Phase 1 First-In-Human Study of KSI-301: A Novel Anti-VEGF Antibody Biopolymer Conjugate With Extended Durability

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▪ Research Grants:
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  – Regeneron
  – Santen

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  – Aerie
  – Boehringer Ingelheim
  – Clearside
  – Novartis
  – Regeneron
  – Santen
Key Points

- **KSI-301** is a novel **Antibody Biopolymer Conjugate** built on Kodiak’s ABC Platform
- Intravitreal KSI-301 inhibits VEGF with enhanced durability, tissue bioavailability, biocompatibility, and stability
- Phase 1a single ascending dose study results:
  - Well-tolerated at all dose levels
  - **Rapid-onset, high-magnitude** BCVA gains and OCT retinal thickness reductions, with **improvements sustained** to 12 weeks
- Objective: first line agent for both induction and maintenance therapy of VEGF-mediated retinal vascular diseases
Real-world outcomes emphasize the limitations of current anti-VEGF therapies

Without high intensity treatment, gradual VA loss can begin after only 3 months of therapy.

Minimal visual gains are achieved in real-world practice. Patients and physicians need VEGF inhibitors with extended durability.

Mean (±SD) injections at Month 12

Ranibizumab: 6.7 (2.5)
Aflibercept: 7.0 (2.4)

Mean change in VA by country

UK 9.0
Netherlands 8.7
Germany 5.6
France 6.3
Italy 5.2

Mean change in VA

Ranibizumab n=3,350
Aflibercept n =4,300

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EMR= Electronic Medical Records
Designer medicines to solve the real-world effectiveness problem

**KSI-301** is an antibody biopolymer conjugate intended to be

### Same where it matters
- Clinically proven target: VEGF
- Antibody-based biologic
- Intravitreal injection
- Optically clear solution
- No ocular residues

### Different where it matters
- Designed-in ocular durability
- Fast systemic clearance
- Improved bioavailability
- Improved biocompatibility
- Improved stability

**Antibody**
IgG1 with inert immune effector function

**Biopolymer**
Optically clear, high molecular weight phosphorylcholine polymer

**ABC Platform Medicines**

Stable linkage
KSI-301 bioconjugate optimizes both size and formulation strength to improve durability.

<table>
<thead>
<tr>
<th>Drug/Candidate:</th>
<th>Brolucizumab</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>
</tr>
<tr>
<td>Molecular structure</td>
<td><img src="image1" alt="Brolucizumab" /></td>
<td><img src="image2" alt="Ranibizumab" /></td>
<td><img src="image3" alt="Aflibercept" /></td>
</tr>
<tr>
<td>Molecular weight</td>
<td>26 kDa</td>
<td>48 kDa</td>
<td>115 kDa</td>
</tr>
<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 Antibody Biopolymer Conjugate (ABC)

- 950 kDa
- 5 mg (by weight of antibody)
- 7
- 4
- 1,000,000

Equivalent values are showed as fold changes relative to Ranibizumab.
KSI-301 bioconjugate is more potent in vitro than unconjugated anti-VEGFs

In vitro assays demonstrate KSI-301 bioconjugate has a deeper potency compared to bevacizumab, ranibizumab, and aflibercept because of the special nature of its phosphorylcholine biopolymer

<table>
<thead>
<tr>
<th>Binding affinity of KSI-301 to VEGF-A</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KinExA (37°C)</strong></td>
</tr>
<tr>
<td>$K_{on} (M)$</td>
</tr>
<tr>
<td>$K_{off} (M)$</td>
</tr>
<tr>
<td>$K_{D} (pM)$</td>
</tr>
</tbody>
</table>

KSI-301 has high binding affinity to VEGF

KSI-301 bioconjugate has a deeper potency than other anti-VEGFs and even its unconjugated starting protein

Kodiak data on file
KSI-301 bioconjugate has greater bioavailability because of its phosphorylcholine biopolymer

Ocular tissue bioavailability after single intravitreal injection
Data from *in vivo* rabbit models

Covance rabbit ADME (absorption, distribution, metabolism, elimination) model:
Aflibercept data (2008): EVER Congress Portoroz Slovenia Struble (Covance), Koehler-Stec (Regeneron)
KSI-301 data (2017): Struble (Covance), Kodiak
Error bars reflects standard error of the mean
KSI-301 bioconjugate has potential for extended durability and more flexible retreatment window

KSI-301 bioconjugate has a flatter (better) ocular PK curve. This translates into multi-Log concentration advantage versus other biologics.

