QSP-model based assessment of mechanistic similarity of disease and response to olipudase alfa between pediatric and adult Acid Sphingomyelinase Deficiency (ASMD) patients

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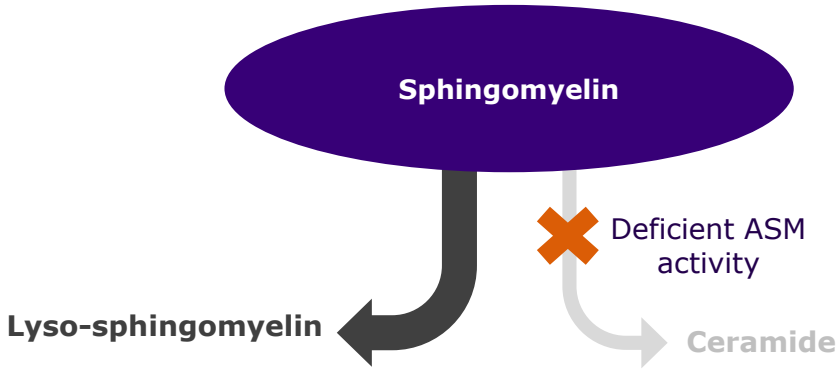
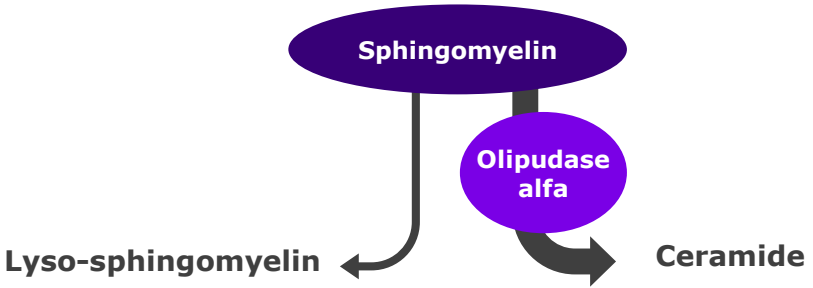
Olipudase alfa (Xenpozyme) is the first treatment for ASMD

Acid sphingomyelinase deficiency (ASMD) is a lysosomal storage disease due to loss-of-function mutations in *ASM* gene

Deficient ASM enzyme activity can lead to progressive sphingomyelin accumulation in macrophages in organs (lung, spleen, etc.)[1,2]



Olipudase alfa (recombinant human ASM) was developed as an enzyme replacement therapy for non-CNS manifestation of ASMD in children and adults[3]



1. Xu YH et al. J Lipid Res. 2010;51:1643–75. 2. Schuchman EH, et al. Niemann-Pick disease types A and B: Acid sphingomyelinase deficiencies. In: Scriver CR et al., eds. The Online Metabolic and Molecular Bases of Inherited Disease (OMMBID). New York, NY: McGraw-Hill. Chap. 144:1–65. 3. Keam SJ. Olipudase Alfa: First Approval. Drugs. 2022;82:941–47.
ASM, acid sphingomyelinase; ASMD, acid sphingomyelinase deficiency.

Xenpozyme is the first treatment for ASMD

CLINICAL DEVELOPMENT

Clinical development program consisted of 5 clinical trials in adult and pediatric patients including

- →One Ph2 open label adult trial[1,2]
- →One placebo-controlled pivotal adult trial[3]
- →One pediatric trial with an open-label design[4]
  - Type A patients were not included in the open label pediatric trial

M&S OBJECTIVES

Substantial evidence of effectiveness was established with the adult pivotal trial

Partial pediatric extrapolation from pivotal ASCEND adult trial

- →Quantitative System Pharmacology (QSP)
  - →Quantify disease and therapeutic response similarity in pediatric and adult ASMD patients

Full extrapolation of type A patients

- →Quantitative System Pharmacology (QSP)
  - →Predict Xenpozyme efficacy in patients with most extreme enzyme deficiency

