AKB-9778: A Novel Approach to Glaucoma Treatment Targeting Tie2 in the Conventional Outflow Pathway

Kevin Peters, MD
CSO and SVP R&D
Aerpio Pharmaceuticals, Inc
Glaucoma 360
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Primary Open Angle Glaucoma: Unmet Medical Need

- Despite advances in therapy, open angle glaucoma remains a major cause of vision loss and blindness with more than 3 million Americans living with glaucoma, 2.7 million of whom—aged 40 and older—are affected with open-angle glaucoma
- IOP reduction is the only known modifiable risk factor for the prevention of glaucomatous neuro-retinal changes that result in loss of visual field and blindness
- Prostaglandins are effective first line IOP lowering therapy, but adjunctive therapy is required as the disease progresses
- Current adjunctive therapies are associated with either limited efficacy or significant side effects; adjunctive therapies represent over 33% of the $6 billion WW glaucoma market

➢ Based on these recognized attributes, there is clearly an unmet need for an effective, well tolerated adjunctive therapy with disease modifying potential

Aerpio Glaucoma Program

- AKB-9778 is a first in class Tie2 activator targeting primary open angle glaucoma (POAG) via the conventional outflow pathway, i.e. Schlemm's canal and the trabecular meshwork

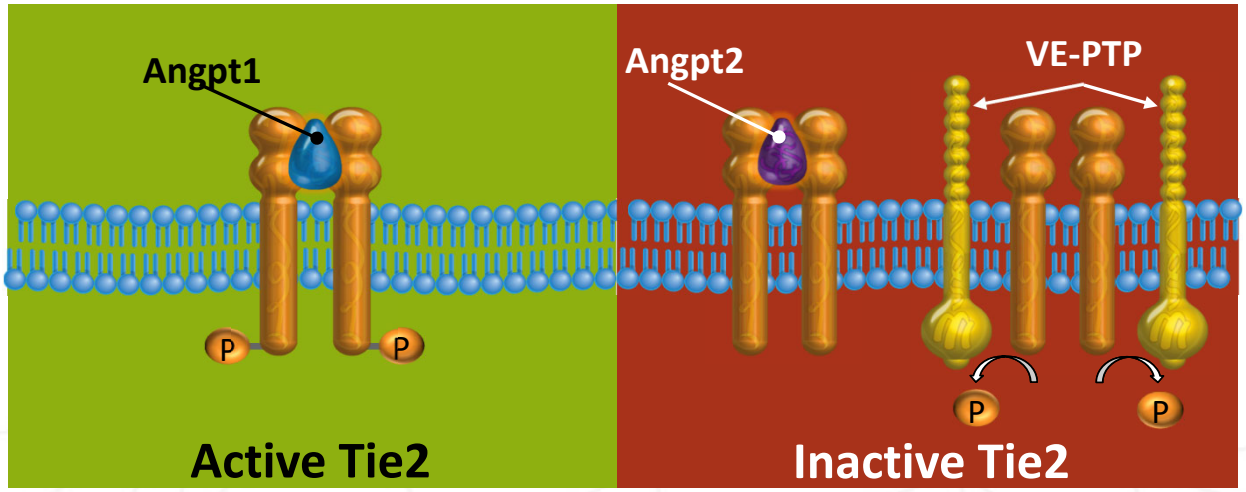
- Emerging literature definitively links Tie2 activation to the integrity of Schlemm's canal, regulation of IOP and neuroprotection in both animal and human genetic studies

- Significant market opportunity as potential best-in-class adjuvant or combination therapy
  - Clinical proof-of-concept demonstrating the ability to lower IOP on top of standard of care prostaglandins that appears similar to or better than published phase 3 data for marketed adjuvant therapies*
  - Observed tolerability that appears to be better than published phase 3 data for marketed adjuvant therapies*
  - Opportunity for disease modifying effects on Schlemm's canal, i.e. potential to repair conventional outflow pathway thereby reducing IOP and reducing or halting the progression of glaucoma

- Potential approach to congenital glaucoma in patients with Tie2 pathway mutations (Rare Pediatric disease opportunity)

*No head-to-head data is yet available comparing AKB-9778 to these marketed therapies in a single trial.

