

Population Pharmacokinetic and Pharmacodynamic Analyses of Olipudase Alfa in Adult and Pediatric Patients with the Rare Acid Sphingomyelinase Deficiency (Niemann-Pick) Lysosomal Storage Disease

Gilles Tiraboschi (1), Jean-Marie Martinez (1), Monica Kumar (3), Sreeraj Macha (2), David Fabre (1), Jing Li (2)

(1) Pharmacokinetics-Dynamics and Metabolism (PKDM), Translational Medicine and Early Development, Sanofi, R&D, Montpellier, France
(2) PKDM, Translational Medicine and Early Development, Sanofi, R&D, Bridgewater, NJ, USA (3) Rare Diseases & Rare Blood Disorders, Sanofi, R&D, Bridgewater, NJ, USA.

Background

Acid sphingomyelinase deficiency (ASMD), historically known as Niemann-Pick disease types A and B, is a rare and potentially life-threatening lysosomal storage disease for which currently only symptomatic treatments are available. It is characterized by reduced ASM activity, which results in progressive lysosomal accumulation of sphingomyelin, leading to tissue damage and organ dysfunction, including splenomegaly and infiltrative lung disease. Olipudase alfa is a recombinant human acid sphingomyelinase enzyme replacement therapy in late-stage development for non-central nervous system manifestations in ASMD patients. In clinical trials in adults and children with ASMD, olipudase alfa breaks down accumulated sphingomyelin, reduces spleen volume, and improves pulmonary function (measured by diffusing capacity of the lung for carbon monoxide, DLco) [1,2,3]. Lyso-sphingomyelin (lyso-SM), a deacylated form of sphingomyelin, is substantially elevated in plasma of ASMD patients. Since plasma lyso-SM is derived from target tissues, its reduction following IV infusion of olipudase alfa reflects its mechanism of action. Olipudase alpha was recognized as potential innovative treatment worldwide with breakthrough therapy designation in the United States (US), SAKIGAKE designation in Japan, PRIME designation in the European Union (EU) and recently approved in EU and Japan.

Objectives

The objectives of these population pharmacokinetic (popPK) and population pharmacokinetic/pharmacodynamic (popPK/PD) analyses were:

- To characterize PK of olipudase alfa in adult and pediatric ASMD patients
- To characterize pharmacokinetic/pharmacodynamic relationships with plasma lyso-SM
- To characterize relationships for spleen volume and DLco efficacy endpoints with plasma lyso-SM

Clinical Studies

Study	Phase	Population	Number of patients	IV infusions of olipudase alfa	
				Design	Doses
NCT00410566	1a	Adult	11	single dose	0.03, 0.1, 0.3, 0.6, 1.0 mg/kg
NCT01722526	1b	Adult	5 ^a	Q2W up to 26 weeks	within-patient dose escalation of 0.1 mg/kg up to 3.0 mg/kg
NCT02292654	1/2	Pediatric	20	Q2W up to 64 weeks	within-patient dose escalation of 0.03 mg/kg up to 3.0 mg/kg.
NCT02004704	2	Pediatric and adult	25 ^b	Q2W up to 9 years or marketing approval	3.0 mg/kg
NCT02004691	2/3	Adult	36	Q2W up to 4 years and 3 months ETP	within-patient dose escalation of 0.1 mg/kg up to 3.0 mg/kg

^a Four patients who participated in both NCT00410566 and NCT01722526 were treated as different individuals in the population PK analysis.
^b 25 patients who participated in both NCT01722526 and NCT02292654 were enrolled in NCT02004704.

