Leveraging Tie2 Activation for Treatment of Ocular Disease

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Overview of Aerpio

- Developing first-in-class Tie2 activators for ocular diseases and complications of diabetes
- Lead product candidate: AKB-9778, a potent and selective VE-PTP inhibitor/Tie2 activator, enhances vascular stability and ocular fluid outflow
- Completed TIME-2b Phase 2 clinical trial in patients with non-proliferative diabetic retinopathy and evidence of Tie2 activation based on:
  - Reproduced the statistically significant reduction in intra-ocular pressure (IOP) seen in TIME-2
  - Reproduced evidence of improved kidney function (UACR) in patients early diabetic nephropathy
- Pipeline opportunities in ophthalmology
  - OHT/OAG: Phase 1b of topical ocular AKB-9778 to support evaluation in open-angle glaucoma ongoing
  - DME: ARP-1536 humanized anti-VE-PTP Mab that activates Tie2 in preclinical development
    - NIH funded for development as an intravitreal adjunct to anti-VEGF therapy in diabetic macular edema
    - Bispecific ARP-1536-anti-VEGF biologics in preclinical development
The ANGPT/Tie2 Pathway Plays a Key Role in Maintenance of Schlemm’s Canal

- In the normal CO pathway, Tie2 is active, and ECs of the inner wall of SC, adjacent to the trabecular meshwork, support the formation of giant vacuoles which provide a conduit for aqueous humor drainage.

- Loss of ANGPT/TIE2 pathway activation leads to loss of SC endothelial cell specialization, ultimately resulting in SC degeneration, increased IOP and glaucomatous retina pathology.

○ Hypothesis: Restoring Tie2 activation will restore SC integrity and improve conventional outflow facility resulting and decreased IOP and reduced progression of glaucoma.
Tie2 Pathway Activation is Critical for Development and Maintenance of Schlemm’s Canal and Conventional Outflow: Mouse and Human Genetic Data

Tie2 KO or Angpt-1/2 KO in mice results in congenital glaucoma due to Schlemm’s canal development.

Families with Tie2 LOF mutations associated with congenital glaucoma.

Mice and humans with LOF Angpt-1 mutations associated with congenital glaucoma.

Several loci support an important role of Tie2/ANGPT signaling in IOP regulation in adults.

Genome-wide analyses identify 68 new loci associated with intraocular pressure and improved risk prediction for primary open-angle glaucoma.

Impaired angiotensin/Tie2 signaling compromises Schlemm’s canal integrity and induces glaucoma.

Families with Tie2 LOF mutations associated with congenital glaucoma.

Tie2 KO or Angpt-1/2 KO in mice results in congenital glaucoma due to Schlemm’s canal development.
VE-PTP is Co-Expressed with Tie2 in Schlemm’s Canal Endothelium and Topical Ocular Dosing of AKB-9778 Activates Tie2

- VE-PTP (b-Gal; purple staining nuclei) and Tie2 are expressed in Schlemm’s canal endothelium (PECAM-1 positive cells)

- Administration of a single topical ocular dose of AKB-9778 activates Tie2 (pTie2) in Schlemm’s canal endothelium

Stamer et al. ARVO 2019 Abstract Number 2186
TIME2b: IOP Effects of Subcutaneous AKB-9778 Confirmed and Extended in 48 Week Trial*

- Clear IOP reduction in both QD and BID groups with trend favoring dose dependence
- Week 24 IOP measured *predose* (red ovals) shows a persistent IOP effect that supports QD dosing (BID >12hr since prior dose; QD >24hr since prior dose)

* MMRM (Mixed-Effect Model Repeated Measures) Analysis LOCF:
  Within Treatment Change from Baseline – AKB-9778 QD p = 0.04; AKB-9778 BID p < 0.0001
  AKB-9778 Group vs Placebo – AKB-9778 QD p = 0.0553; AKB-9778 BID p < 0.0002
Phase 1b Study Design: Ascending Dose Study to Assess the Safety, Tolerability, PK, and PD of Single and Twice Daily Doses of AKB-9778 Ophthalmic Solution

