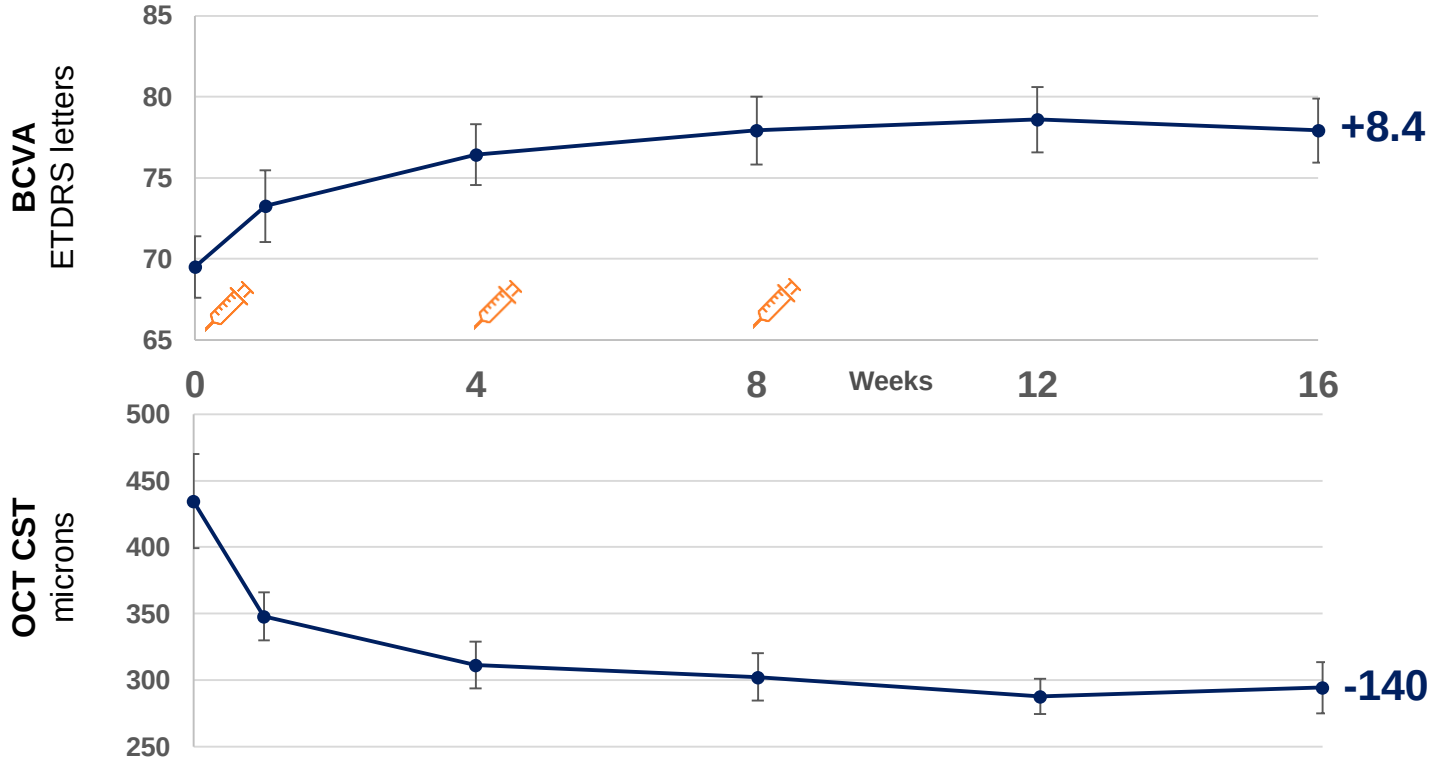
10% (2/20) retreated at 3 months

87% (20/23) have gone longer than 3 months after the last loading dose

Interim data. Includes patients that reached the first retreatment opportunity (Week 12 visit) by the data cutoff date of 10 Oct 2019.
Each bar represents an individual patient. All depicted patients continue to be followed (no discontinuations)