The Tie2 Pathway is an Emerging Target for Vascular Stabilization

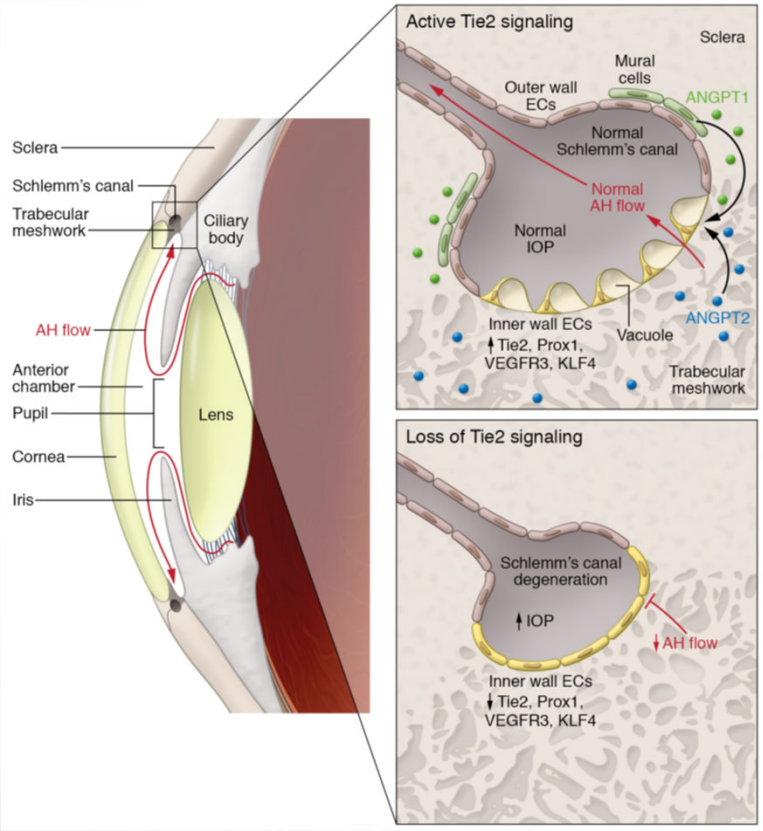


Angpt1 responsive, Stable vasculature

Angpt1 resistant, Destabilized vasculature

- Increased Angpt2 competes with Angpt1 for Tie2 binding and reduces Tie2 activation (Watanabe et al. Am J Ophthalmol 139:476, 2005, Kinnunen et al. Br J Ophthalmol 93:1109, 2009; Regula et al. EMBO Mol Med 8:1265, 2016)
- Increased VE-PTP expression further limits Tie2 activation (Shen et al. JCI 124:4564, 2014)

The ANGPT/Tie2 Pathway Plays a Key Role in Maintenance of Schlemm's Canal and the Regulation of IOP



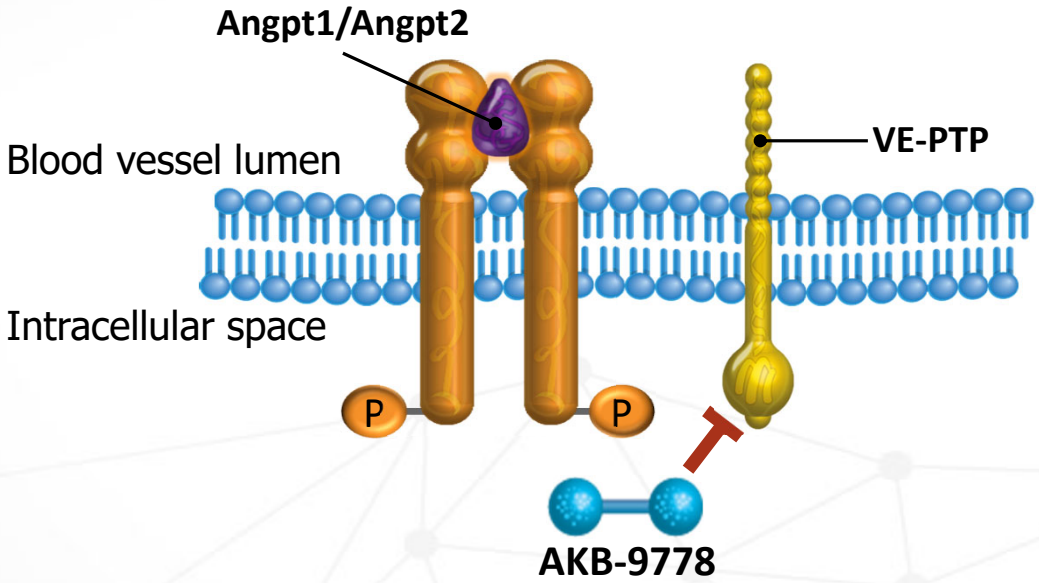
Bernier-Latmani and Petrova J Clin Invest 127:3594-3597, 2017

