Phase 1 First-In-Human Study of KSI-301: A Novel Anti-VEGF Antibody Biopolymer Conjugate With Extended Durability Following a Single Dose Administration (3670)

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Background

- Current anti-VEGF agents have limited durability resulting in narrow re-treatment windows, burdensome treatment regimens, repeated undertreatment, and poor real world outcomes.
- KSI-301 is a novel Antibody Biopolymer Conjugate designed to solve this real world problem.

ABC PLATFORM™

ANTIBODY
IgG1 with inert immune effector function

BIOPOLYMER
Optically clear, high molecular weight phosphorylcholine polymer

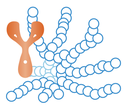
ANTIBODY BIOPOLYMER CONJUGATE MEDICINES

KSI-301 objective: to develop the next front line therapy for all patients with retinal vascular disease

SAME WHERE IT MATTERS
- Clinically proven target: VEGF
- Antibody-based biologic
- Intravitreal injection
- Optically clear solution
- No ocular residues

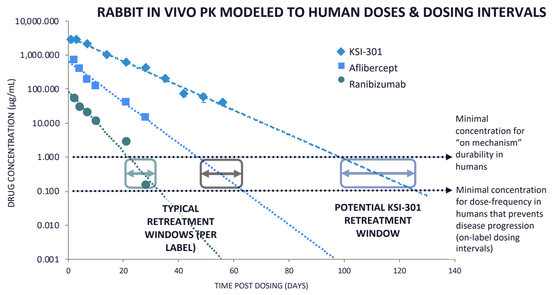
DIFFERENT WHERE IT COUNTS
- Designed-in ocular durability
- Fast systemic clearance
- Improved bioavailability
- Improved biocompatibility
- Improved stability

The science behind the ABC Platform and KSI-301's design optimizes for durability and potency across molecular size (ocular PK), formulation strength (clinical dose) & ocular target tissue bioavailability

Drug/Candidate:	BROLUCIZUMAB	RANIBIZUMAB	AFLIBERCEPT	KSI-301
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.

KSI-301 bioconjugate has potential for extended durability and a more flexible retreatment window



KSI-301 bioconjugate has a flatter (better) ocular PK curve

This results in an increasing concentration advantage versus other biologics over time

Lucentis 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 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

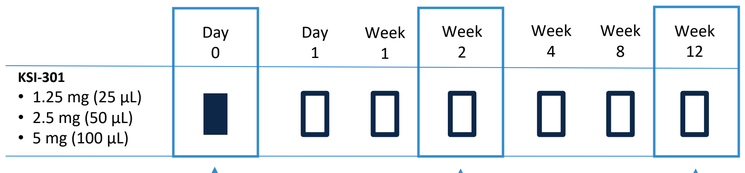
Purpose

This first-in-human study sought to explore initial safety and tolerability of KSI-301 and to establish a maximum tolerated dose. Bioactivity was evaluated by measuring visual function and retinal anatomy.

Methods

Open-label, single ascending dose study in subjects with DME. Study eyes received one intravitreal injection of KSI-301 (1.25 mg, 2.5 mg, or 5 mg) and were then followed for 12 weeks. The primary endpoint was Week 2. Three subjects were enrolled in each dose cohort. Subjects in the 1st cohort were sequentially assessed with a waiting period of at least 24 hours. The waiting period between cohorts was 7 days. Dose escalation was based on DSMC safety review. The study was conducted at 5 US sites.

Design of Single Ascending Dose Study in Diabetic Macular Edema Patients



Demographics and Safety Results

DEMOGRAPHICS	
Age (years, mean)	62
Gender	7M, 2F
OCULAR CHARACTERISTICS Study Eye, n=9	
Previously Received Anti-VEGF	8/9
Number of Anti-VEGF Treatments in Last Year median (range)	3 (0, 7)
Time Since Last Anti-VEGF, Days median (range)	95 (52,>365)
IOP, mmHg mean (SD)	15 (2)
OCT Central Subfield Thickness, Microns mean (SD)	565 (182)
Baseline BCVA, ETDRS Letters mean (SD)	47 (12)
Baseline BCVA, Snellen Equivalent	20/100

Every dose level was well-tolerated through the 12 week follow-up period

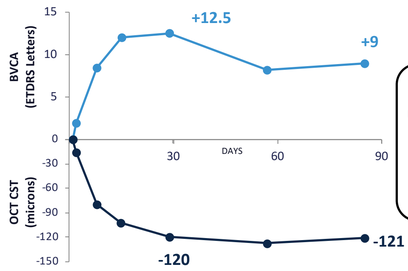
- No dose limiting toxicities
- No drug-related adverse events or drug-related serious adverse events
- No intraocular inflammation
- Optically clear media after each injection
- No anti-drug antibodies detected in any patient
- Systemic levels 1/3 of bevacizumab C_{max} and 1/6 of D28 level (1.25mg dose)[1]