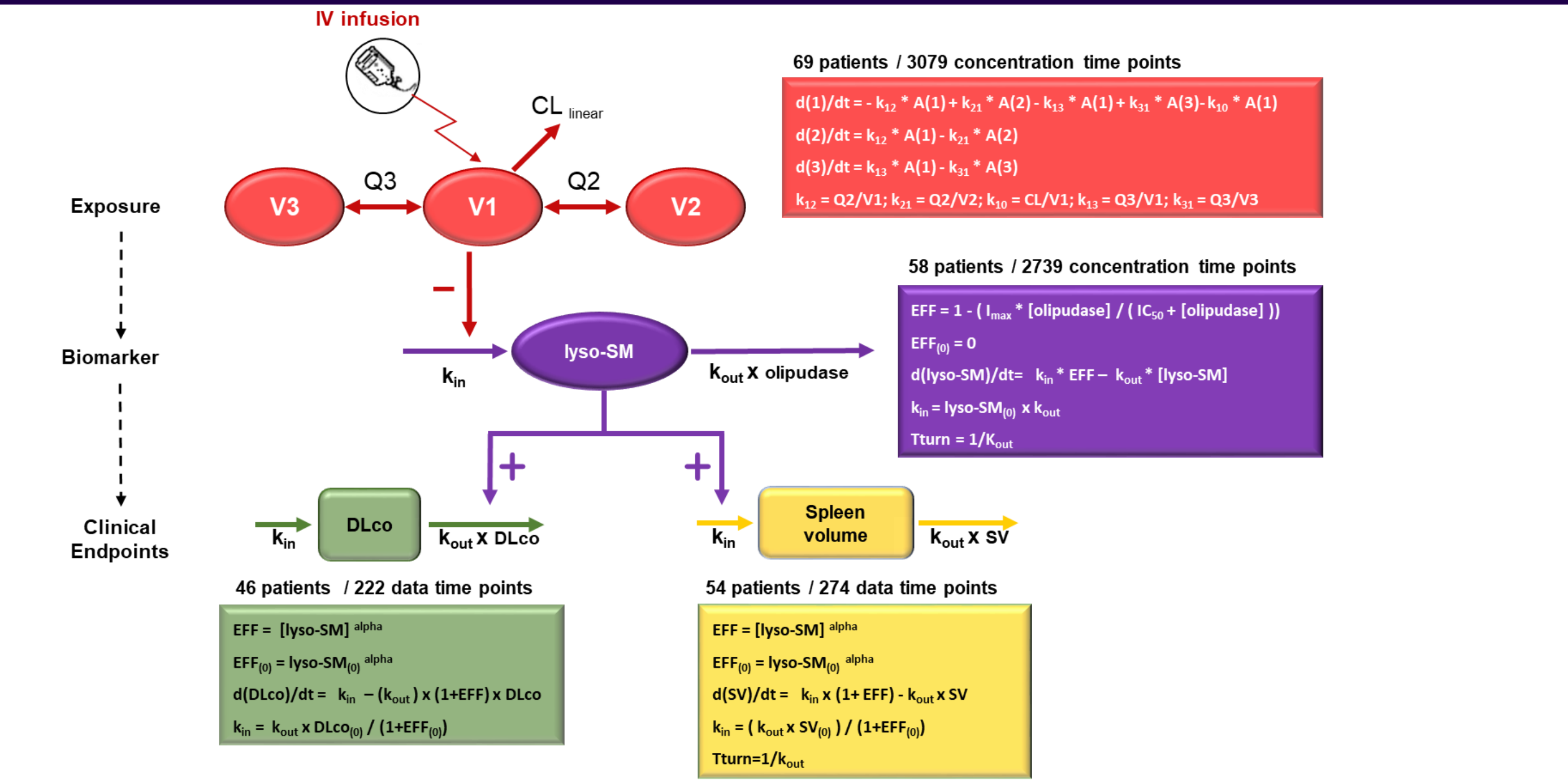
Methods

The popPK and popPKPD analyses were conducted using data pooled from adult and pediatric patients who received olipudase alfa with an intra-patient dose escalation (from 0.1 to 3 mg/kg for adult and from 0.03 to 3 mg/kg for pediatric patients, with target maintenance dose of 3 mg/kg) administered every 2 weeks intravenously.

A sequential approach was used to develop the popPK model followed by the development of the lyso-SM popPK/PD model using the predicted olipudase alfa plasma concentrations. Then the predicted lyso-SM concentrations were used to develop two models to characterize the time course of spleen volume and DLco clinical endpoints. For each model, a covariate analysis was performed and significant covariates were selected through a forward/backward selection process.

Models were developed in NONMEM 7.4.1 [4] using FOCEI algorithm for optimization. The qualification step was assessed using Prediction-Corrected Visual Predictive Check [5] and Sampling Importance Resampling iterative [6] methods. For the computation of exposure parameters and simulations, the mrgsolve package [7], embedded in an in-house shiny application [8], was used.