Rabbit *in vivo* PK modeled to human doses and dosing intervals

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.
KSI-301 Phase 1 clinical study: single ascending dose study design

- **KSI-301**
  - 1.25 mg (25 μL)
  - 2.5 mg (50 μL)
  - 5 mg (100 μL)

- **Time:**
  - Day 0: Single intravitreal injection
  - Day 1
  - Day 7
  - Wk 2: Primary objective: 2-week Safety
  - Wk 4
  - Wk 8
  - Wk 12: Extended follow-up

- **Eyes with diabetic macular edema (DME), one eye per subject**
- 9 subjects – 3 per dosing cohort, 7-day safety review between each cohort
- Conducted at 5 US sites
- Single dose with observation to 12 weeks (no retreatment)
## Demographic and ocular baseline characteristics

### Demographics, n=9

<table>
<thead>
<tr>
<th>Age (years, mean)</th>
<th>62</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender</td>
<td>7M, 2F</td>
</tr>
</tbody>
</table>

### Ocular Characteristics, Study Eye, n=9

<table>
<thead>
<tr>
<th>Previously received Anti-VEGF</th>
<th>8/9</th>
</tr>
</thead>
<tbody>
<tr>
<td># of anti-VEGF treatments in last year - median (range)</td>
<td>3 (0, 7)</td>
</tr>
<tr>
<td>Time since last anti-VEGF, days - median (range)</td>
<td>95 (52, &gt;365)</td>
</tr>
<tr>
<td>IOP, mmHg - mean (SD)</td>
<td>15 (2)</td>
</tr>
<tr>
<td>OCT Central Subfield Thickness, microns - mean (SD)</td>
<td>565 (182)</td>
</tr>
<tr>
<td>Baseline BCVA, ETDRS letters - mean (SD)</td>
<td>47 (12)</td>
</tr>
<tr>
<td>Baseline BCVA, Snellen equivalent</td>
<td>20/100</td>
</tr>
</tbody>
</table>
Safety outcomes: every dose level well-tolerated through 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)\(^1\)

<table>
<thead>
<tr>
<th>Number of patients with any AE = 4</th>
<th>N</th>
<th>Serious</th>
<th>Related</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ocular AEs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Foreign body sensation</td>
<td>1</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Subconjunctival hemorrhage</td>
<td>2</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Floaters (reported in both eyes)</td>
<td>1</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Visual flashes</td>
<td>1</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td><strong>Non-Ocular AEs</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fall</td>
<td>1</td>
<td>N</td>
<td>N</td>
</tr>
<tr>
<td>Worsening of coronary artery disease</td>
<td>1</td>
<td>Y</td>
<td>N</td>
</tr>
<tr>
<td>Swollen feet</td>
<td>1</td>
<td>N</td>
<td>N</td>
</tr>
</tbody>
</table>

Improvements in vision and retinal thickness after **single-dose** KSI-301 through 12 weeks

Rapid, high magnitude responses **as early as 1 week** after dosing

Durable improvements out to 12 weeks

Median changes from baseline to week 12 pooled across 3 dose groups (n=9 patients total)
Case example: resolution of macular edema sustained through 12 weeks in patient with prior suboptimal response

Clinical history summary (site reported):

<table>
<thead>
<tr>
<th>Date</th>
<th>Treatment</th>
<th>VA Snellen</th>
<th>CST</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2018</td>
<td>Retrospective</td>
<td>20/40</td>
<td>-</td>
</tr>
<tr>
<td>4/2018</td>
<td>Bevacizumab</td>
<td>20/40</td>
<td>431</td>
</tr>
<tr>
<td>6/2018</td>
<td>Bevacizumab</td>
<td>20/60</td>
<td>655</td>
</tr>
<tr>
<td>8/2018</td>
<td>KSI-301</td>
<td>20/160</td>
<td>636</td>
</tr>
</tbody>
</table>

Change from baseline to week 12

- Change in BCVA (ETDRS Letters): +18.5
- Change in OCT CST (microns): -294
Case example: **improvement through 12 weeks** of subretinal fluid in patient with extensive foveal lipid exudates

Baseline: Improvement through 12 weeks of subretinal fluid in patient with extensive foveal lipid exudates