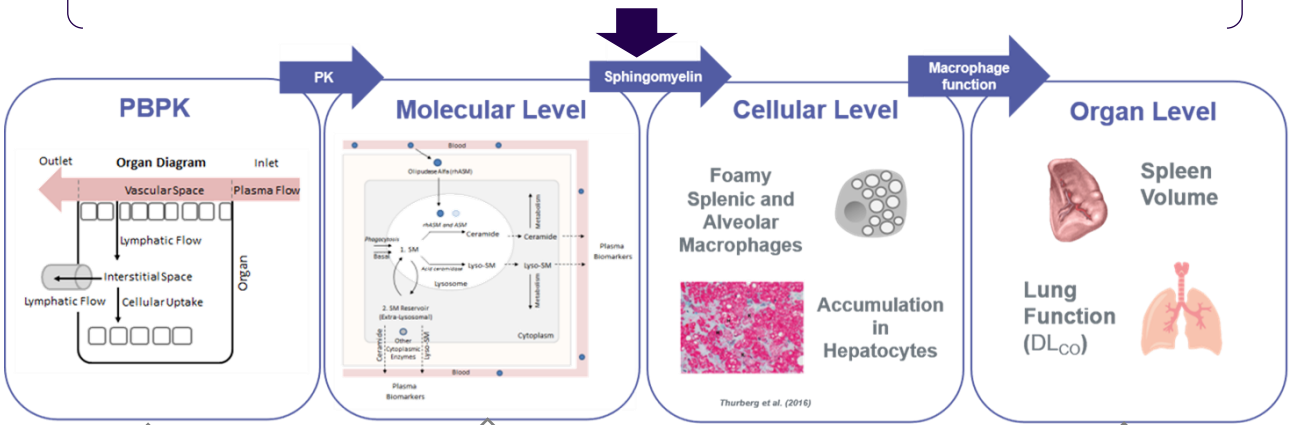
1. Wasserstein, M. P. et al. Successful within-patient dose escalation of olipudase alfa in acid sphingomyelinase deficiency. Mol. Genet. Metab. 116, 88–97 (2015). 2. Wasserstein, M. P. et al. Olipudase alfa for treatment of acid sphingomyelinase deficiency (ASMD): safety and efficacy in adults treated for 30 months. J. Inherit. Metab. Dis. 41, 829–838 (2018). 3. Wasserstein M, Lachmann R, Hollak C, Arash-Kaps L, Barbato A, et al. A randomized, placebo-controlled clinical trial evaluating olipudase alfa enzyme replacement therapy for chronic acid sphingomyelinase deficiency (ASMD) in adults: One-year results. Genet Med. 2022 Jul;24(7):1425-1436.. 4. Diaz, G.A., Jones, S.A., Scarpa, M. et al. One-year results of a clinical trial of olipudase alfa enzyme replacement therapy in pediatric patients with acid sphingomyelinase deficiency. Genet Med 23, 1543–1550 (2021).

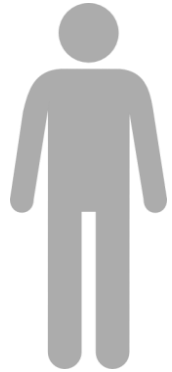
QSP model allows for multiscale representation of ASMD that integrates diverse datasets

