Objective: GSK933776 is a humanized IgG1 monoclonal antibody with high affinity for the N-terminal amino acid residues of β-amyloid protein (Aβ). A Proof of Concept study (NCT01342926, GSK-funded study BAM114341) was conducted to evaluate the effects of GSK933776 on patients with geographic atrophy (GA) a form of age-related macular degeneration leading to blindness with no current therapy. This interim analysis is aimed to characterize the PK and the concentration-response relationship between plasma GSK933776 and free Aβ (FBAM) in GA patients.

Methods: Patients (n=191) were randomized 1:1:1:1 to receive placebo or 3, 6, 15 mg/Kg of GSK933776 intravenously every 28±3 days for 18 months. On selected visits at pre-determined time points, plasma samples were collected for the analysis of GSK933776 and FBAM concentrations. Population PK/PD analysis was performed using NONMEM. Final model selection was based on evaluation of goodness-of-fit plots, biological plausibility and precision of parameter estimates. Visual predictive checks (VPC) were implemented for final model evaluation.

Results: A two compartment model adequately described the PK of GSK933776 in GA patients. The inter-individual variability on CL and Vc decreased after adjusting for WT and gender. The exposure parameters (AUC, Cmin, Cmax) at steady-state showed dose proportionality over the range of 3–15 mg/Kg. A sigmoidal Emax inhibition model described the concentration-response relationship in GA patients with moderate variability. The VPC plots suggested that the model adequately predicted the observed GSK933776 effects on FBAM levels in GA patients.

Conclusions: The two-compartment model with linear elimination adequately described the PK of GSK933776. WT and gender were significant predictors of variability in PK. A sigmoidal inhibition model adequately described the effects of GSK933776 on reduction of plasma FBAM levels.