Efficacy of KSI-301 in DME

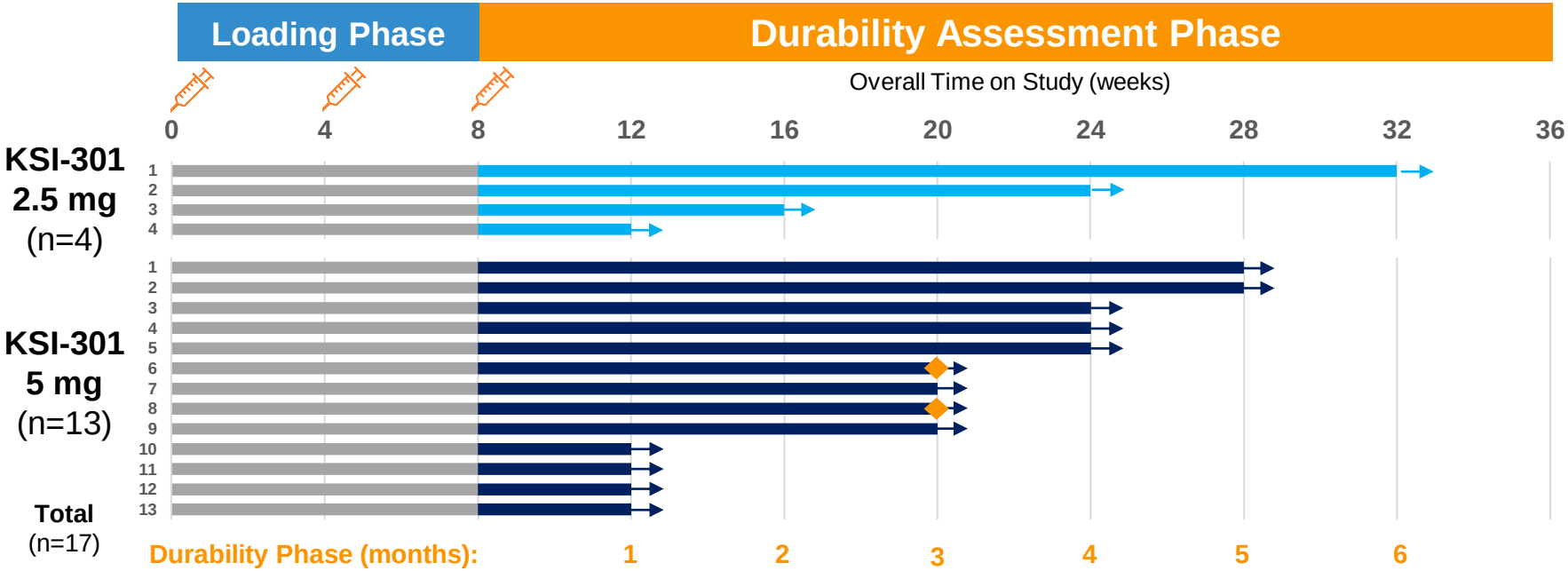
change from baseline to week 16 in mean BCVA & OCT



Interim data. Includes only randomized patients that reached Week 16 visit by the data cutoff date of 10 Oct 2019; 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

n= 12 **Patients reaching Week 16 visit by data cutoff**

KSI-301 in DME: *3 loading doses can provide sustained disease control of 3 months or longer*



◆ 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 10 Oct 2019.
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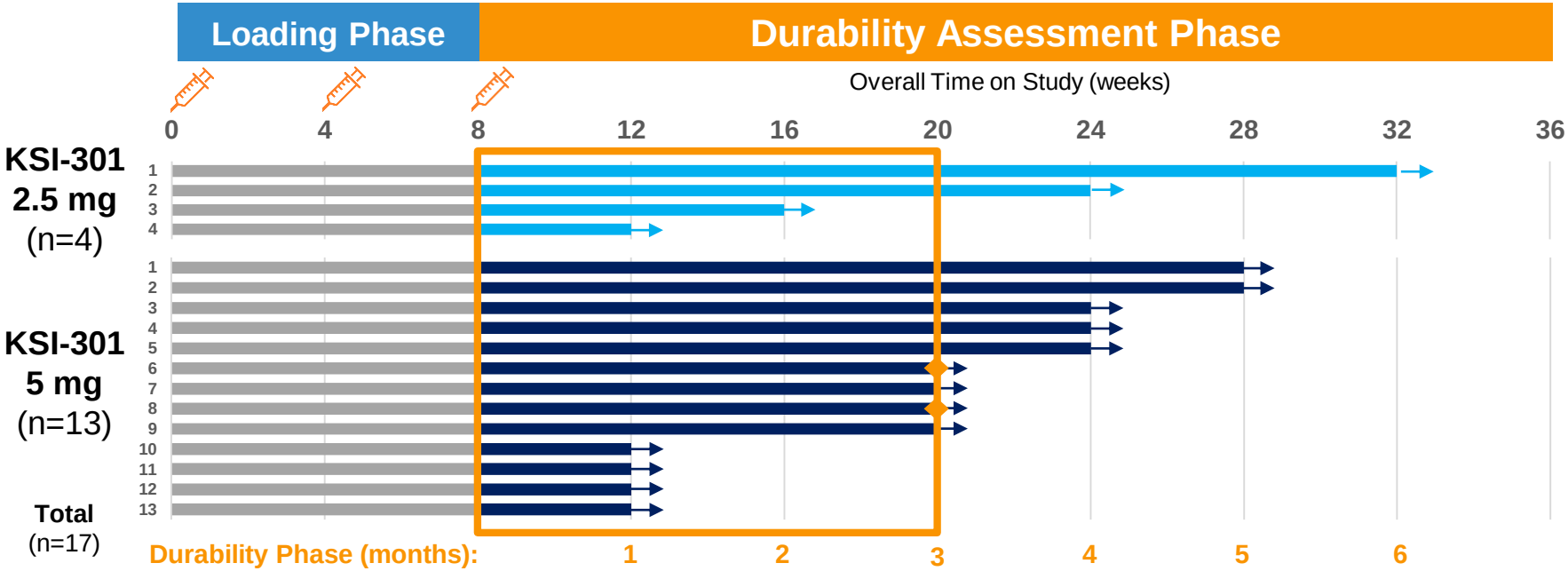
KSI-301 in DME: *3 loading doses can provide sustained disease control of 3 months or longer*