PRECLINICAL DATA
in-vitro assays
Preclinical datasets

PRIOR KNOWLEDGE
Physiology
Sphingomyelin biology

CLINICAL DATA
Natural History Studies
Clinical trials





Quantitative Systems Pharmacology based **virtual patients**

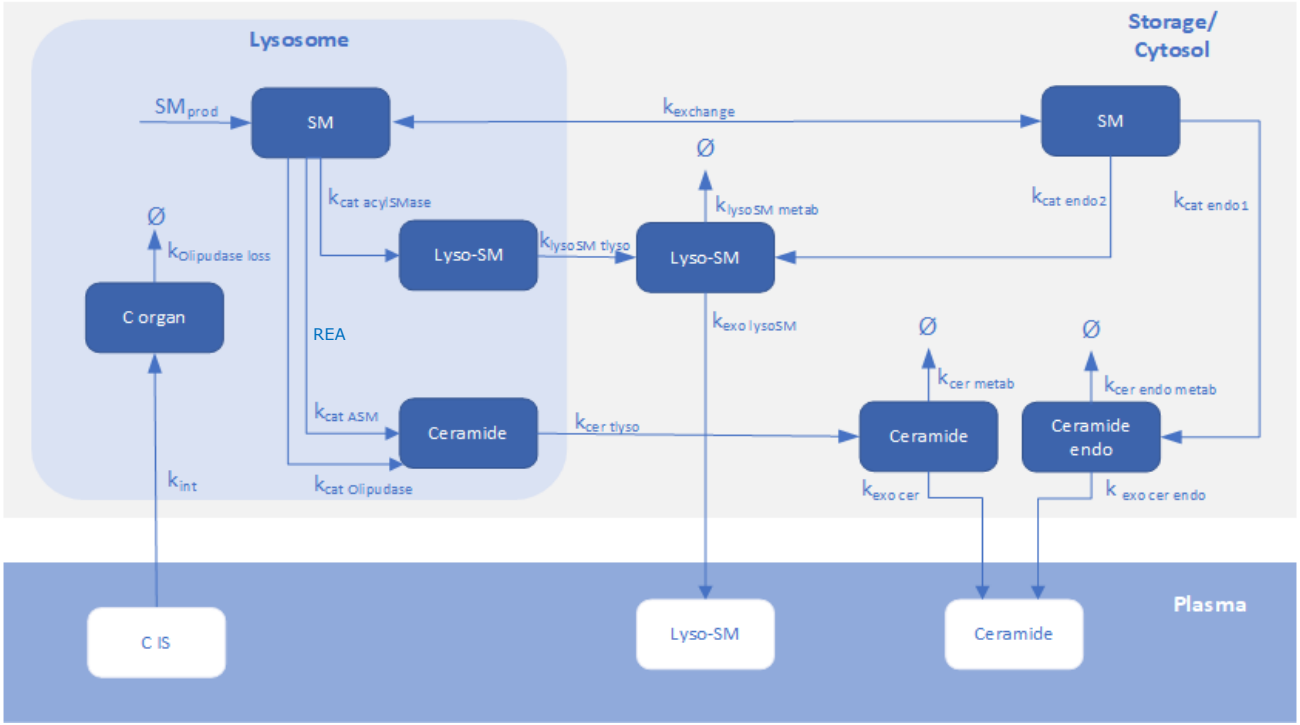
PK

Plasma Ceramide and Lyso-sphingomyelin

Clinical endpoints: Spleen Volume, DLco

Kaddi CD, Niesner B, Baek R, et al.,. Quantitative Systems Pharmacology Modeling of Acid Sphingomyelinase Deficiency and the Enzyme Replacement Therapy Olipudase Alfa Is an Innovative Tool for Linking Pathophysiology and Pharmacology. CPT Pharmacometrics Syst Pharmacol. 2018 Jul;7(7):442-452.

QSP molecular sub-model describes mechanistically ASM enzyme deficiency and the MoA of Olipudase alfa



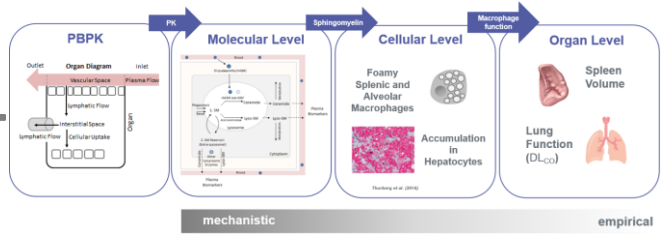
QSP model contains biologically interpretable processes and associated parameters to quantify disease severity

Observed individual patient data

Adult Patients

Pediatric Patients

individual patient calibrations to generate virtual twins



Generate virtual twins

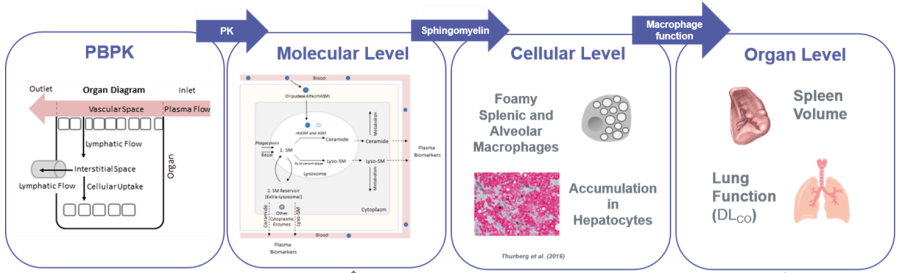
Adult Virtual Twins

Pediatric Virtual Twins

Virtual Twins: QSP model to bench-mark pediatric vs adults AMSD patients

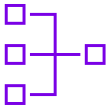
- Identification of subset of parameters to generate virtual twins
- Modular and sequential parameterization of sub-models
- Same calibration strategy for both pediatric and adult patients

individual patient calibrations strategy



Model output Calibration parameters	PK n=1	Plasma Ceramide and Lyso-sphingomyelin n= 5	Clinical endpoints: Spleen Volume n=4, DLco n=2

