Antibody Biopolymer Conjugates: a Novel Scientific Approach and Platform for Extended-Durability Retinal Medicines

First Results from a Phase 1b Proof of Concept Study of KSI-301, an anti-VEGF ABC

Pravin U. Dugel, MD

Clinical Professor
Department of Ophthalmology
Roski Eye institute
USC Keck School of Medicine
University of Southern California
Los Angeles, California

Managing Partner
Retinal Consultants of Arizona
Retinal Research Institute
Phoenix, Arizona

American Society of Retina Specialists Annual Meeting
July 27, 2019

Relevant Financial Disclosures

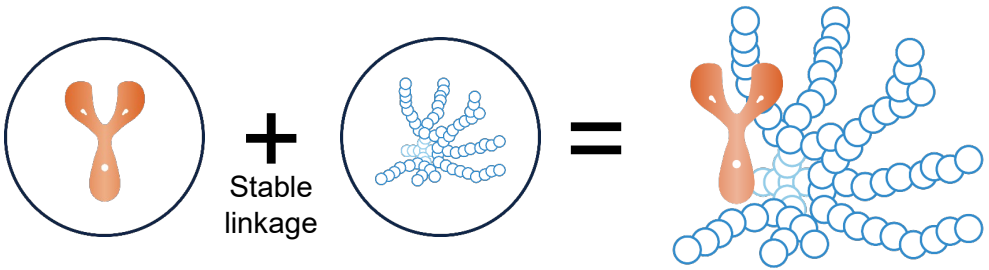
- Consultant to Kodiak Sciences

Key Points

- Antibody Biopolymer Conjugates are a new scientific approach and design platform for intravitreal drugs
- KSI-301 (Kodiak Sciences) has achieved its early development goals of demonstrating strong efficacy and excellent safety in the major retinal vascular diseases
- Current data warrant further evaluation in randomized pivotal studies

Antibody Biopolymer Conjugates (ABC) are designed for increased durability and efficacy

ABC PLATFORM



ANTIBODY

IgG1 with inert immune effector function

BIOPOLYMER

Optically clear, high molecular weight phosphorylcholine polymer

CONJUGATE

Antibody and biopolymer covalently bound via single site-specific linkage

SCIENTIFIC DESIGN OBJECTIVES

SAME WHERE IT MATTERS

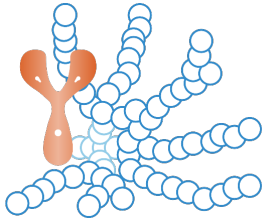
- Clinically proven targets
- Antibody-based biologic
- Intravitreal: safest method of administration
- Optically clear, no residues
- Fast and potent clinical responses

DIFFERENT WHERE IT COUNTS

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

Go Big, Not Small

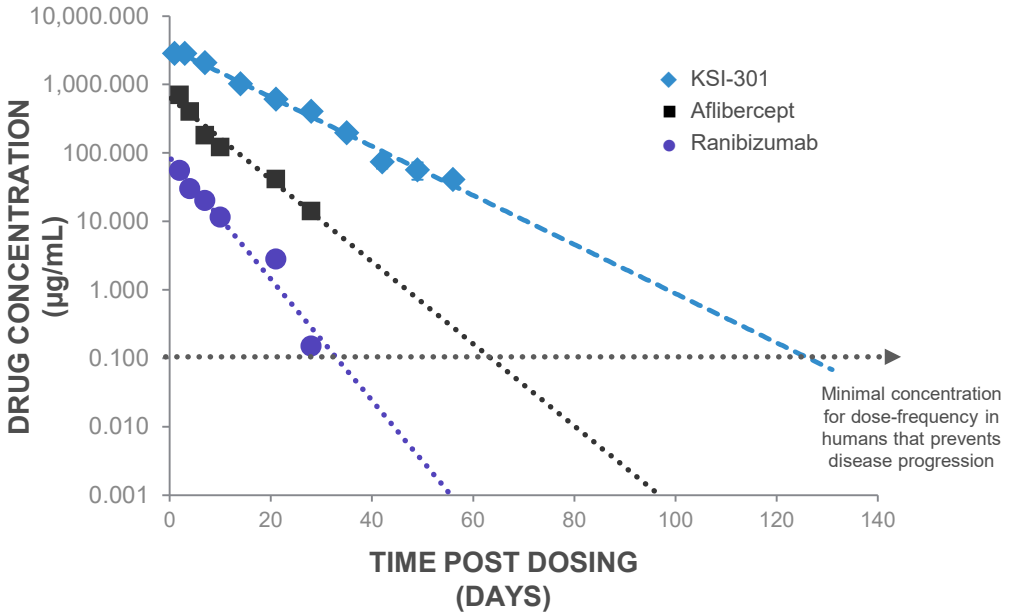
The high molecular weight of KSI-301 can provide an important dosing advantage