- Tie2 is expressed in Schlemm's canal (SC) endothelial cells and not in trabecular meshwork (TM) cells.
- In mice, loss of Tie2 pathway activation leads to loss of SC EC specialization, SC agenesis or degeneration, and ultimately increased IOP and glaucomatous retina pathology.
- In humans, Tie2 or Angpt1 loss of function mutations are associated with congenital glaucoma and Angpt1 SNPs are associated with IOP and the risk of developing OAG.

➢ Hypothesis: Restoring Tie2 activation will restore SC integrity and improve CO facility resulting in decreased IOP and reduced progression of glaucoma.

1. Thomson et al, *J Clin Invest* 2014;124:4320-4
2. Thomson et al. *J Clin Invest* 2017;127:4421-36
3. Kim et al, *J Clin Invest* 2017;127(10):3877-96
4. Souma et al, *J Clin Invest* 2016; **126:**2575–2587
5. Khawaja et al, *Nat Genet* 2018;50:778-782
6. Gao et al, *Human Mol Genet* 2018; 27:2205-2213
7. MacGregor et al, *Nature Genet* 2018; 50:1067-1071

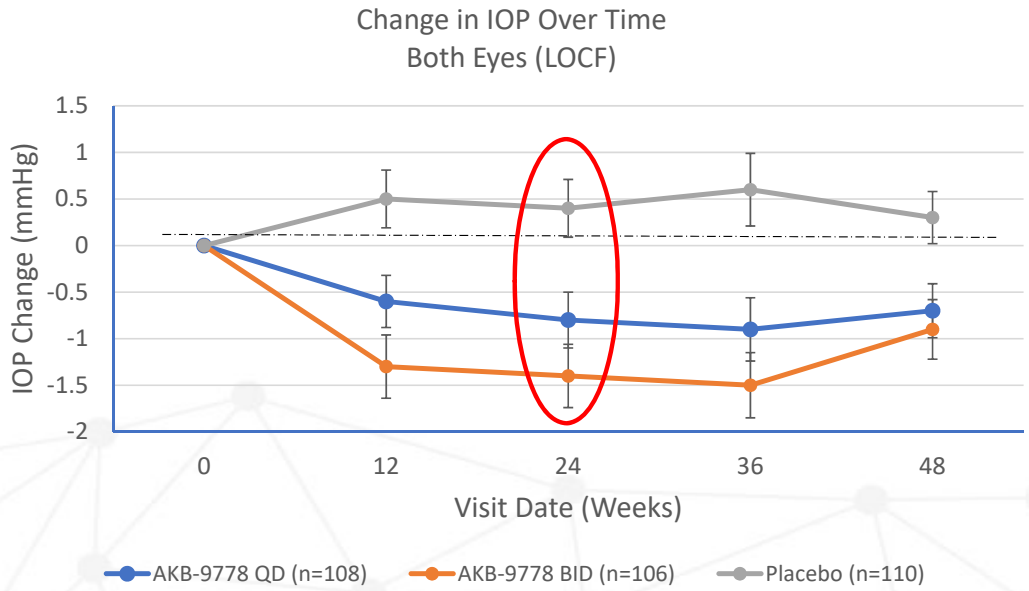
Targeting VE-PTP: The Clinically-Proven Pharmacological Approach to Restore Tie2 Activation



