

May 2026

Editor-in-Chief

CPT: Pharmacometrics & Systems Pharmacology

American Society for Clinical Pharmacology & Therapeutics (ASCPT)

**Subject: Manuscript submission — Mechanistic AI-QSP modelling of olipudase alfa in ASMD**

Dear Editor,

We are pleased to submit our manuscript entitled "Mechanistic AI-QSP Modelling of Olipudase Alfa Therapy in Acid Sphingomyelinase Deficiency: Adult-to-Paediatric Bridging and Regulatory-Grade Credibility Assessment" for consideration as an original research article in CPT: Pharmacometrics & Systems Pharmacology.

Olipudase alfa (Xenpozyme) is the first approved enzyme replacement therapy for non-CNS manifestations of acid sphingomyelinase deficiency (ASMD), with EMA registration in 2022 and FDA approval in 2024. Despite three published trials (ASCEND adult, ASCEND-Peds, ASCEND-OLE 2-year), no mechanistic model has yet been published that simultaneously calibrates adult and paediatric responses, projects long-term efficacy beyond the 2-year follow-up, and identifies an ADA-positive sub-population. Our work fills this gap with a regulatory-grade quantitative systems pharmacology (QSP) model encoded in SBML L3v2 and built using a 14-stage AI-assisted master pipeline.

We highlight the following novel contributions of the manuscript:

- First mechanistic QSP model jointly calibrated against adult and paediatric olipudase alfa data, with regulatory-grade ASME V&V40-2018 credibility documentation. All ten credibility gates G1–G10 are PASS or PASS-CONDITIONAL.

- Hierarchical Bayesian random-effects meta-analysis (PyMC NUTS,  $\hat{R} \leq 1.01$ , ESS > 400) yielding pooled Week-52/W104 estimates that lie inside the 94 % credibility interval of the v2.0 model on every analysed endpoint.
- Identification of saturation as the structural mechanism behind the absence of dose-response gradients in the ASCEND-OLE extension data, providing a quantitative argument for the current 3 mg/kg q2w label dose as the minimum effective dose at the 2-year horizon.
- Cross-population coherence of the global sensitivity dominance pattern between adult and paediatric populations, supporting unified parameter framework with paediatric rate-constant overrides — directly relevant to ICH E11(R1) paediatric extrapolation guidance.

All SBML files, calibration code, and the full regulatory artefact bundle are made available open-source under MIT/CC-BY-4.0 dual licence at <https://iqanova.org/atlas/asmd-xenpozyme-v2> to support reproducibility and community extension. We declare the conflicts of interest as listed in the manuscript.

We confirm that this manuscript has not been published elsewhere and is not under consideration by another journal. All authors have approved the manuscript.

Thank you for your consideration. We look forward to your editorial decision.

Sincerely,

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