Drug/Candidate:	BROLUCIZUMAB	RANIBIZUMAB	AFLIBERCEPT	KSI-301 Anti-VEGF ABC
Molecule type	Single-chain antibody fragment	Antibody fragment	Recombinant fusion protein	**Antibody Biopolymer Conjugate (ABC)**
Molecular structure				
Molecular weight	26 kDa	48 kDa	115 kDa	**950 kDa**
Clinical dose	6 mg	0.3-0.5 mg	2 mg	**5 mg** (by weight of antibody)
Equivalent molar dose	22	1	2	**7**
Equivalent ocular PK	<1	1	1.5	**4**
Equivalent ocular concentration at 3 months	10	1	1,000	**1,000,000**

Equivalent values are showed as fold changes relative to ranibizumab. kDa= kilodalton

ABCs have the optimal ocular anti-VEGF PK curve

INTRAOCULAR DURABILITY OF KSI-301, RANIBIZUMAB & AFLIBERCEPT BASED ON DATA FROM RABBIT MODEL[1]



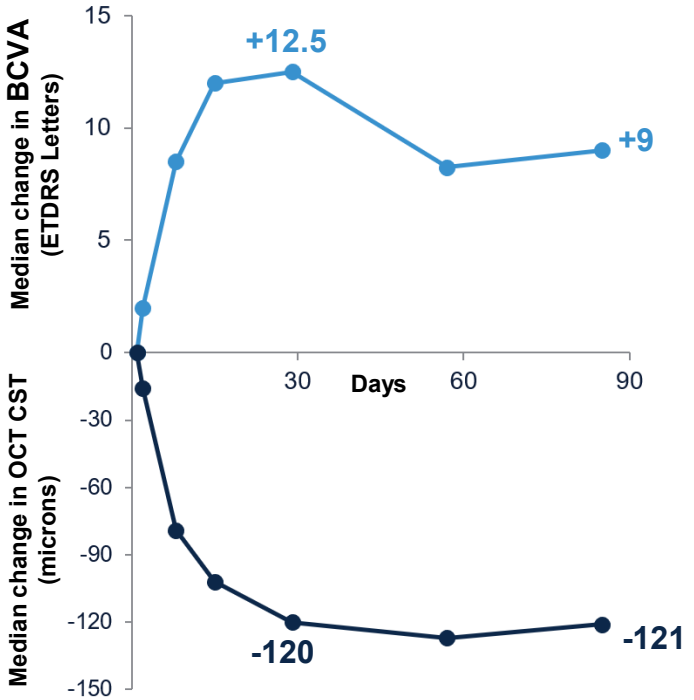
SPECIAL FEATURES OF ABCs DUE TO PHOSPHORYLCHOLINE BIOPOLYMER[2]

- **Better tissue bioavailability**
  ~8x greater than aflibercept
- **Better stability**
- **Deeper potency**
- **Excellent biocompatibility**
- **Fast systemic clearance**
  Reduced binding to FcRn recycling receptor

1. 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 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. Kodiak Sciences data on file and Patel et al., ARVO 2019

