**Objectives:** Biologics targeting vascular endothelial growth factor (VEGF) are highly effective for age-related macular degeneration (AMD) treatment. The efficacy of anti-VEGF biologics is determined by ocular drug exposure and their ability to neutralize VEGF in the vitreous and aqueous humor. This study aims to identify the relationship between local VEGF suppression and clinical efficacy of biologics targeting VEGF.

**Methods:** A target-mediated drug disposition (TMDD)-based pharmacokinetic/target engagement (PK/TE) model was developed using literature data. Clinical data of ranibizumab PK and VEGF in the aqueous humor, as well as preclinical PK data of ranibizumab and aflibercept in the vitreous and/or aqueous humor, were used. Model fitting and simulations were conducted using NONMEM® V7.2.0.

**Results:** The PK of ranibizumab in human aqueous humor was described by a one compartment model. The degradation rate constant of VEGF in human aqueous humor was estimated using VEGF baseline and suppression data post ranibizumab intravitreal injection in three clinical studies. Clinically, ranibizumab dosed at 0.5mg Q4W showed similar efficacy (i.e. visual acuity) when compared with aflibercept dosed at 2mg Q4W (3 doses)+Q8W. Interestingly, our PK/TE model predicted similar magnitude of VEGF lowering following 0.5mg Q4W ranibizumab and 2mg Q8W aflibercept. In addition, it had been shown that aflibercept dosed at 2mg Q4W is no more efficacious than 0.5mg Q4W, while 2mg Q12W is less efficacious. Based on these findings, the PK/TE model was able to identify the levels of VEGF suppression associated with compromised efficacy, and where further suppression of VEGF had no additional benefit.

**Conclusions:** A mechanism-based PK/TE model that integrated drug PK, target-binding affinity and target kinetics was developed to benchmark the desired local target suppression and clinical efficacy. Such modeling approach can be used to determine dosing regimens for new investigational biologics with similar mechanism of action.