Mechanistic similarity between pediatric and adult patients can be quantified from QSP-virtual twins analysis with these criteria:



Same model structure
The same mathematical representation of key pathophysiology is used to construct both pediatric or adult virtual twins

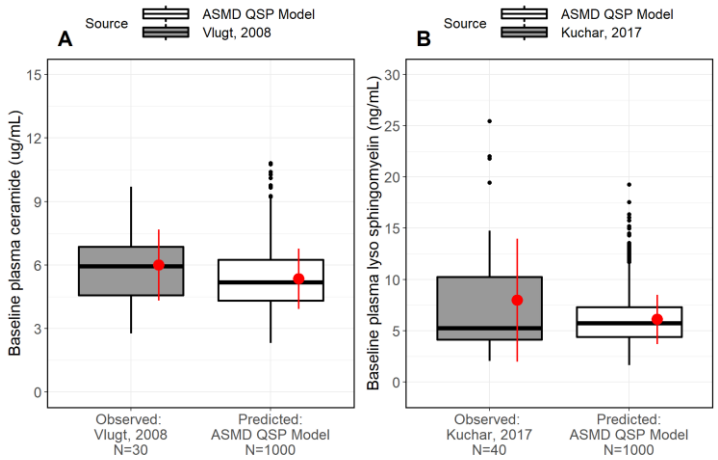
Similar accuracy
Biology represented in QSP model describes pediatric and adult patient data in a similar manner

Similar parameter values
Parameters that describe biologically interpretable processes are similar in magnitude in pediatric and adult virtual twins

Similar parameter sensitivities
The influence of each key parameter on an endpoint or biomarker is similar in pediatric or adult virtual twins

QSP model performance was validated using datasets not utilized during model development

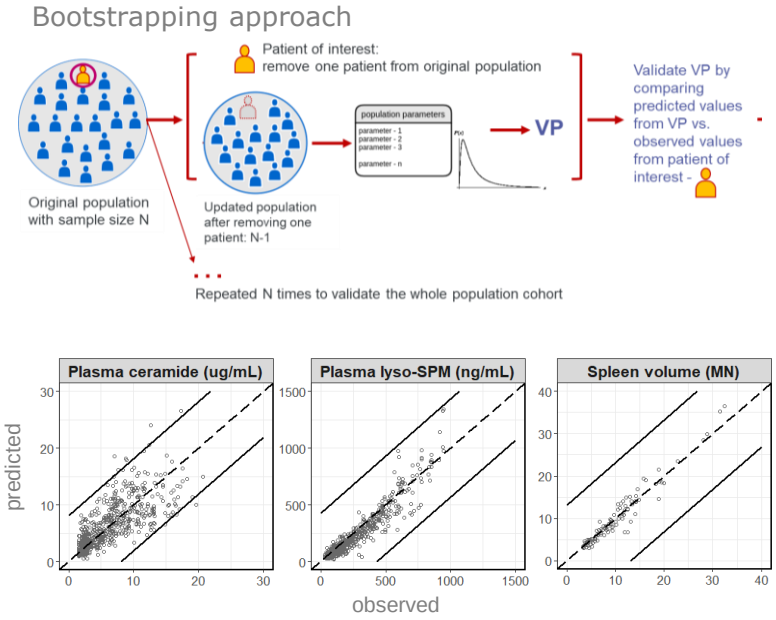
Virtual population of healthy individuals



Black thick line = median; Grey/White box = 25th – 75th percentile; red dot with red point range = mean +/- standard deviation observed data