Key Entry Criteria:
- Subjects with no history of OHT/OAG
- Screening IOP ≥ 16 mmHg and ≤ 23 mmHg on two separate occasions
- VA ≥ 20/30 (spectacle corrected)

Key Study Features:
- Four cohorts of 12 subjects, randomized 3:1 to active and placebo, respectively
- 7 Days of dosing once daily (cohorts 1-3) or twice daily (cohort 4)
- Diurnal IOP (predose, 2, 4 and 8 hours post-dose) on days -1, 1 and 7.
- Red eye formally assessed on days -1, 1 and 7 prior to IOP assessment.
- PK assessments on days 1 and 6.
IOP Change from Day -1 Placebo Corrected

- Dose dependent IOP reduction at four hours post dose on days 1 and 7 which was statistically significant at 4 hours (-1.47 mmHg; p = 0.041)/-10.64%; p = 0.027; prespecified two tailed t-test compared to placebo) and persisted out to at least 8 hour on day 7
- Transient minimal to mild conjunctival hyperemia in 15 and 40 mg/ml groups
- Based on these encouraging data, we’ve decided to add a cohort of up to 24 patients with OHT/OAG to inform the design of a planned Phase 2 study
Topical AKB-9778 in Primary Open-Angle Glaucoma

Near-Term Development Plan

- **2019**
  - Q1: Initiate Phase 1b study

- **2020**
  - Q1: Top-line results from Phase 1b study
  - Q2: Initiate 28-day Phase 2a study
TIME-2: First Demonstration of Improved Efficacy of Combined Tie2 Activation/VEGF Inhibition

- Reduction of macular edema with AKB-9778 + Lucentis is significantly greater than either agent alone (left panel)
  - Trajectory of combination curve favors continued improvement with longer duration therapy
- Translates into higher percentage of patients with dry retinas (right panel: CST ≤ 300 μm)
- Visual acuity trended in favor of AKB-9778 + Lucentis treatment at 3 months particularly in patients with indicators of advanced disease (CST > 450 um and DME duration > 5 years)

ARP-1536-AV (anti-VEGF): Aerpio Biologic Approach to Combined Tie2 Activation/ VEGFR2 Inhibition

- Stabilizes retinal vasculature
  - Reduces vascular leakage and neovascularization
  - Reduces inflammation

**Tie2 Activation**

- Tyrosine Phosphatase

**VEGFR2 Inhibition**

- Tyrosine Kinase

**ARP-1536-AV**

- Lucentis
ARP-1536 Brolucizumab and ARP-1536 Aflibercept Activate Tie2 and Inhibit VEGR2: an IP/western-based Study
Summary: Tie2 Activation for OHT/POAG and Combined Tie2 Activation/VEGF Inhibition for DME

- Preclinical and clinical data supports pursuing topical ocular AKB-9778 as the first SC targeted OHT/OAG therapy
  - Mouse and human genetic data support a role for the Tie2 pathway in development and maintenance of Schlemm’s canal and conventional outflow facility
  - In mice, VE-PTP and Tie2 are co-expressed in SC and topical ocular AKB-9778 increases Tie2 activation in SC resulting in enhanced outflow facility and reduced IOP
  - In ocular normotensive patients, subcutaneous AKB-9778, a VE-PTP inhibitor and Tie2 activator, reduces IOP in a pressure dependent manner confirmed in two Phase 2 studies with treatment for up to 1 year
  - Dose dependent IOP reduction in ocular normotensive subjects with excellent safety profile
  - Phase 1b study including patients with OHT/OAG on-going with results in Q1 2020

- Preclinical and clinical data supports pursuing Aerpio’s biologic approach to combination of Tie2 activation and VEGF inhibition in DME with potential to extend to wAMD, RVO and other sight threatening retinopathies
Thank you!