

Population PK/PD Modeling Supporting Accelerated Approval of an Intravenous Brain-Penetrant Enzyme Replacement Therapy for Mucopolysaccharidosis Type II

Mahdiar Sadeghi, Hunter Stephens, Heller Chen, Akhil Bhalla, Lorna Damo, Meng Fang, Fabian Model, Kirk Henne, Mirjam Trame, Shyeilla Dhuria

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Objectives: Tividenofusp alfa is an intravenous (IV) enzyme replacement therapy comprising iduronate 2-sulfatase enzyme fused to an engineered transferrin receptor (TfR)-binding Fc domain [1]. Tividenofusp alfa is the first FDA-approved medicine designed to leverage the TfR to enable delivery across the blood–brain barrier and address both central nervous system (CNS) and somatic manifestations of mucopolysaccharidosis type II (MPS II), a rare X-linked lysosomal disease. This analysis characterized the population pharmacokinetics (PK) and pharmacodynamics (PD) of tividenofusp alfa in participants with MPS II, linking exposure to heparan sulfate (HS) levels in cerebrospinal fluid (CSF) and urine, and evaluating covariate effects.

Methods: Population PK and sequential PK/PD modeling were performed using data from a Phase 1/2 study in 47 participants with MPS II (NCT04251026) [2], including serum PK and longitudinal CSF and urine HS concentrations following weekly IV infusions of tividenofusp alfa. The M3 method [3] was used to handle observations below the quantification limit. Semi-quantitative anti-drug antibody (ADA) titer levels were used to characterize ADA impact on PK. Covariate analysis was conducted based on FDA guidance [4]. Effect compartment models were used for CSF and urine HS biomarkers to characterize CNS and peripheral effects of tividenofusp alfa, and simulated PD data were normalized to age-dependent normal ranges [5]. The final PK/PD models were used to investigate exposure/response relationships for probability of normalization of PD biomarkers via simulation.

Results: The model that best captured PK was a two-compartment model incorporating linear clearance, and two nonlinear clearance mechanisms [6] representing target-mediated drug disposition (TMDD) and ADAs. Key covariates included age, body weight, and genotype. Post hoc PK simulations showed no significant differences across covariate subgroups for maximum concentration, and differences in area under the curve were within interparticipant variability. For the PK/PD model of CSF HS, increased ADA titers were associated with a prolonged effect compartment half-life ($t_{1/2}$), and lower baseline HS levels were associated with decreased maximal effect (I_{max}). For the urine HS model, I_{max} decreased with both decreasing age and baseline HS levels and half-maximal inhibitory concentration increased with higher ADA titers. Lower baseline urine HS levels were also associated with shorter effect compartment $t_{1/2}$. For both CSF and urine, the effect of baseline HS levels on I_{max} suggests a lower limit defined by normal ranges. Based on the population PK/PD simulations, higher serum tividenofusp alfa concentrations were associated with greater reductions of CSF and urine HS from baseline, with maximum effect achieved at 15 mg/kg weekly.

Conclusions: A population PK model incorporating TMDD- and ADA-related clearances, together with effect compartment PK/PD models, characterized tividenofusp alfa exposure and PD biomarkers. Simulated exposure differences across covariate subgroups were not statistically significant. Population PK/PD simulations supported the maintenance dose of 15 mg/kg for the accelerated approval of tividenofusp alfa.

Citations : [1] Arguello A et al. J Exp Med 2022;219:e20211057. [2] Muenzer J et al. N Engl J Med 2026;394:39–50. [3] Beal SL. J Pharmacokinet Pharmacodyn 2001;28:481–504. [4] FDA. 2022. Available from: <https://www.fda.gov/media/128793/download> (Accessed December 14, 2023). [5] Herber CB, et al. Mol Genet Metab 2026:109862. [6] Gibiansky L, Gibiansky E. J Pharmacokinet Pharmacodyn 2010;37:323–46. Keywords : Anti-drug antibody (ADA), target-mediated drug disposition (TMDD), transferrin receptor (TfR)

Reference

<https://acop2026.eventscribe.net/fsPopup.asp?PosterID=834039&efp=SkhTQIZDVkcyMjQ4NQ&mode=posterInfo>