No patient has been retreated yet before 3 months

18% (2/11) retreated at 3 months

◆ 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 10 Oct 2019.
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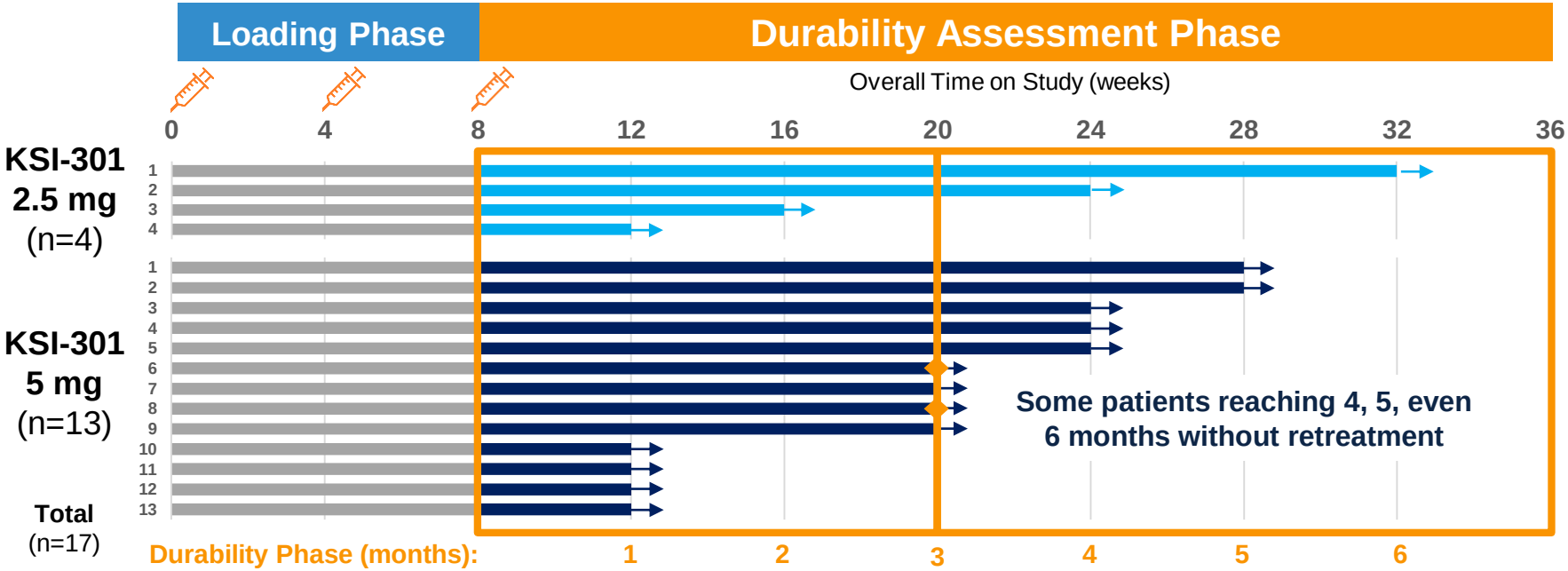
KSI-301 in DME: *3 loading doses can provide sustained disease control of 3 months or longer*