KSI-301 demonstrated an excellent safety profile and bioactivity in first-in-human Phase 1a

- Diabetic macular edema (DME) patients with severe disease (n=9)
- Previously treated with limited to no response despite multiple prior anti-VEGF treatments and severe disease
- A single injection of KSI-301 resulted in rapid, high-magnitude responses durable to 12 weeks
- 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

Clinical Proof of Concept Study of KSI-301

Phase 1b, open-label, randomized study

- Key questions in early development of KSI-301 and the ABC Platform:
  - Multiple-dose safety
  - Bioactivity in VEGF-driven diseases: wAMD, DME, RVO
- Study design:
  - Anti-VEGF treatment-naïve patients, BCVA ~20/25 - 20/320 Snellen equivalent
  - 1:3 randomization to KSI-301 2.5 mg (50 μL) or 5 mg (100 μL)
  - N=90 patients – recruitment ongoing

		Loading Phase			Durability Assessment Retreatment					End of follow-up
Week		0	4	8	12	16	20	24	28	32	36
KSI-301 2.5 or 5 mg	wAMD DME RVO	■	■	■	□	□	□	□	□	□	

Clinicaltrials.gov ID: NCT03790852

KSI-301 Phase 1b Baseline Characteristics

Variable	wAMD Cohort (n=29)	DME Cohort (n=18)	RVO Cohort (n=30)
Age (years, median)	76	59	64
Gender (Female, %)	69.0	33.3	36.7
BCVA (ETDRS letters, median)	66	70.5	57
OCT CST (microns, median)	366	402	658

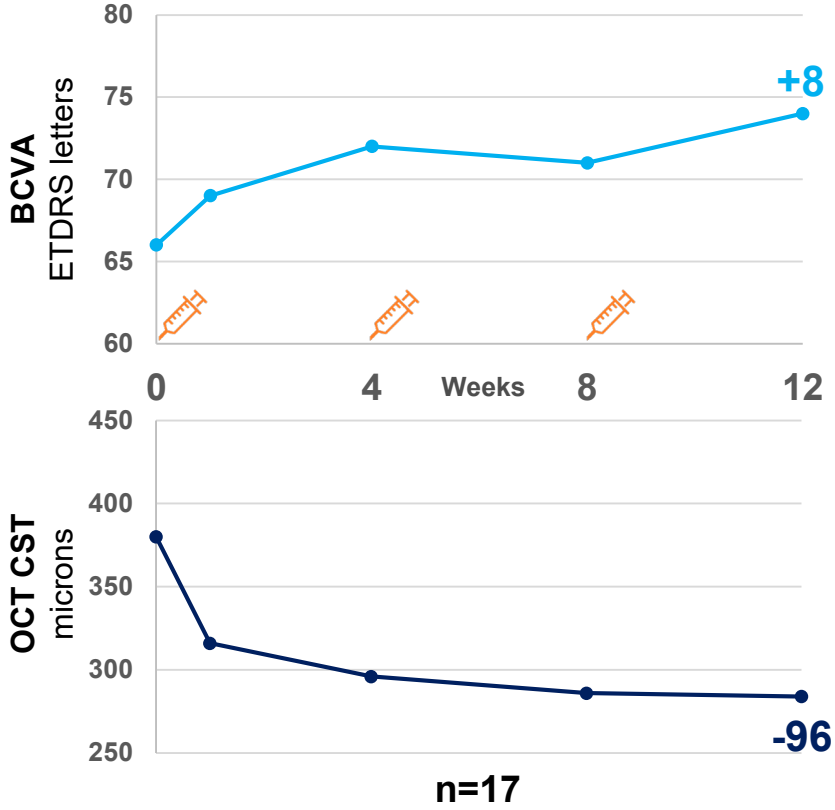
Includes all patients randomized as of 24 July 2019

