

# IQANOVA ATLAS

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## ASMD / Xenpozyme QSP v2.0 — Model Equations Document

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### 1. Scope and Context-of-Use

This document specifies the differential-algebraic system underlying the IQANOVA ATLAS ASMD/Xenpozyme QSP v2.0 model. The Context-of-Use is adult-to-paediatric dose-bridging for olipudase alfa (Xenpozyme), long-term efficacy projection beyond the 2-year ASCEND-OLE horizon, and identification of an ADA-positive sub-population. The model is encoded in SBML Level 3 Version 2 with kinetic laws expressed as rate rules and dose administrations expressed as events. All equations are reproduced below in the same compartmental and naming convention used in the SBML files (`ASMD\_Xenpozyme\_QSP\_v2\_0\_adult.xml` and `ASMD\_Xenpozyme\_QSP\_v2\_0\_paediatric.xml`).

### 2. State variables (11)

Olipudase concentrations: plasma ( $E_p$ ), peripheral tissue ( $E_t$ ), and lysosomal ( $E_L$ ). Anti-drug antibody titre  $A$ . Lysosomal sphingomyelin  $S_L$ . Plasma biomarkers: lyso-sphingomyelin  $L$  and ceramide  $C$ . Tissue burdens: spleen  $B_s$ , liver  $B_l$ , lung  $B_g$ . Paediatric height- $Z$   $Z$ .

### 3. Pharmacokinetic equations (Layer 1)

$$dE_p/dt = -k_{p2t} \cdot E_p - k_{clr} \cdot E_p + \text{dose\_event}(t)$$

$$dE_t/dt = +k_{p2t} \cdot E_p - k_{t2l} \cdot E_t - k_{t2p} \cdot E_t$$

$$dE_L/dt = +k_{t2l} \cdot E_t - k_{lyse} \cdot E_L$$

Dose events deliver bolus to  $E_p$  every 14 days for 2 years (27 events).

### 4. Anti-drug antibody dynamics (Layer 2)

$$dA/dt = k_{ADA\_gen} \cdot E_p - k_{ADA\_clr} \cdot A$$

$$\text{Effective ASM activity: } k_{eff} = k_{cat} \cdot (1 - \epsilon_{neut} \cdot A / (1 + A))$$

$\epsilon_{neut}$  = ADA neutralisation potency. v2.0 sets  $\epsilon_{neut} = 0.20$  at population mean; sub-population analysis assumes  $\epsilon_{neut}$  up to 0.45.

### 5. Substrate and lysosomal compartment (Layer 3)

$$dS_L/dt = k_{in} - k_{eff} \cdot E_L \cdot S_L / (K_m + S_L)$$

### 6. Plasma biomarker dynamics (Layer 4)

$$dL/dt = k_{LSM\_gen} \cdot S_L - k_{LSM\_clr} \cdot L$$

$$dC/dt = \gamma_{cer} \cdot k_{eff} \cdot E_L \cdot S_L / (K_m + S_L) - k_{cer\_clr} \cdot C + \alpha_{burden} \cdot (B_s + B_l + B_g)$$

### 7. Tissue burden dynamics (Layer 5)

$$dB_s/dt = -k_{s\_res} \cdot \max(0, B_s - (1 - f_{s\_max}) \cdot B_{s,0}) \cdot ASM\_scale_s \cdot k_{eff}$$

$$dB_l/dt = -k_{l\_res} \cdot \max(0, B_l - (1 - f_{l\_max}) \cdot B_{l,0}) \cdot ASM\_scale_l \cdot k_{eff}$$

$$dB_g/dt = -k_{g\_res} \cdot \max(0, B_g - (1 - f_{g\_max}) \cdot B_{g,0}) \cdot ASM\_scale_g \cdot k_{eff}$$

Saturation maxima  $f_{*_max}$  enforce that no organ can resolve below  $(1 - f_{*_max}) \cdot baseline$ . These were calibrated in Stage 5 to ASCEND/ASCEND-OLE long-term plateau values.

### 8. Clinical observable mapping (Layer 6)

$$DLCO\_pct(t) = DLCO\_max\_pp \cdot \max(0, B_{g,0} - B_g(t)) / (B_{g,0} \cdot f_{g\_max})$$

$$Platelet\_pct(t) = 100 \cdot plt\_max\_frac \cdot \max(0, B_{s,0} - B_s(t)) / (B_{s,0} \cdot f_{s\_max})$$

$$Spleen\_pct(t) = -100 \cdot (B_{s,0} - B_s(t)) / B_{s,0}$$

$$Liver\_pct(t) = -100 \cdot (B_{l,0} - B_l(t)) / B_{l,0}$$

$$LysoSM\_pct(t) = -100 \cdot (L_0 - L(t)) / L_0$$

$$Ceramide\_pct(t) = -100 \cdot (C_0 - C(t)) / C_0$$

These linear-proportional formulae replaced the exponential-saturating forms used in v1.3. The change was made in Stage 5 of the pipeline because the exponential form operated in the linear regime over the ASCEND/ASCEND-OLE observation window, which prevented the fitter from converging. The reformulation reduced calibration SSR from 259 to 10.75.

### 9. Paediatric height-Z block

$$dZ/dt = k_{h\_catch} \cdot (Z_{asy} - Z(t))$$

Adult:  $k_{h\_catch} = 0$ ; paediatric:  $k_{h\_catch} \approx 3.5 \times 10^{-3} \text{ day}^{-1}$ ,  $Z_{asy} = +1.3$ .

### 10. Population-specific parameter overrides

Adult and paediatric populations share the structural model. Paediatric overrides (applied after v1.3 → v2.0 calibration): faster  $k_{p2t}$  (+38 %), faster  $k_{t2l}$  (+50 %), deeper  $f_{s\_max}$  and  $f_{l\_max}$

(+15 %), faster  $k_{h\_catch}$  ( $3.5 \times 10^{-3}$ ),  $Z_{asy} = +1.3$  (full catch-up). Full numerical comparison in `ASMD\_Xenpozyme\_QSP\_v2\_0\_parameter\_table.xlsx`, Sheet 3.

## 11. Initial conditions

All olipudase species and ADA titre start at zero. SM\_lysozyme, LysoSM and ceramide start at their physiological baselines (10, 15, 2 a.u. respectively for adult). Tissue burdens start at the population baselines ( $B_{s,0} = 11.7$  MN,  $B_{l,0} = 1.4$  MN,  $B_{g,0} = 6.0$  a.u. for adult; population-specific in paediatric). Height-Z starts at 0.0 for paediatric (defined relative to baseline at first dose).

## 12. Numerical solver

Python `scipy.integrate.solve\_ivp` LSODA,  $rtol = 1 \times 10^{-6}$ ,  $atol = 1 \times 10^{-9}$ . Dosing is implemented through impulsive event injections at the start of each interval. Calibration uses Nelder-Mead with the linear-proportional observable formulae; verification uses the same solver with halved tolerances (Stage 6 V&V).