- AKB-9778 is a highly optimized small molecule inhibitor of the catalytic activity of VE-PTP
- VE-PTP inhibition with AKB-9778 restores Tie2 activation irrespective of the presence of Angpt1 or Angpt2

➢ We believe targeting VE-PTP is the most robust approach to restoring Tie2 activation

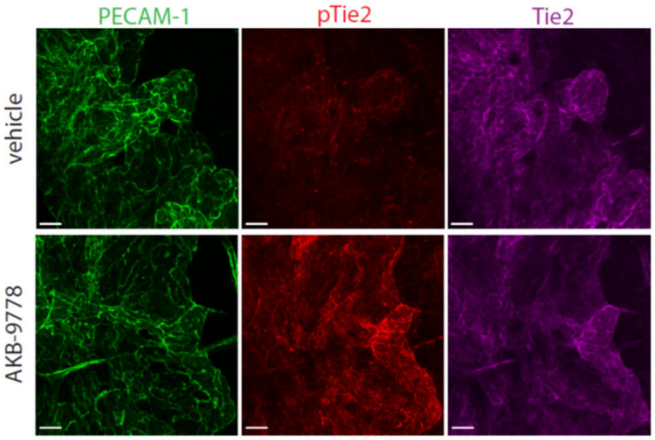
TIME2b: Subcutaneous AKB-9778 Reduced IOP in Ocular Normotensive Patients with Diabetic Retinopathy

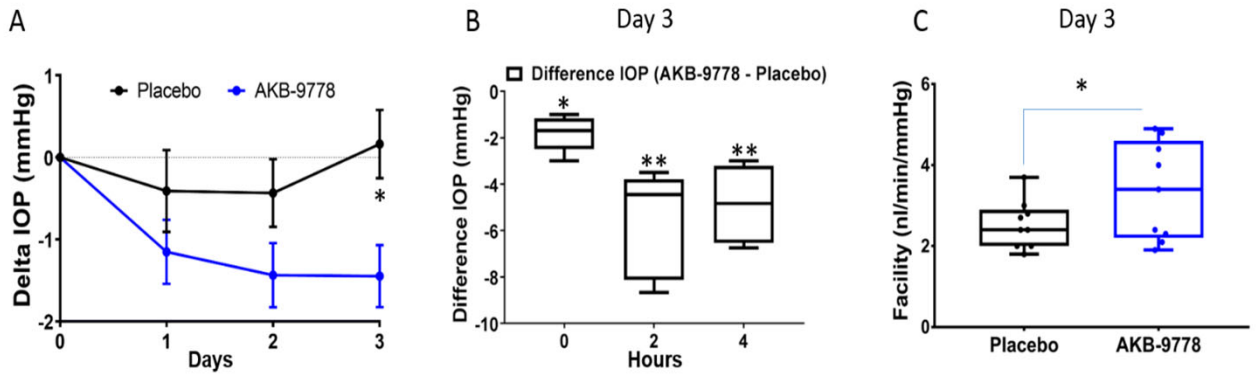


- Statistically significant IOP reduction in both QD and BID groups with trend favoring dose dependence*
- Week 24 IOP measured **predose** (red ovals) showed a persistent IOP effect

* 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 $p < 0.0002$

Topical Ocular AKB-9778 Activated Tie2 in Schlemm's Canal and Decreased IOP via Enhanced Outflow Facility