KSI-301 Phase 1b

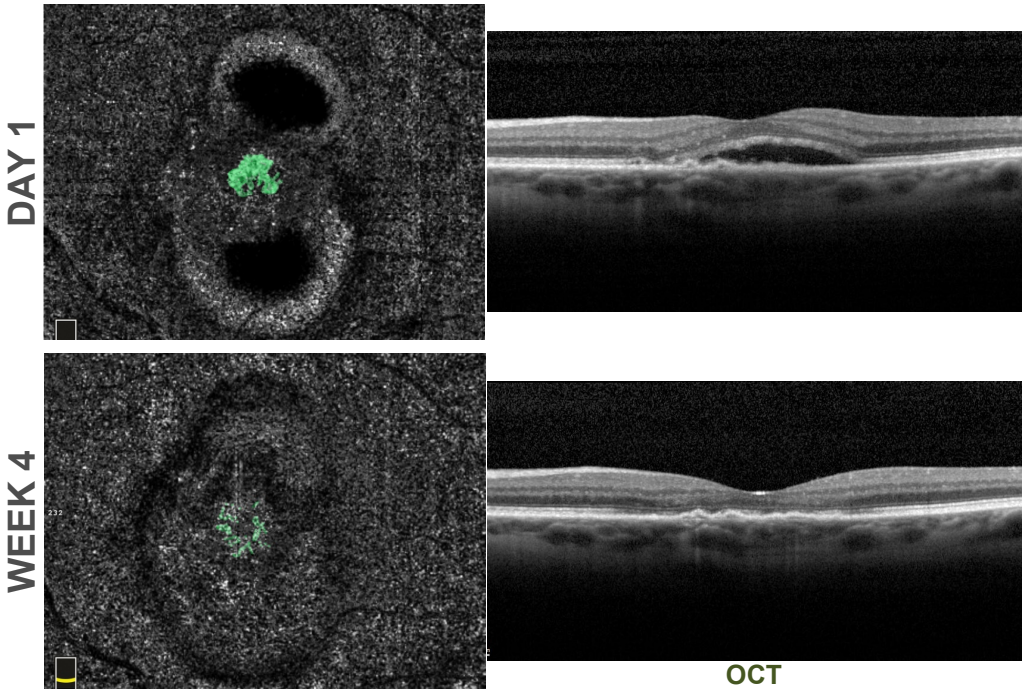
First time results

Efficacy of KSI-301 in Wet AMD

Change from Baseline to Week 12 in median BCVA and OCT CST



Direct reduction in size and vascular flow rate of the choroidal neovascularization, effectively eliminating subretinal fluid