No patient has been retreated yet before 3 months

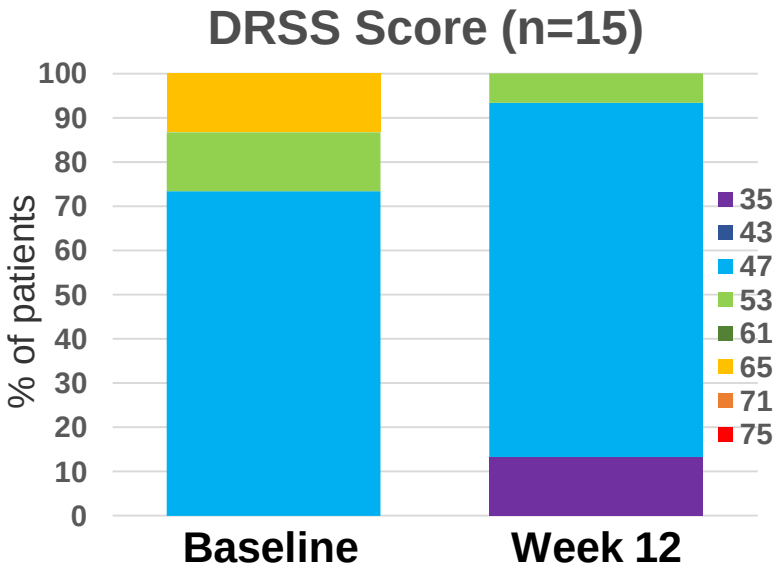
18% (2/11) retreated at 3 months

82% (9/11) have gone longer than 3 months after the last loading dose

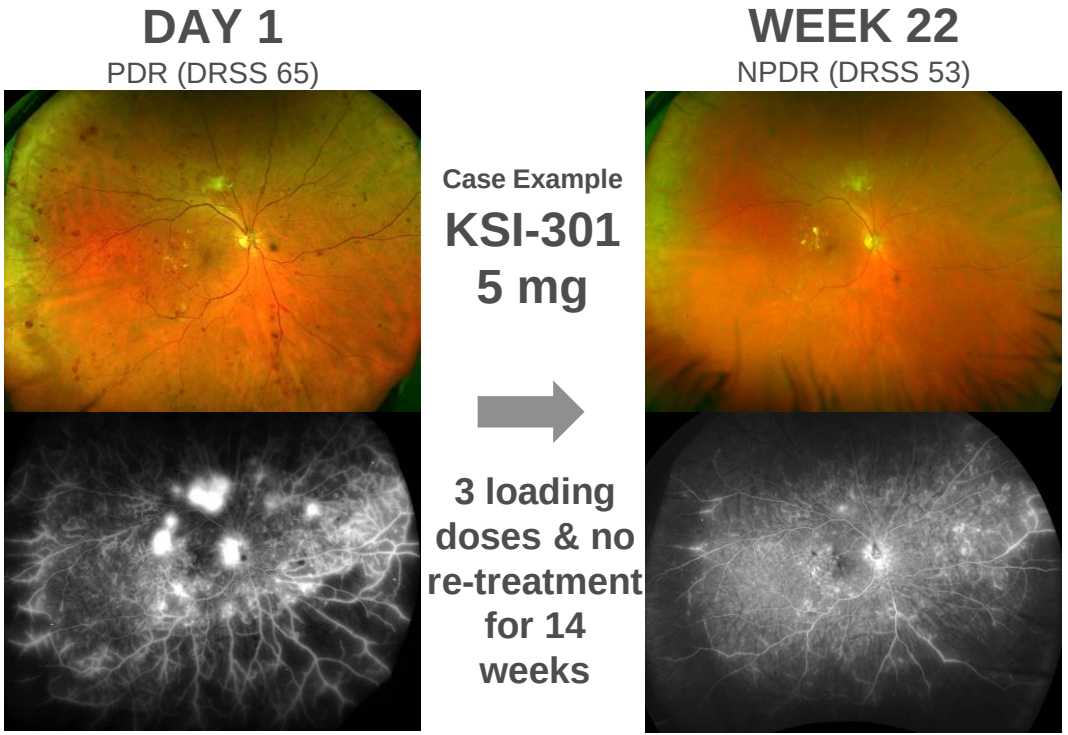
◆ Retreatment with KSI-301
→ Continuing follow-up

Interim data. Includes only randomized patients that reached the first retreatment opportunity (Week 12 visit) by the data cutoff date of 10 Oct 2019.
Each bar represents an individual patient. All depicted patients continue to be followed (no discontinuations)

KSI-301 in DR: *signs of disease modification seen within 12 weeks*



- **All patients have improved (40%) or maintained (60%) DR severity level**
- **No patient developed a PDR event**