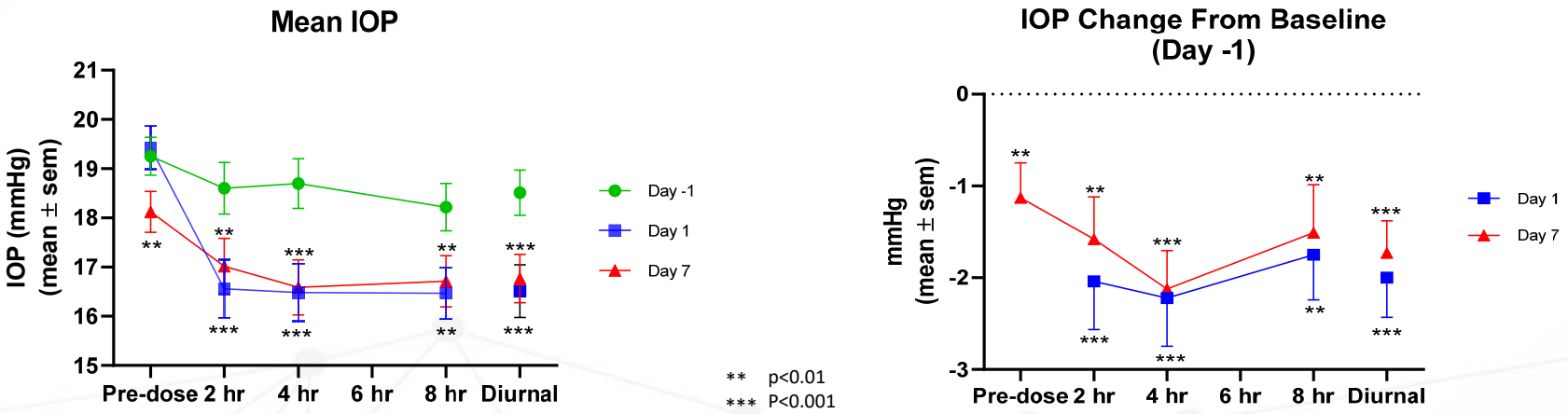


- Robust Tie2 activation in Schlemm's canal endothelium 1 hour after a single topical ocular dose of AKB-9778
- AKB-9778 reduced IOP in ocular normotensive mice (panels A and B) via enhanced outflow facility (panel C)

Topical Ocular AKB-9778 is Well Tolerated and Reduces IOP in OHT/OAG Patients on Standard of Care Prostaglandin Therapy

- Phase 1b Cohorts 1-4 (12 ocular normotensive volunteers/cohort randomized 3:1 active to placebo): AKB-9778 was well tolerated with IOP lowering up to the highest 40 mg/ml BID dose
- Cohort 5: 43 OHT/glaucoma patients on standard of care PM prostaglandin with IOP of 17-27 mmHg, were randomized 3:1 drug to placebo
- Patients were dosed for 7 days with AKB-9778 (40 mg/ml) or placebo once daily in AM and continued SOC prostaglandin in PM
- IOP measured predose (0hr) and 2hrs, 4hrs, and 8hrs post dose on Day -1, Day 1 and Day 7
- Utilized 4 highly qualified sites with well balanced enrollment (8-12 patients/site)

Phase 1b Cohort 5: Significant IOP Reduction with Topical Ocular AKB-9778 in OHT/OAG Patients on SoC PGA Therapy



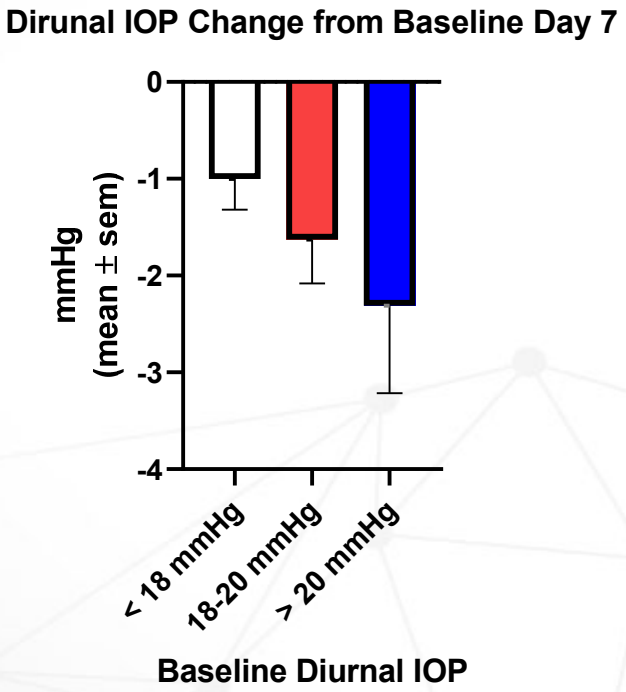
- Statistically significant difference from baseline at all post-dose timepoints including Day 7 predose
- The diurnal mean reduction on Day 7 was -1.58 mmHg ($p < 0.001$) compared to 0.06 for placebo ($p = 0.462$)

