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TIME-2 Phase 2a study: Reminder

**Primary Analysis**
- Patients with DME
- Three Arms (n = 144*)
  - SQ/Systemic + Study Eye
    - bid AKB-9778 + monthly x 3 IVT Sham (n=46)
    - bid AKB-9778 + monthly x 3 IVT Lucentis (n=48)
    - bid Placebo + monthly x 3 IVT Lucentis (n=47)
- Primary Endpoint
  - Change in retinal thickness at month 3
- Secondary Measurements
  - 2-step DRSS change at month 3

**Secondary Analysis (Prospective)**
- Patients with DRSS 2-6 in study and fellow eye
- Two Arms (n = 128)
  - SQ/Systemic + Fellow Eye
    - bid AKB-9778 + None (n=90)
    - bid SQ Placebo + None (n=38)
- Prospective Measurements
  - 2-step DRSS change at month 3


**Percentage of Patients with a ≥ 2-Step Improvement in DRSS from Baseline**

- Study Eye
  - AKB-9778 (N=40): 10%
  - RBZ (N=34): 8.8%
  - AKB-9778 + RBZ (N=44): 11.4%

- Fellow Eye
  - Placebo Arm (N=24): 4.2%
  - AKB-9778 Arms (N=70): 11.4%

**Retrospective Analysis Shows Renal Benefit of AKB-9778 in Diabetic Patients with Albuminuria**

- % Change UACR (Geometric Mean ± 95% CI)
TIME-2b Phase 2b study of AKB-9778 in NPDR fully enrolled

Study Objective: Assess the potential benefits of systemic Tie2 activation to slow progression of diabetic eye disease and possibly other diabetic complications such as nephropathy

15 mg AKB-9778 subcutaneous BID

Placebo subcutaneous QD + 15 mg AKB-9778 subcutaneous QD

Placebo subcutaneous BID

• Phase 2b study in pts with moderate to severe non-proliferative diabetic retinopathy (NPDR) without DME and VA 20/40 or better
• 1° Endpoint: ≥ 2-step improvement in DRSS at 48 weeks
• Key 2° Endpoints: development of DME/PDR, DR progression, renal function
• Enrollment commenced June 2017, enrollment closed February 2018
• 167 patients enrolled
• Data expected early Q2 2019
Tie2 Activation: A New Mechanism of Action to Treat Glaucoma
Significant reduction in IOP with subcutaneous AKB-9778 in a 3-month trial in diabetics with normal IOP

From TIME-2 Safety Database

<table>
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<tr>
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<th>AKB-9778 Monotherapy</th>
<th>AKB-9778 + Lucentis®</th>
<th>Lucentis® monotherapy</th>
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<tr>
<td></td>
<td>SE</td>
<td>FE</td>
<td>SE</td>
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<tr>
<td>Mean Baseline IOP (mmHG)</td>
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<td>Mean Δ from BL (mmHG)</td>
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BL = baseline; SE = study eye; FE = Fellow eye
Larger IOP changes seen in patients with higher baseline pressure

* p<.01
Loss of Tie2 function leads to increased IOP and glaucoma phenotype in mice and humans

Loss of Tie2 activity in ANGPT-1 KO mice results in congenital glaucoma due to a failure of the development of Schlemm’s canal.

Families with mutations in the Tie2/ANGPT pathway associated with congenital glaucoma.

“Several loci support an important role of Tie2/ANGPT signaling in IOP regulation, and Tie2/ANGPT may thus be a therapeutic target.”
Evidence of the role of the Tie2/angiopoietin pathway in IOP regulation

- Loss of Tie2 activity in ANGPT-1 KO mice results in congenital glaucoma due to a failure of the development of Schlemm’s canal (1)
- In a conditional KO mouse model, IOP is elevated due to reduced outflow through Schlemm’s canal and an OAG-like retinal phenotype develops (2)

- Recent studies in humans have identified families with mutations in the Tie2/ANGPT pathway with congenital glaucoma (3), and SNP variants in this pathway that increase the risk of POAG (4).

1. Thompson et al, J Clin Invest 2014;124:4320-4
Pathology of glaucoma involves dysregulation of normal aqueous outflow via the conventional outflow pathway

Conventional Outflow Pathway
- Comprised of the trabecular meshwork, Schlemm’s canal and collecting vessel network
- Responsible for majority of aqueous humor outflow
- Site of pathological changes in POAG
- Current standard of care drugs increase outflow via the uveoscleral pathway (unconventional outflow tract) or reduce production of aqueous humor but do not target conventional outflow
Tie2 activation plays a key role in maintenance of the inner wall of Schlemm’s Canal

Schematic diagrams depicting how impairment of Angpt-Tie2 signaling disrupts SC integrity, leading to glaucomagenesis.
Tie2 activation via VE-PTP inhibition: a novel conventional outflow targeted approach for glaucoma treatment

**Tie-2** is expressed in conventional outflow (CO) tract cells (endothelium-like cells)

**Tie-2** activity
- Maintains normal CO cell contractile state
- Enhances CO cell viability
- Maintains normal CO ECM
- Inhibits inflammation and reduces fibrosis

**Active Tie-2 = Conventional Outflow Stability**
Dose-related IOP decrease observed after topical ocular drop administration of AKB-9778

- Dose dependent decrease in IOP with topical ocular dosing
- Topical ocular dosing yielded larger decreases in IOP than subcutaneous dosing
- Decrease in IOP persisted for 24 hours after the last dose
Conclusions

• Activation of the Tie2 pathway via AKB-9778 reduces IOP in humans and rabbits with normal IOP
• The proposed mechanism of this effect is decreased resistance in the conventional outflow pathway (including Schlemm’s Canal) consistent with non-clinical and human genetic evidence of this pathway’s role in controlling IOP
• A topical ocular formulation is being developed to pursue the treatment of elevated IOP with planned Phase 1 program 1H ‘19