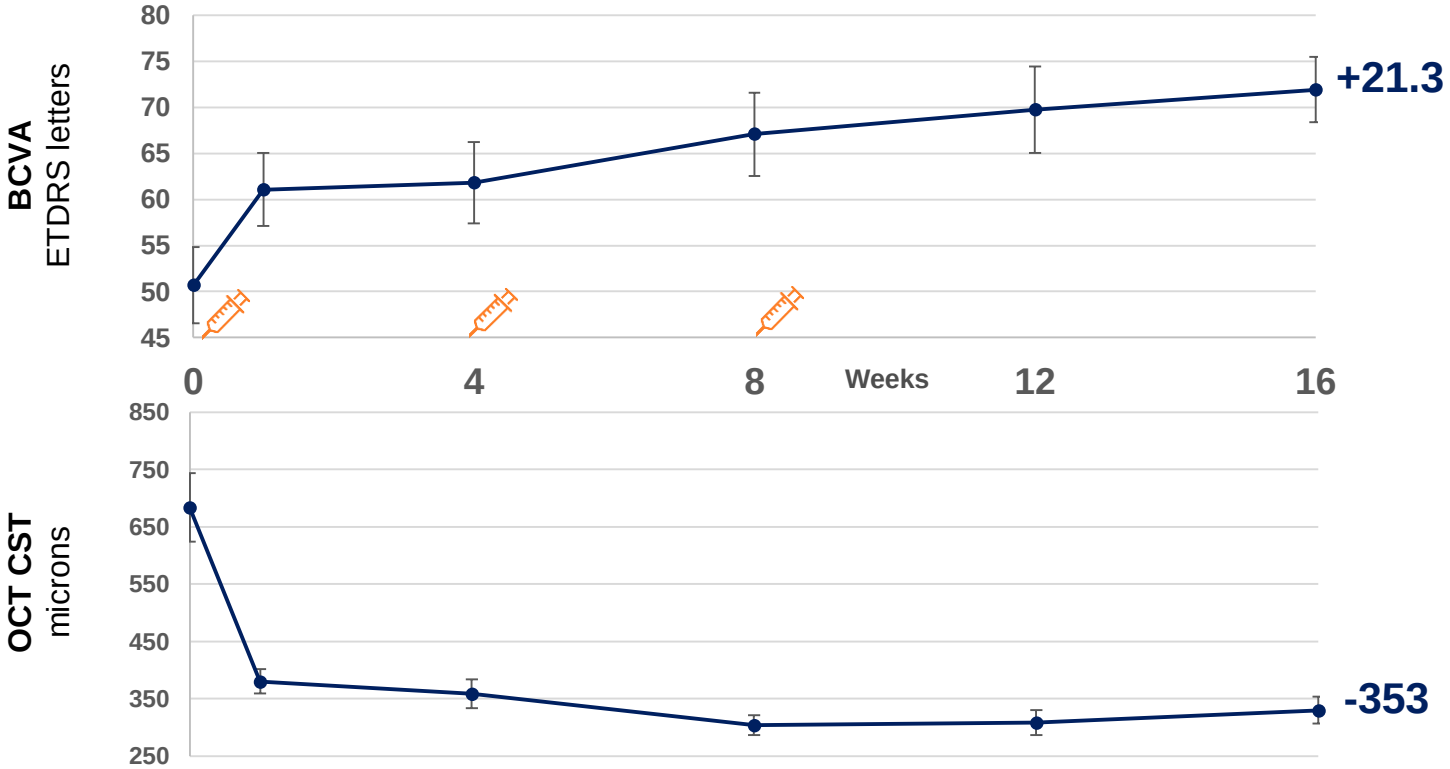


Meaningful DRSS score improvement (PDR to NPDR; 2-steps) sustained 14 weeks after last loading dose

Includes only randomized patients that reached Week 12 and have gradable color fundus photos by the data cutoff date of 10 Oct 2019 DR= Diabetic Retinopathy; PDR= Proliferative DR; NPDR= Non-Proliferative DR; DRSS = DR Severity Scale; DRSS 53 = Severe NPDR; DRSS 65 = Moderate PDR; need for panretinal photocoagulation or vitrectomy