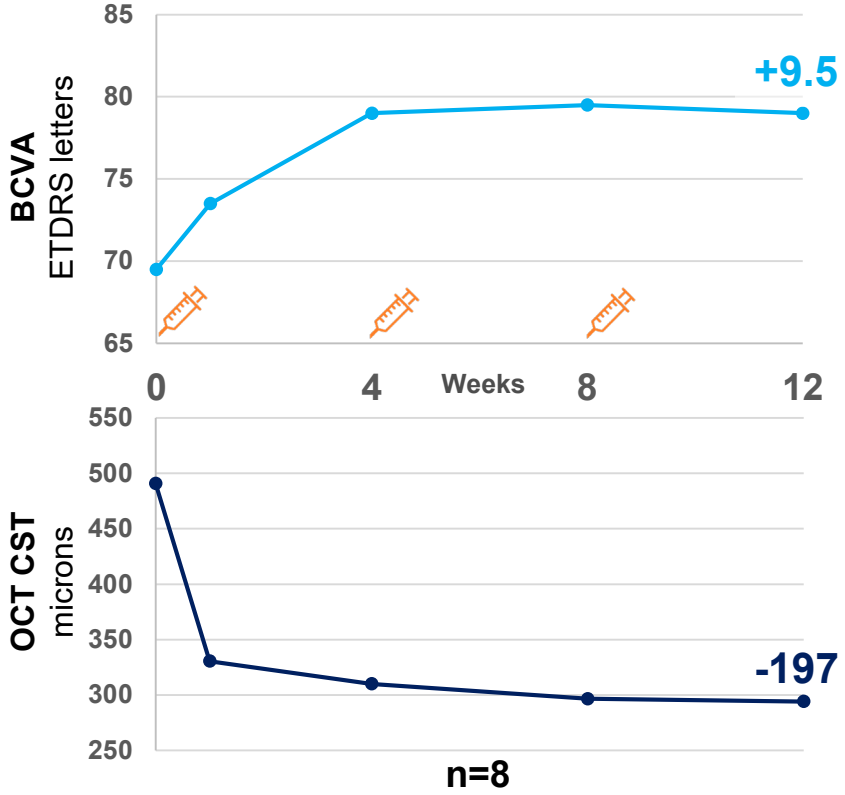


Interim data. Includes only randomized patients that reached Week 12 visit by the data cutoff date of July 24 2019; 2.5 & 5 mg doses pooled. BCVA= best corrected visual acuity; OCT= optical coherence tomography; CST= central subfield thickness; OCT-A CNV image colored for visualization purposes

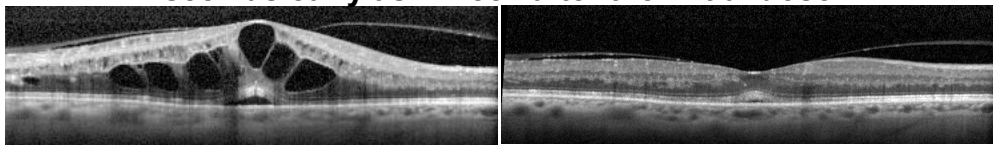
Case Example of KSI-301 5 mg in wAMD

Efficacy of KSI-301 in DME and DR

Change from Baseline to Week 12 in median BCVA and OCT CST

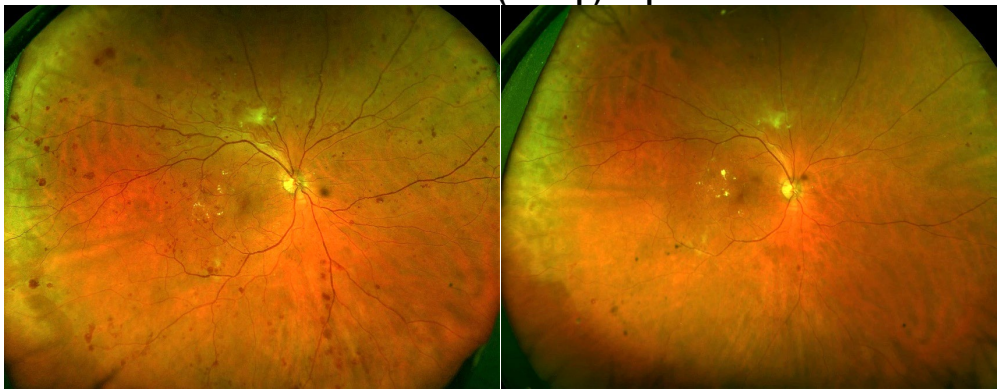


Rapid DME resolution
seen as early as 1 week after the initial dose



DAY 1 WEEK 1

Diabetic Retinopathy Severity Improvement
Fast and substantial (2-step) improvement



DAY 1
Proliferative DR (DRSS 65)