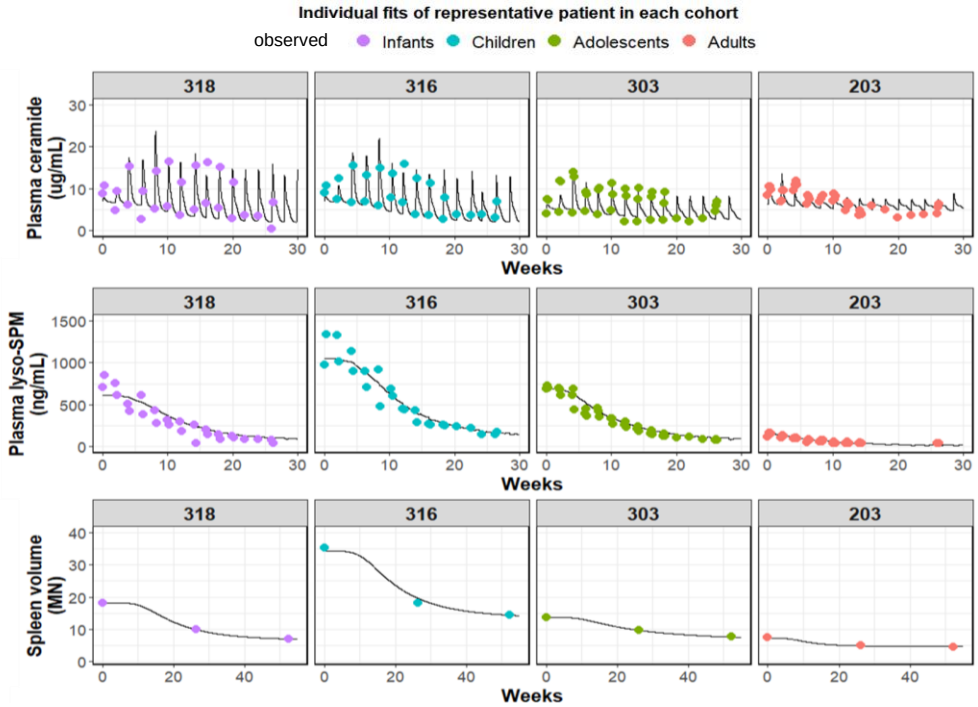
Kuchar L, Sikora J, Gulinello ME, Poupetova H, Lugowska A, Malinova V, et al. Quantitation of plasmatic lysosphingomyelin and lysosphingomyelin-509 for differential screening of Niemann-Pick A/B and C diseases. Anal Biochem. 2017 May 15;525:73–7
Ghauharali-van der Vlugt K, Langeveld M, Poppema A, Kuiper S, Hollak CEM, Aerts JM, et al. Prominent increase in plasma ganglioside GM3 is associated with clinical manifestations of type I Gaucher disease. Clin Chim Acta Int J Clin Chem. 2008 Mar;389(1–2):109–13.

Virtual population of paediatric ASMD patients



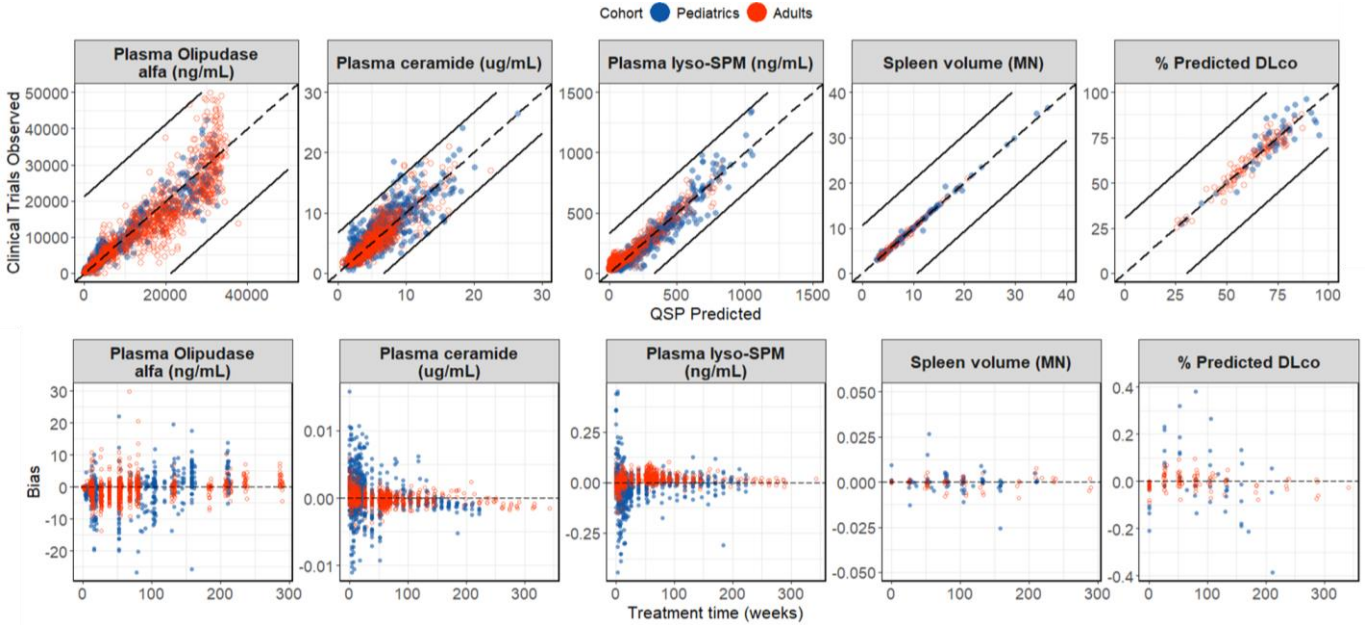
Same QSP model structure for both pediatric and adult virtual twins

