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

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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

<table>
<thead>
<tr>
<th>Drug/Candidate:</th>
<th>BROLCIZUMAB</th>
<th>RANIBIZUMAB</th>
<th>AFLIBERCEPT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Molecule type</td>
<td>Single-chain antibody fragment</td>
<td>Antibody fragment</td>
<td>Recombinant fusion protein</td>
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<tr>
<td>Molecular structure</td>
<td><img src="image1" alt="Molecule structure" /></td>
<td><img src="image2" alt="Molecule structure" /></td>
<td><img src="image3" alt="Molecule structure" /></td>
</tr>
<tr>
<td>Molecular weight</td>
<td>26 kDa</td>
<td>48 kDa</td>
<td>115 kDa</td>
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<tr>
<td>Clinical dose</td>
<td>6 mg</td>
<td>0.3-0.5 mg</td>
<td>2 mg</td>
</tr>
<tr>
<td>Equivalent molar dose</td>
<td>22</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Equivalent ocular PK</td>
<td>&lt;1</td>
<td>1</td>
<td>1.5</td>
</tr>
<tr>
<td>Equivalent ocular concentration at 3 months</td>
<td>10</td>
<td>1</td>
<td>1,000</td>
</tr>
</tbody>
</table>

KSI-301
Anti-VEGF ABC

Antibody Biopolymer Conjugate (ABC)

<table>
<thead>
<tr>
<th>950 kDa</th>
</tr>
</thead>
<tbody>
<tr>
<td>5 mg (by weight of antibody)</td>
</tr>
</tbody>
</table>

| 7 |
| 4 |

| 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**

- KSI-301
- Aflibercept
- Ranibizumab

**SPECIAL FEATURES OF ABCs DUE TO PHOSPHORYLCHOLINE BIOPOLYMER**

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

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2. 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.  
3. Patel et al, ARVO 2019

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0.001 0.010 0.100 1.000 10.000 100.000 1,000.000 10,000.000

0 20 40 60 80 100 120 140

TIME POST DOSING (DAYS)

DRUG CONCENTRATION (µg/mL)

Minimal concentration for dose-frequency in humans that prevents disease progression

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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

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

Clinical Proof of Concept Study of KSI-301
Phase 1b, open-label, randomized study

<table>
<thead>
<tr>
<th>Week</th>
<th>Loading Phase</th>
<th>Durability Assessment Retreatment</th>
<th>End of follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>KSI-301 2.5 or 5 mg</td>
<td>wAMD</td>
<td>DME</td>
</tr>
<tr>
<td></td>
<td></td>
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</table>

Clinicaltrials.gov ID: NCT03790852
## KSI-301 Phase 1b Baseline Characteristics

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

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

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

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

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

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

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

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
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 At Day 1**
- **60 At Week 4**
- **44 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:
  o Data pending - emerging durability data planned for AAO Retina Subspecialty Day¹

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*

<table>
<thead>
<tr>
<th>Week</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
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<th>40</th>
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<tbody>
<tr>
<td>KSI-301 5 mg</td>
<td>Q20W</td>
<td>☐</td>
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<tr>
<td>Aflibercept 2 mg</td>
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*After the loading phase

Study expected to begin recruiting in August 2019

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

*Primary endpoint

Durability Assessments

Sham injection

Matched Phase

Disease Activity

Dosing Adjustment
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
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