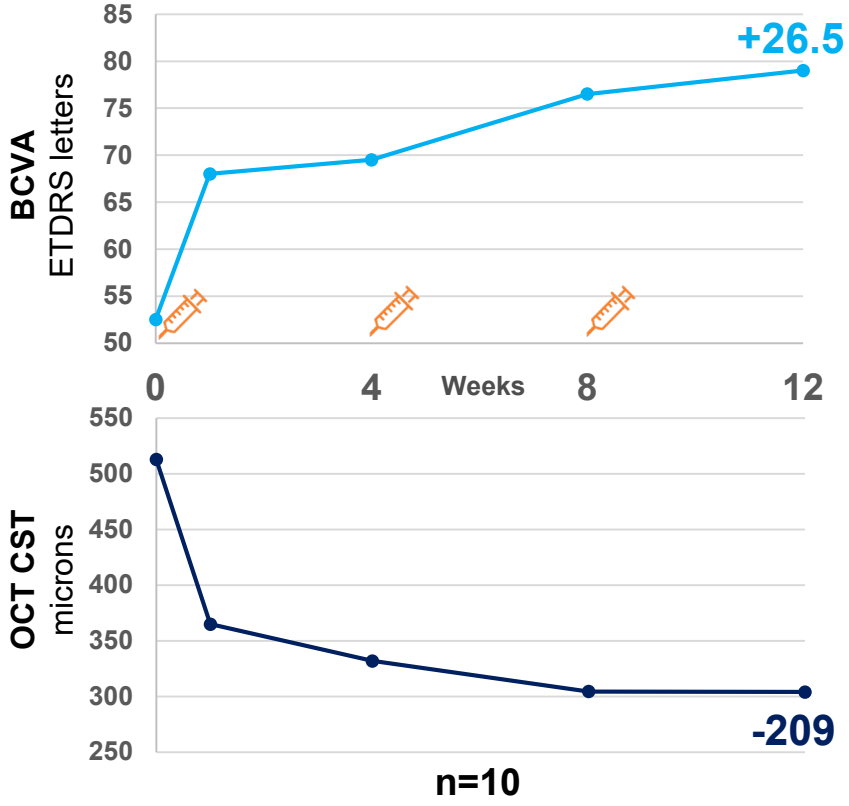
WEEK 12
Non-Proliferative DR (DRSS 53)

Interim data. Includes only randomized patients that reached Week 12 visit by the data cutoff date of July 24 2019; 2.5 & 5 mg doses pooled. BCVA= best corrected visual acuity; OCT= optical coherence tomography; CST= central subfield thickness; DR= Diabetic Retinopathy; PDR= Proliferative DR; NPDR= Non-Proliferative DR; DRSS = DR Severity Scale; DRSS 53 = Severe NPDR; DRSS 65 = Moderate PDR

Case Examples of KSI-301 5 mg in DME/DR

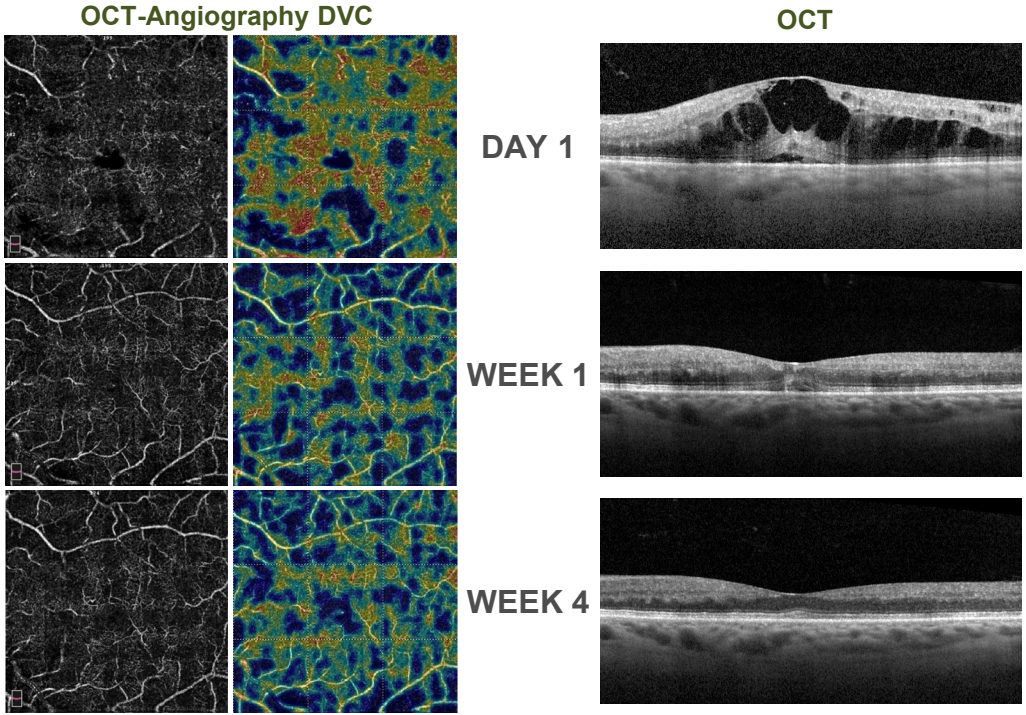
Efficacy of KSI-301 in Retinal Vein Occlusion