Same biological representations can describe adequately observed biomarker and endpoint datasets irrespective of severity or age



Similar accuracy for pediatric and adult virtual twins

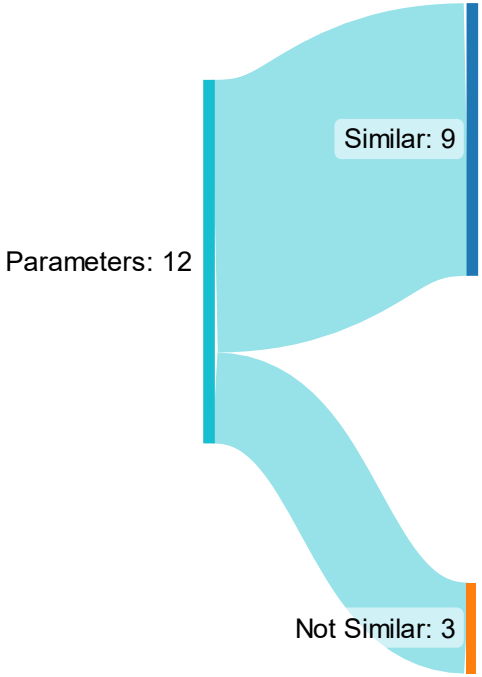
Goodness of fit plots exhibit similar agreement with data for patients of all age cohorts

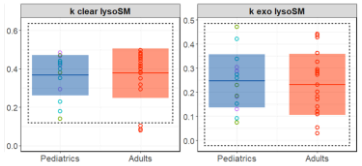


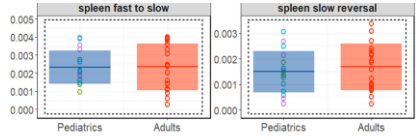
Accuracy metrics were comparable across cohorts

Most model parameters values that defined virtual twins were similar in pediatric and adult cohorts

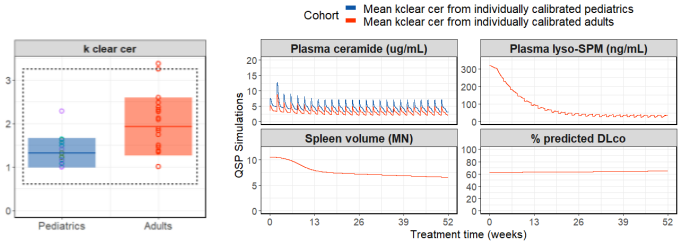
Similar parameters values between pediatric and adults that describe biomarkers and endpoints dynamics

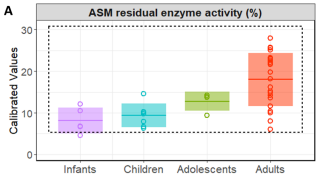






- Solid line: Cohort mean
- Shaded box: Mean +/- St. dev.
-- Dashed line: Two st. dev. from adult mean

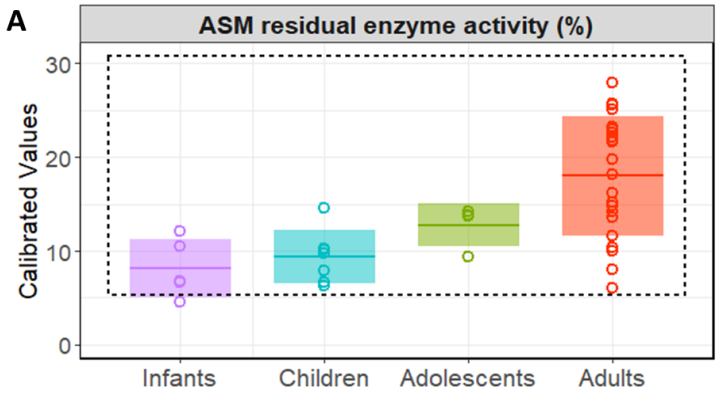




ASM residual enzyme activity (REA), a clinically meaningful parameter, differs in adult vs pediatric virtual twins