Efficacy of KSI-301 in RVO

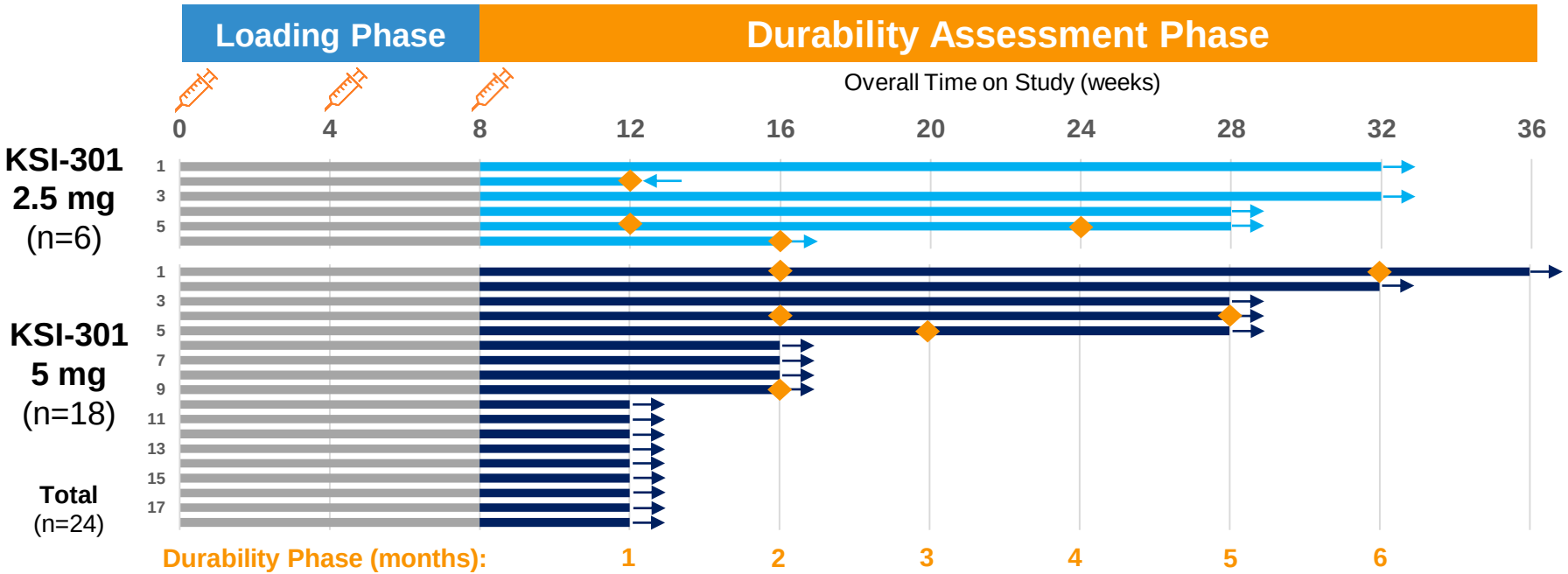
change from baseline to week 16 in mean BCVA & OCT



Interim data. Includes only randomized patients that reached Week 16 visit by the data cutoff date of 10 Oct 2019; 2.5 & 5 mg doses pooled. Datapoints include one subject 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

n= 15 **Patients reaching Week 16 visit by data cutoff**

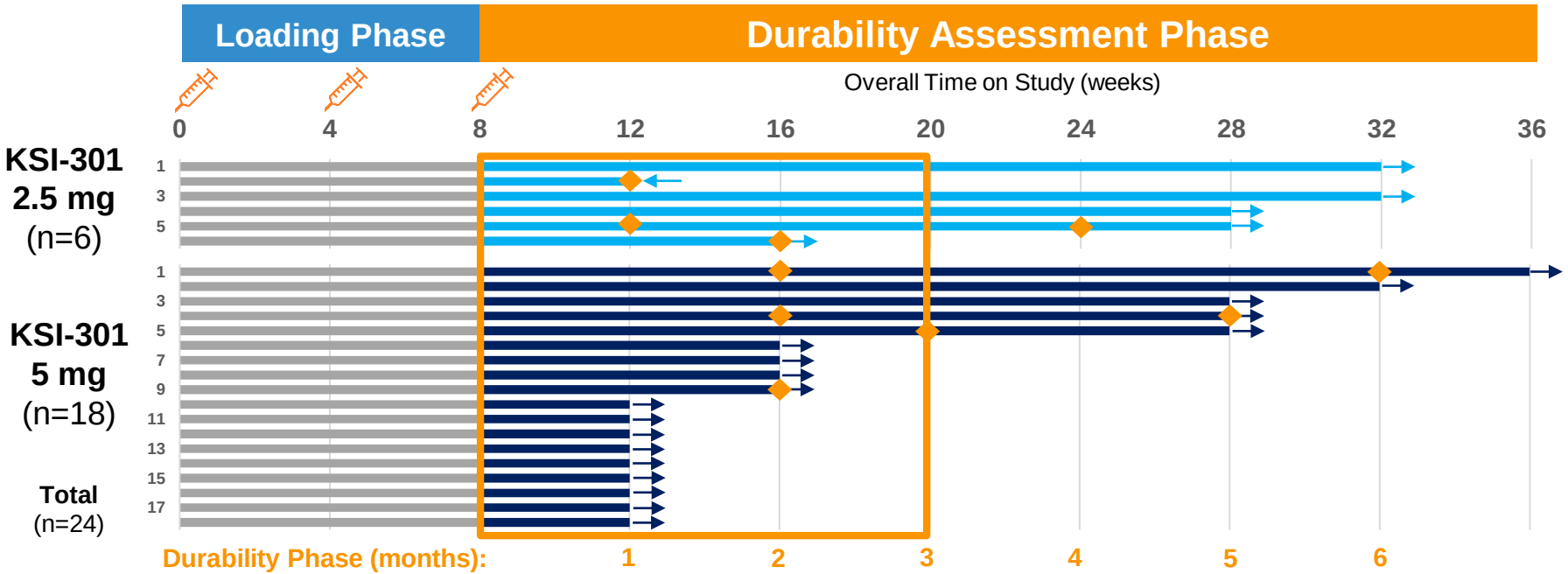
KSI-301 in RVO: *emerging durability data show potential for 2 to 3 month or longer dosing*