[1] Avery RL et al. Retina. 2017 Oct;37(10):1847-1858

NUMBER OF PATIENTS WITH ANY AE=4	N	SERIOUS	RELATED
OCULAR AEs			
Foreign body sensation	1	N	N
Subconjunctival hemorrhage	2	N	N
Floaters (reported in both eyes)	1	N	N
Visual flashes	1	N	N
NON-OCULAR AEs			
Fall	1	N	N
Worsening of coronary artery disease	1	Y	N
Swollen Feet	1	N	N

Single-Dose Bioactivity Observations

MEDIAN CHANGES FROM BASELINE TO WEEK 12
pooled across 3 dose groups (n=9 patients total)



Rapid, high magnitude responses

Durable improvements to 12 weeks after single dose

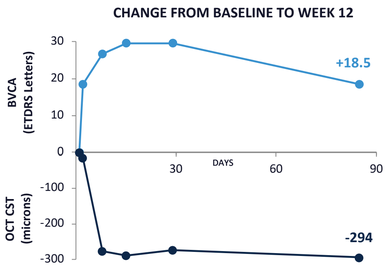
Phase 1 Single Dose Study - Summary

- Rapid high-magnitude and durable treatment responses were seen at all dose levels tested.
- Twelve weeks after a single dose, median BCVA improvement from baseline of +9 ETDRS chart letters and median improvement in retinal edema of -121 microns (OCT CST) were observed.
- No dose-limiting toxicities, drug-related adverse events, or intraocular inflammation were observed through each patients' last visit at 12 weeks.

Case Study 1

Resolution of chronic macular edema sustained through 12 weeks in patient with prior suboptimal response

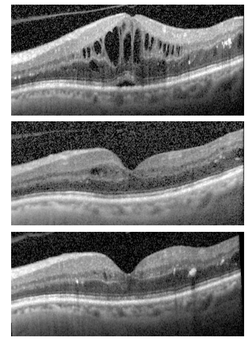
CHANGE FROM BASELINE TO WEEK 12



CLINICAL HISTORY SUMMARY (SITE REPORTED):

	Date	Treatment	VA Snellen	CST
Retrospective	1/2018		20/40	-
	4/2018	Bevacizumab	20/40	431
	6/2018	Bevacizumab	20/60	655
	8/2018	**KSI-301**	20/160	636

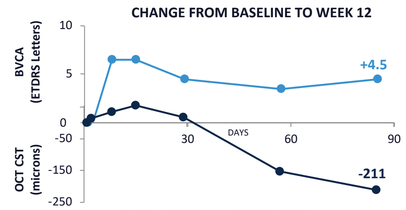
First post study treatment **155 days (22 Weeks)** following KSI-301 5 mg injection



Case Study 2

Resolution of subretinal fluid through 12 weeks in patient with chronic edema and extensive foveal lipid exudates

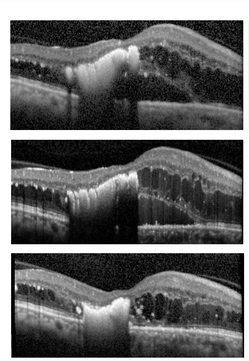
CHANGE FROM BASELINE TO WEEK 12



CLINICAL HISTORY SUMMARY (SITE REPORTED):

	Date	Treatment	VA Snellen
Retrospective	1/2018	Bevacizumab	20/60
	3/2018	Bevacizumab	20/100
	4/2018	Bevacizumab	20/150
	5/2018		20/350
	7/2018	**KSI-301**	20/80

First post study treatment **146 days (21 Weeks)** following KSI-301 1.25 mg injection



Conclusions

- A novel anti-VEGF antibody biopolymer conjugate showed safety and rapid-onset durable effects in a single ascending dose clinical study.
- A Phase 1b multiple dose study in 50+ patients with treatment naïve wet AMD, DME, and RVO is now ongoing (NCT03790852).
- A Phase 2 pivotal study of KSI-301 5 mg *vs.* aflibercept in naïve wet AMD is being initiated, with all KSI-301 subjects on Q12W-Q20W dosing.

Participating Sites:
- Dr. David Boyer, Beverly Hills, CA; Dr. Pravin Dugel, Phoenix, AZ ;
- Dr. Richard McDonald, San Francisco, CA; Dr. Sunil Patel, Abilene, TX
- Dr. Mark Wieland, Mountain View, CA

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- Naor, Qudrat, Beutelspacher, Liang, Perlroth: Kodiak Sciences Inc, Code E