Change from Baseline to Week 12 in median BCVA and OCT CST



n=10

Case Example of KSI-301 5 mg in RVO



Vascular flow normalization on OCT-A 1 week after the initial dose and continued to Week 4

Edema resolution seen as early as 1 week after the initial dose

Interim data. Includes only randomized patients that reached Week 12 visit by the data cutoff date of July 24 2019; 2.5 & 5 mg doses pooled. BCVA= best corrected visual acuity; OCT= optical coherence tomography; CST= central subfield thickness; DVC= Deep Vascular Complex

Multiple-dose exposure to KSI-301 is well-tolerated with no intraocular inflammation in 181 doses

77
Subjects dosed in Phase 1b

181
Total doses in Phase 1b

77	60	44
At Day 1	At Week 4	At Week 8

Subjects with # of loading doses received

- **No intraocular inflammation** or ocular SAEs reported to date
- No drug-related AEs or drug-related SAEs reported to date
- Most AEs were assessed as mild (70%) 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 24 July 2019, all doses administered across cohorts
Interim safety data as of 24 July 2019; AE: adverse event; SAE: serious adverse event

KSI-301 and ABC Platform
Development Goals Achieved

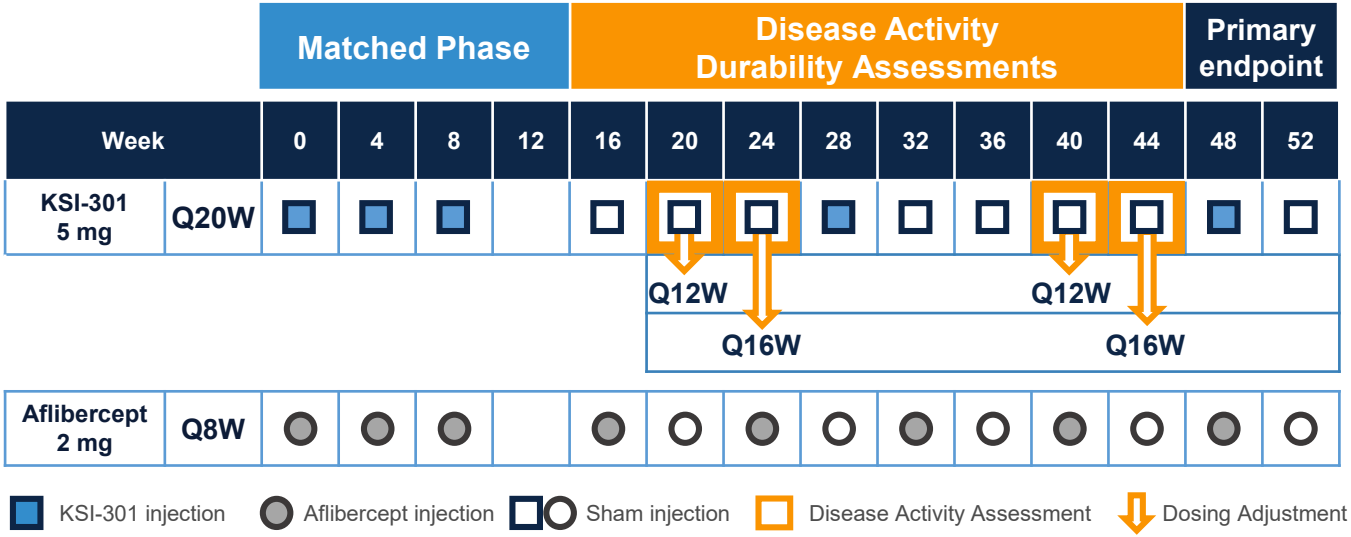
- **Safety:**
  - ✓ Both single and multiple sequential doses of KSI-301 are well-tolerated to date
  - ✓ No intraocular inflammation observed in 190 total doses in 86 subjects (Phase 1a + 1b)
- **Efficacy:**
  - ✓ Rapid-onset, high magnitude improvements in both function (BCVA) and retinal anatomy (OCT) observed in all three VEGF-driven diseases under study
- **Durability:**
  - Data pending - emerging durability data planned for AAO Retina Subspecialty Day[1]