Phase 1b Cohort 5: Significant Percentage of Patients with IOP < 16 mmHg and IOP Reduction > 3 mmHg at 4 and 8 hours Post Dose

	AKB-9778 plus PG	PG plus Placebo
Day 7, 4 Hour		
IOP < 16 mmHg	14 (43.8%)	1 (9.1%)
IOP Decrease >= 2 mmHg	17 (53.1%)	2 (18.2%)
IOP Decrease >= 3 mmHg	12 (37.5%)	1 (9.1%)
Day 7, 8 Hour		
IOP < 16 mmHg	15 (46.9%)	1 (9.1%)
IOP Decrease >= 2 mmHg	14 (43.8%)	1 (9.1%)
IOP Decrease >= 3 mmHg	11 (34.4%)	1 (9.1%)

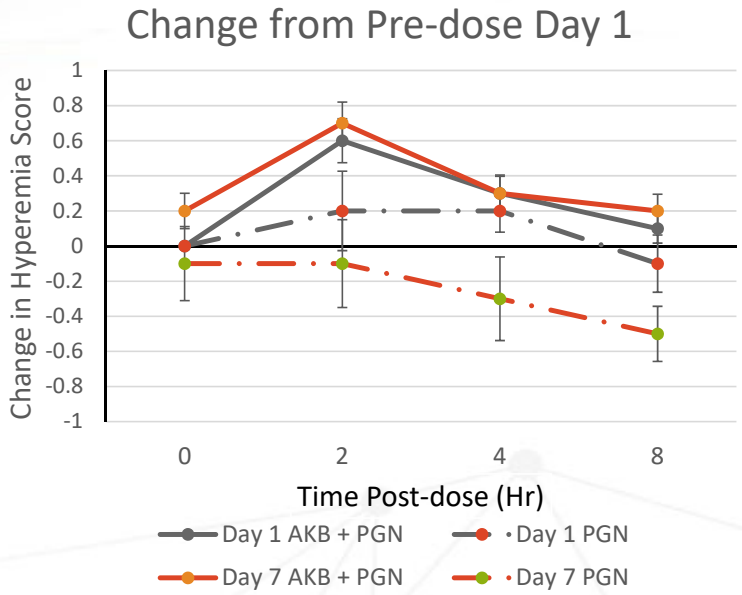
- Over 40% of patients achieved <16 mmHg IOP at both 4 and 8 hours post dose on Day 7 with over 30% achieving >3 mmHg decrease in IOP

Phase 1b Cohort 5: Larger IOP Reductions in Patients with Higher Baseline IOP



- IOP reduction was dependent on baseline IOP consistent with outflow through the pressure dependent conventional outflow tract
- Suggests potential for larger reductions with AKB-9778 as an adjuvant in OHT/OAG patients with higher baseline IOP on standard of care prostaglandin therapy

Phase 1b Cohort 5: Observed Hyperemia Minimal-Mild and Resolved within 8-hours Post Dose



- Small increase in hyperemia over baseline at 2 hours which returns to baseline levels by 4-8 hours post- dose
- Only minimal to mild hyperemia even dosed as an adjuvant to PGAs
- No other ocular or systemic adverse events noted

- **None (0)** - Normal. Appears white with a small number of conjunctival blood vessels easily observed
- **Minimal (1) -** Trace pinkish color of either the bulbar or palpebral conjunctiva
- **Mild (2) -** Prominent, pinkish-red color of both the bulbar and palpebral conjunctiva
- **Moderate (3)** - Scarlet red color of the bulbar and palpebral conjunctiva
- **Severe (4) -** ‘‘Beefy Red’’ with petechiae. Dark red bulbar and palpebral conjunctiva with or without evidence of subconjunctival hemorrhage.

Summary: AKB-9778 as a Novel Conventional Outflow Targeted Approach to OHT/OAG

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