

# A Small Molecule Inhibitor of VE-PTP Activates Tie2 in Schlemm's Canal Increasing Outflow Facility and Reducing Intraocular Pressure

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**PURPOSE:** Tyrosine kinase with immunoglobulin-like and EGF-like domains 2 (Tie2) activation in Schlemm's canal (SC) endothelium is required for the maintenance of IOP, making the angiopoietin/Tie2 pathway a target for new and potentially disease modifying glaucoma therapies. The goal of the present study was to examine the effects of a Tie2 activator, AKB-9778, on IOP and outflow function.

**METHODS:** AKB-9778 effects on IOP was evaluated in humans, rabbits, and mice. Localization studies of vascular endothelial protein tyrosine phosphatase (VE-PTP) , the target of AKB-9778 and a negative regulator of Tie2, were performed in human and mouse eyes. Mechanistic studies were carried out in mice, monitoring AKB-9778 effects on outflow facility, Tie2 phosphorylation, and filtration area of SC.

**RESULTS:** AKB-9778 lowered IOP in patients treated subcutaneously for diabetic eye disease. In addition to efficacious, dose-dependent IOP lowering in rabbit eyes, topical ocular AKB-9778 increased Tie2 activation in SC endothelium, reduced IOP, and increased outflow facility in mouse eyes. VE-PTP was localized to SC endothelial cells in human and mouse eyes. Mechanistically, AKB-9778 increased the filtration area of SC for aqueous humor efflux in both wild type and in Tie2<sup>+/-</sup> mice.

**CONCLUSIONS:** This is the first report of IOP lowering in humans with a Tie2 activator and functional demonstration of its action in remodeling SC to increase outflow facility and lower IOP in fully developed mice. Based on these studies, a phase II clinical trial is in progress to advance topical ocular AKB-9778 as a first in class, Tie2 activator for treatment for ocular hypertension and glaucoma.

Invest Ophthalmol Vis Sci. 2020 Dec 1;61(14) :12. doi: 10.1167/iovs.61.14.12.

PMID: 33315051