Baseline

Single dose KSI-301 (1.25 mg)

Week 4

Week 12

<table>
<thead>
<tr>
<th>Date</th>
<th>Treatment</th>
<th>VA Snellen</th>
</tr>
</thead>
<tbody>
<tr>
<td>1/2018</td>
<td>Bevacizumab</td>
<td>20/60</td>
</tr>
<tr>
<td>3/2018</td>
<td>Bevacizumab</td>
<td>20/100</td>
</tr>
<tr>
<td>4/2018</td>
<td>Bevacizumab</td>
<td>20/150</td>
</tr>
<tr>
<td>5/2018</td>
<td></td>
<td>20/350</td>
</tr>
<tr>
<td>7/2018</td>
<td>KSI-301</td>
<td>20/80</td>
</tr>
</tbody>
</table>

Clinical history summary (site reported):

- Change from baseline to week 12
  - Change in BCVA (ETDRS Letters): +4.5
  - Change in OCT CST (microns): -211
Important early development questions successfully addressed in KSI-301 Phase 1 study

- ✓ Manufacturability
- ✓ Optical Clarity
- ✓ Target Tissue Access
- ✓ Safety
- ✓ Speed of Onset
- ✓ Potency
- ✓ Clinical Durability
Key Takeaways

- **KSI-301** is a novel **Antibody Biopolymer Conjugate** that inhibits VEGF

- Phase 1a single ascending dose study results:
  - Well-tolerated at all dose levels
  - Rapid-onset, high-magnitude improvements sustained to 12 weeks

- Objective: the “go-to drug” for induction and maintenance therapy of retinal vascular diseases

- Phase 1b evaluating multiple doses in treatment-naïve wet AMD, DME, and RVO currently enrolling (NCT03790852)

- Phase 2 in treatment-naïve wAMD starting in 2019 with dosing as infrequently as Q20W and all patients ≥Q12W

- Additional studies in DME, NPDR in planning

- Dedicated China pivotal programs in planning
Acknowledgements

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  - Victor Perlroth, MD
  - Almas Qudrat, MSc
  - Pablo Velazquez-Martin, MD

- **Ocular Imaging Research and Reading Center**
Appendix
**Phase 1b** open-label study in wet AMD, DME and RVO

<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>
<th>28</th>
<th>32</th>
<th>36</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>KSI-301</strong>&lt;br&gt;5 or 2.5 mg</td>
<td><strong>wAMD</strong>&lt;br&gt;</td>
<td></td>
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<tr>
<td><strong>DME/DR</strong>&lt;br&gt;</td>
<td></td>
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<td>□</td>
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<tr>
<td><strong>RVO</strong>&lt;br&gt;</td>
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<td>□</td>
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</tbody>
</table>

- **Primary Endpoint**

- **Study now recruiting** (NCT03790852)
- Open-label study to further explore KSI-301 safety, bioactivity, durability (~50 patients)
- Anti-VEGF treatment naïve patients only
- 3 loading doses followed by indication-specific re-evaluation and retreatment criteria
- OCT Angiography to generate novel data for “on mechanism” durability
**Phase 2 study in wet AMD (US/EU)**

*Pivotal study design, head-to-head against standard of care aflibercept*

<table>
<thead>
<tr>
<th>AMD</th>
<th>0</th>
<th>4</th>
<th>8</th>
<th>12</th>
<th>16</th>
<th>20</th>
<th>24</th>
<th>28</th>
<th>32</th>
<th>36</th>
<th>40</th>
<th>44</th>
<th>48</th>
<th>52</th>
</tr>
</thead>
<tbody>
<tr>
<td>KSI-301 5 mg</td>
<td>Q20W</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>Q20W</td>
<td>[ ]</td>
<td>[ ]</td>
<td>Q20W</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
<td>[ ]</td>
</tr>
<tr>
<td>Aflibercept 2 mg</td>
<td>q8w</td>
<td>[ ]</td>
<td>[ ]</td>
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<td>[ ]</td>
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</tbody>
</table>

- **Primary Endpoint**
- **All patients ≥Q12W with KSI-301**
- **As infrequent as Q20W dosing with KSI-301**
- **Non-inferiority pivotal design study**
- **Estimated ~400 patients (US/EU)**
- **On track to begin enrolling in 2Q 2019, with interim and primary readouts in 2020 and 2021**

![Diagram](image)