1. Wykoff CC, Presentation currently scheduled for 10/11/19, 4:58pm

Phase 2 DAZZLE Study in Wet AMD

Dosing with KSI-301 as infrequently as every 20 weeks

- **Pivotal study design**, head-to-head against aflibercept
- US & EU study sites
- ~400 treatment naïve wAMD patients
- **All patients dosed every 12 weeks or less frequently (≥Q12W) with KSI-301***



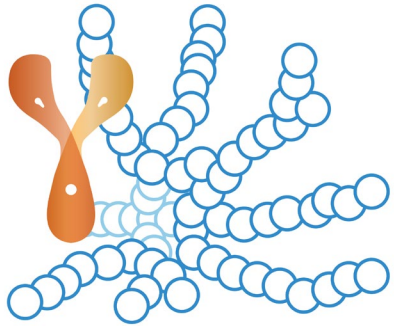
Dosing with **KSI-301 as infrequently as every 20 weeks*** based on disease activity assessments

*After the loading phase
Study expected to begin recruiting in August 2019

Developing a Pipeline of ABCs for Retinal Disease

Dual and triplet inhibitors that merge biologics with small molecules

BISPECIFIC ABC

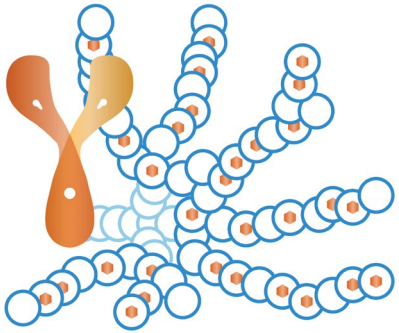


1 Molecule, 2 Targets

Bispecific antibody conjugated to phosphorylcholine biopolymer

KSI-501 inhibits VEGF and IL-6 for retinal diseases with inflammatory component

TRIPLET ABC



1 Molecule, 3 Targets

Bispecific antibody conjugated to phosphorylcholine biopolymer embedded with 100's of copies of small-molecule drug

For high-prevalence multifactorial diseases, e.g. dry AMD and glaucoma

Key Points

- Antibody Biopolymer Conjugates are a new scientific approach and design platform for intravitreal drugs
- KSI-301 (Kodiak Sciences) has achieved its early development goals of demonstrating strong efficacy and excellent safety in the major retinal vascular diseases
- Current data warrant further evaluation in randomized pivotal studies

Acknowledgements

Principal Investigators:

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

Kodiak Sciences:

- Pablo Velazquez-Martin, MD
- Bryce Miller, MPA
- Desiree Beutelspacher
- Amy Duguay, BS
- Hong Liang, PhD
- Joel Naor, MD MSc
- Almas Qudrat, MSc
- Jason Ehrlich, MD, PhD
- Victor Perlroth, MD

OIRRC Reading Center

- Mohamed Ahmed, PhD
- Ryan Wilson