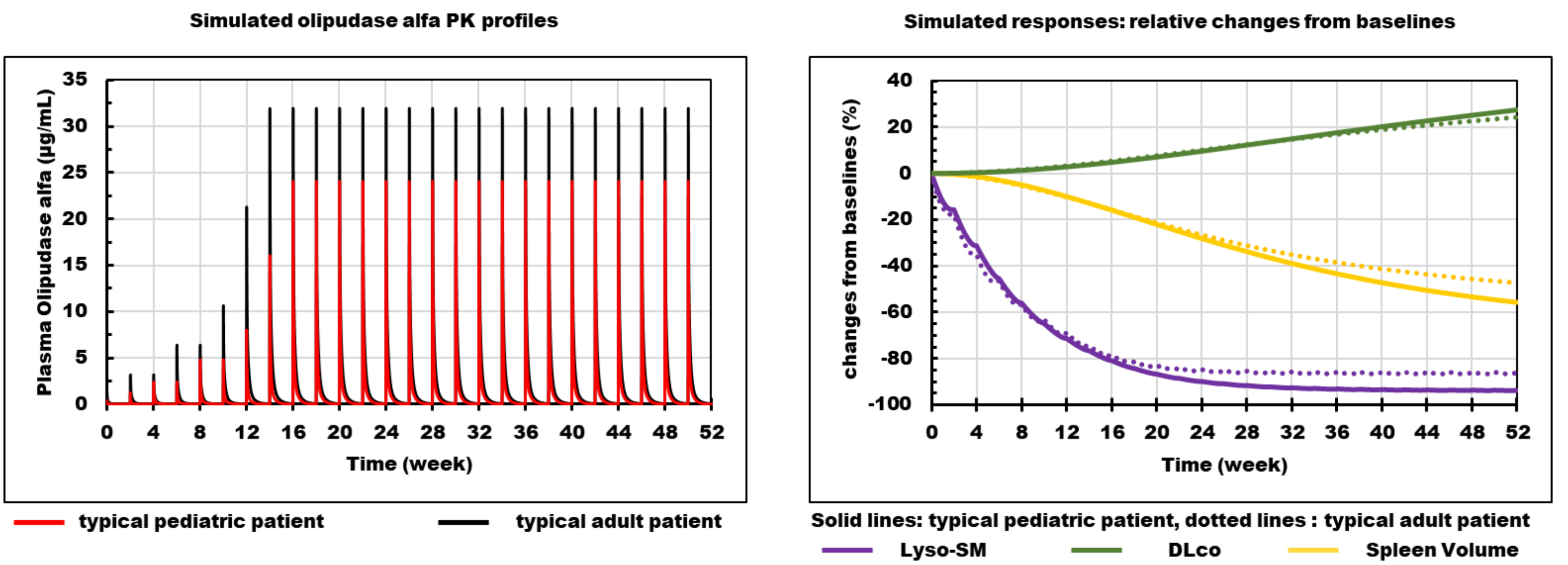
Results



Olipudase alfa PK model parameters			
Parameter	Estimate (CV%)	RSE (%)	Shrinkage (%)
Typical value of CL (L/h)	0.303	2.70%	-
Effect of PROD on CL	1.33	1.36%	-
Effect of WT on CL	0.545	7.72%	-
Typical value of V1 (L)	4.30	3.69%	-
Effect of WT on V1 (L)	0.993	6.61%	-
Effect of PROD on V1	1.22	3.32%	-
Typical value of V2 (L)	3.88	4.28%	-
Effect of WT on V2	0.938	6.62%	-
Effect of PROD on V2	1.26	4.46%	-
Typical value of V3 (L)	4.26	3.89%	-
Effect of WT on V3	0.519	11.1%	-
Typical value of Q2 (L/h)	0.586	4.62%	-
Typical value of Q3 (L/h)	0.0695	6.01%	-
Inter-individual variability			
$\omega^2 CL$	0.0489 (20.4%)	22.7%	2.96 %
$\omega^2 V1$	0.0393	24.2%	-
$\omega^2 V2$	0.0567 (24.2%)	23.2%	6.63 %
$\omega^2 V3$	0.0275 (16.7%)	38.3%	30.4 %
Residual variability			
Proportional term	0.0409 (20.4%)	22.7%	-
RSE: Percentage of Relative Standard Error (100% * SE / Estimate)			
The coefficient of variations were calculated considering log-normal variability for parameters using $CV(\hat{\theta}) = \sqrt{(\hat{\theta}^2 - 1)}$			
The expression of linear elimination clearance including covariates effects is: $CL = TVCL \times COV1^{1.000} \times (WT/63.9)^{0.002}$			
The expression of the central volume (V1) including covariates effects is: $V1 = TVV1 \times (WT/63.9)^{0.000} \times COV3^{0.000}$			
The expression of the first peripheral volume (V2) including covariates effects is: $V2 = TVV2 \times (WT/63.9)^{0.000} \times COV4^{0.000}$			
The expression of the second peripheral volume (V3) including covariate effect is: $V3 = TVV3 \times (WT/63.9)^{0.000}$			
PROD is the manufacturing process (0 or 1)			