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 10 Oct 2019. Each bar represents an individual patient.

KSI-301 in RVO: *emerging durability data show potential for 2 to 3 month or longer dosing*

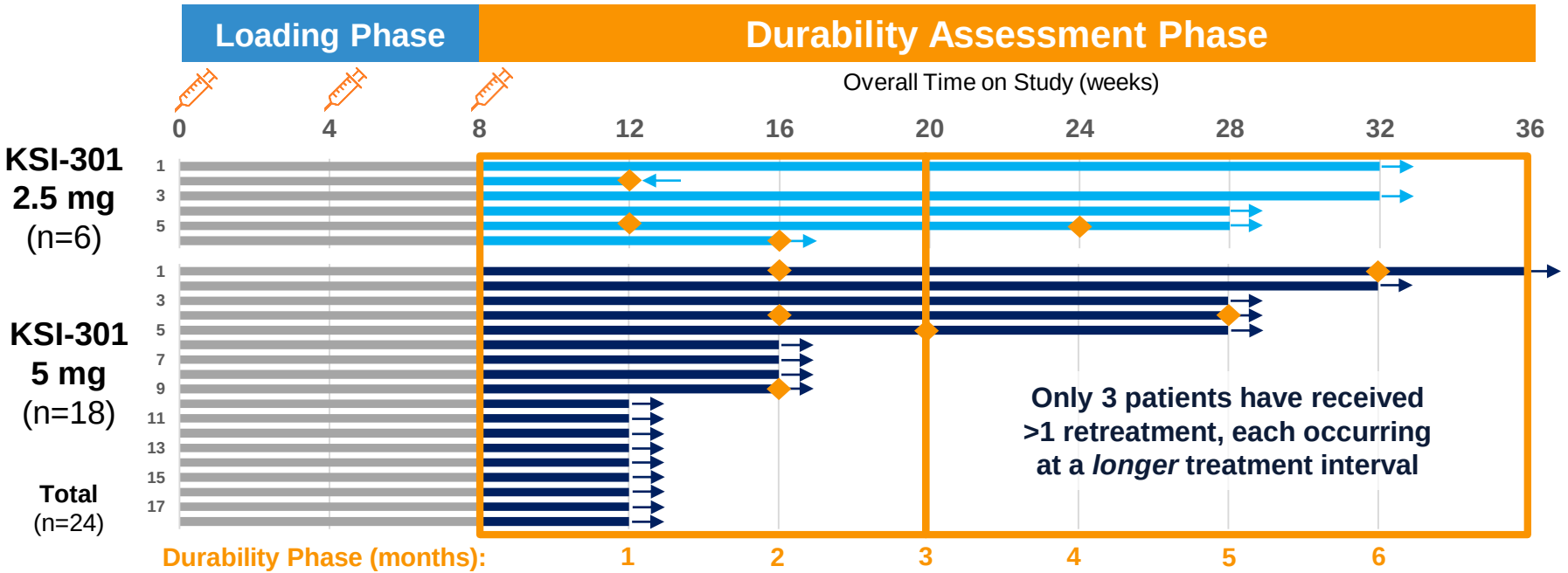


8% (2/24), 28% (4/14) & 11% (1/9) received first retreatment at 1, 2 & 3 months respectively

- 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 10 Oct 2019. Each bar represents an individual patient.

KSI-301 in RVO: *emerging durability data show potential for 2 to 3 month or longer dosing*



8% (2/24), 28% (4/14) & 11% (1/9) received first retreatment at 1, 2 & 3 months respectively

56% (5/9) have gone longer than 3 months after the last loading dose

◆ 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 10 Oct 2019. Each bar represents an individual patient.

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

113
Subjects dosed in Phase 1a+1b

316
Total doses given in Phase 1a+1b

104
At Day 1

99
At Week 4

86
At Week 8

Phase 1b subjects with # of loading doses received

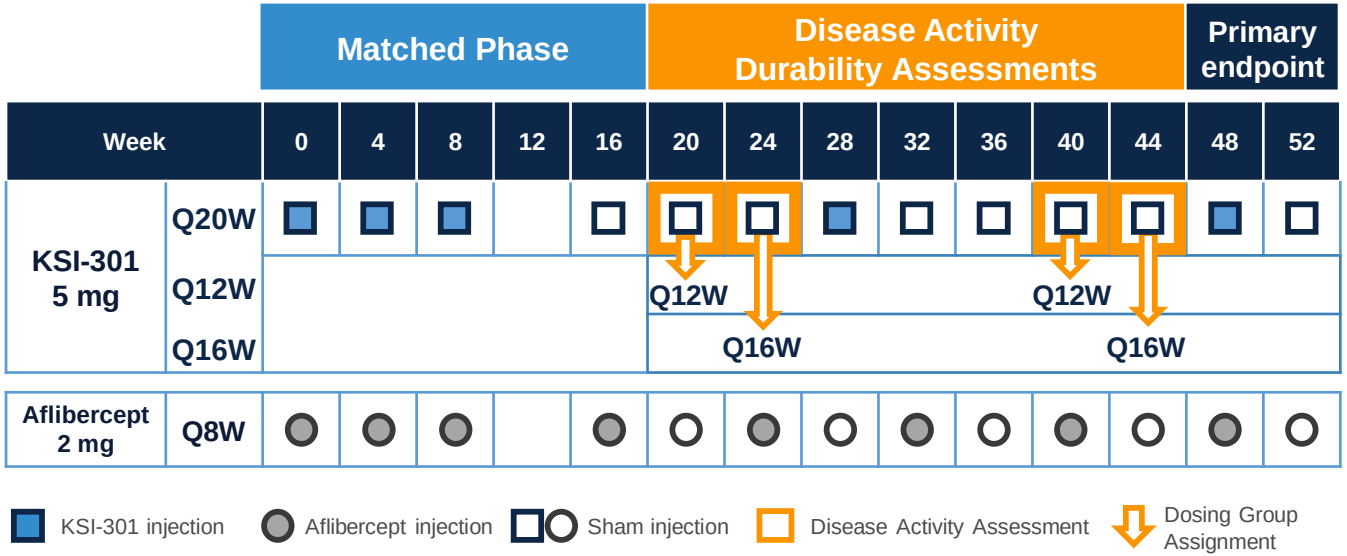
- No intraocular inflammation or ocular SAEs in the study eye reported to date
- No drug-related AEs or drug-related SAEs reported to date
- Most AEs were assessed as mild and are consistent with profile of intravitreal anti-VEGFs
- 8 non-ocular SAEs that were not drug-related have been reported in 4 subjects:
  - One 92 y/o RVO subject with hospitalization related to a pre-existing condition that resulted in death
  - One 66 y/o RVO subject with hospitalization related to dizziness
  - One 43 y/o DME subject with hospitalization related to a pre-existing condition
  - One 56 y/o DME subject with hospitalization related to a pre-existing condition

Includes all patients randomized as of 10 Oct 2019, all doses administered across cohorts
Interim safety data as of 10 Oct 2019; AE: adverse event; SAE: serious adverse event

Now Recruiting: Pivotal Phase 2 DAZZLE Study

Dosing with KSI-301 in wet AMD as infrequently as every 20 weeks

- ~400 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

Conclusion: KSI-301 is Demonstrating Promising Safety, Efficacy and Durability

- Antibody Biopolymer Conjugates (ABCs) are a new design platform for long durability intravitreal medicines
- KSI-301 (anti-VEGF ABC) has achieved important development milestones
  - **Excellent Safety:** zero cases of intraocular inflammation after 300+ doses
  - **Strong Efficacy:** across 3 major phenotypically variable retinal diseases wet AMD, DME/DR & RVO
  - **Remarkable Biological Durability:** majority of treated eyes extended to 4 months or beyond without retreatment after 3 loading doses. Potential is being demonstrated for:
    - 3 to 5+ month interval in wAMD
    - 3 to 5+ month interval in DME
    - 2 to 3+ month interval in RVO
- Next steps
  - Phase 1b study has been extended to 18 months to collect additional durability outcomes
  - Pivotal ‘DAZZLE’ study of KSI-301 vs aflibercept in treatment-naïve wet AMD now recruiting

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