Lyso-SM, Spleen Volume and DLco model parameters			
Parameter	Estimate (CV%)	RSE (%)	Shrinkage (%)
Typical value of Turn (h)	828	6.07%	-
Effect of AGE on Turn	-16.5	10.9%	-
Typical value of Imax	0.905	0.73%	-
Effect of WT on Imax	-0.241	18.4%	-
Typical value of IC50 (mg/L)	0.00838	12.4%	-
Effect of WT on IC50	2.6	9.67%	-
Typical value of Turn (h)	3808	10.4%	-
Typical value of alpha	0.456	3.70%	-
Typical value of Kin (1/% predict DLco)/h	0.00693	18.6%	-
Typical value of alpha	0.264	8.06%	-
Typical value of Baseline (1/% predict DLco)	49.7	3.6%	-
Inter-individual variability			
$\omega^2 Turn$	0.234 (51.4 %)	24.7%	6.56 %
$\omega^2 Imax$	0.14 (38.8 %)	41.8%	28.2 %
$\omega^2 IC50$	2.43 (322 %)	24.5%	3.34 %
$\omega^2 Turn$	0.221 (49.7 %)	35.7%	19.8 %
$\omega^2 alpha$	0.0322 (18.1 %)	28.9%	18.9 %
$\omega^2 alpha$	0.202 (47.4 %)	34.5%	4.86 %
Correlation $\rho_{Baseline} - \rho_{alpha}$	-0.103	27.4%	-
$\omega^2 Baseline$	0.0586 (24.6 %)	22.2%	0.802 %
$\omega^2 Kin$	1.26 (159 %)	30.7%	18.6 %
Residual variability			
Proportional term	0.035 (18.7 %)	4.52%	-
Additive term (ng/mL) ²	48	21.5%	-
Proportional term	0.00778 (8.82 %)	10.9%	-
Proportional term	0.00426 (6.53 %)	12.7%	-
$T_{turn} = 1/k_{out}$ turnover time			
RSE: Percentage of Relative Standard Error (100% * SE / Estimate)			
The coefficient of variations were calculated considering log-normal variability for parameters using $CV(\hat{\theta}) = \sqrt{(\hat{\theta}^2 - 1)}$			
The expression of Turnover time including covariate effect is: $Turn = TVTurn \times COV5 \times (AGE - 25.83)$			
The expression of Imax including covariate effect is: $Imax = TVImax \times (WT/60.5)^{0.001}$			

Simulations



Conclusions

A sequential modeling approach was used to characterize the relationship between olipudase alfa plasma concentrations and reduction of plasma lyso-SM, and subsequent reduction of spleen volume or elevation of DLco over the time course of treatment. Olipudase alfa exposures were lower in pediatric patients than in adult patients. However, for both adult and pediatric populations, plasma concentrations are maintained above IC50 value, leading to comparable reduction of plasma lyso-SM. The simulated responses of spleen volume decrease and DLco increase were similar in pediatric and adult patients.

References

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Disclosures:

All authors are employees of Sanofi and may hold shares and/or stock options in the company. The opinions, conclusions, and interpretation of the data are the responsibility of the authors.

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