Percent of ASM enzyme activity compared to healthy value

Represents the severity of enzyme deficiency



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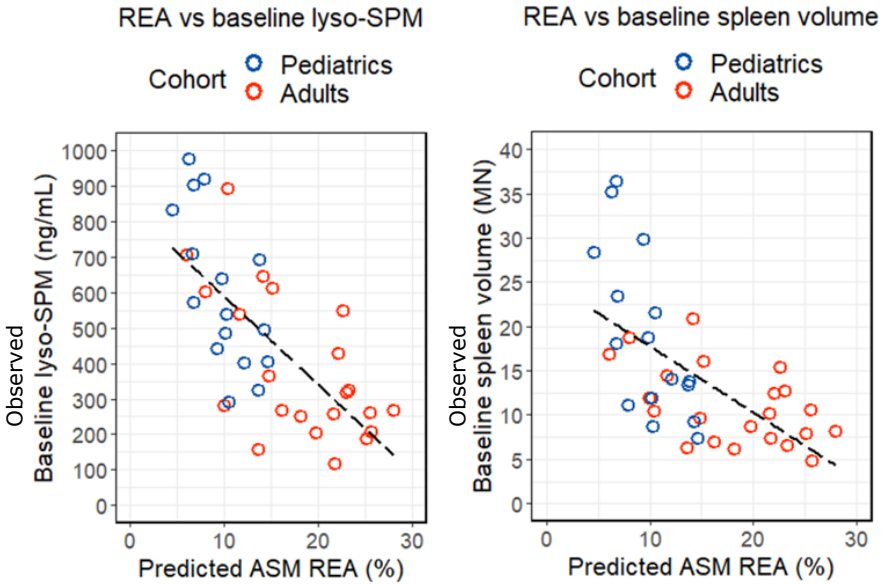
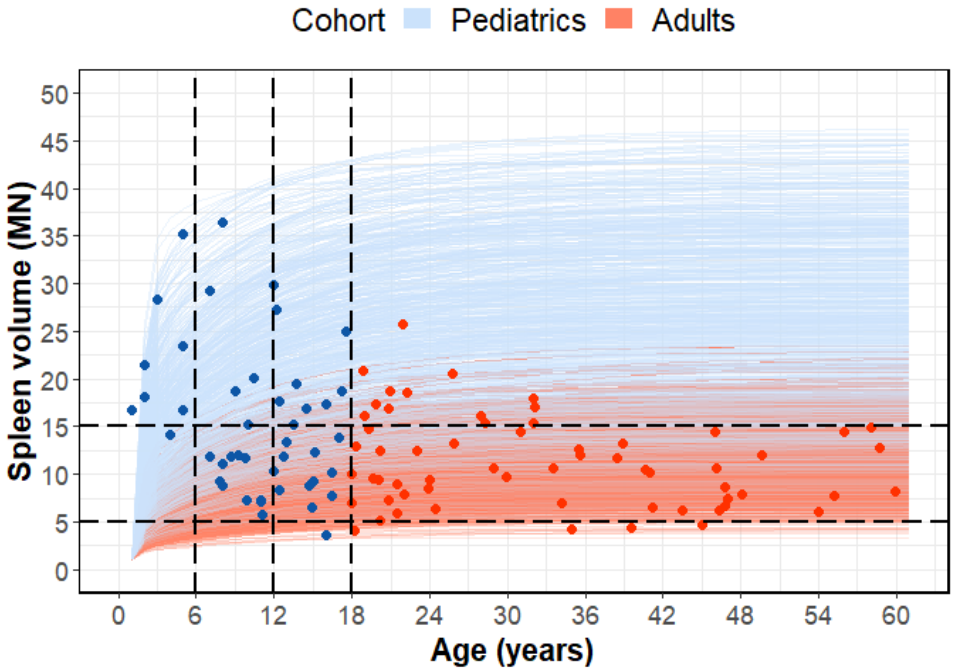
REA parameter values correlate with observed endpoint severity



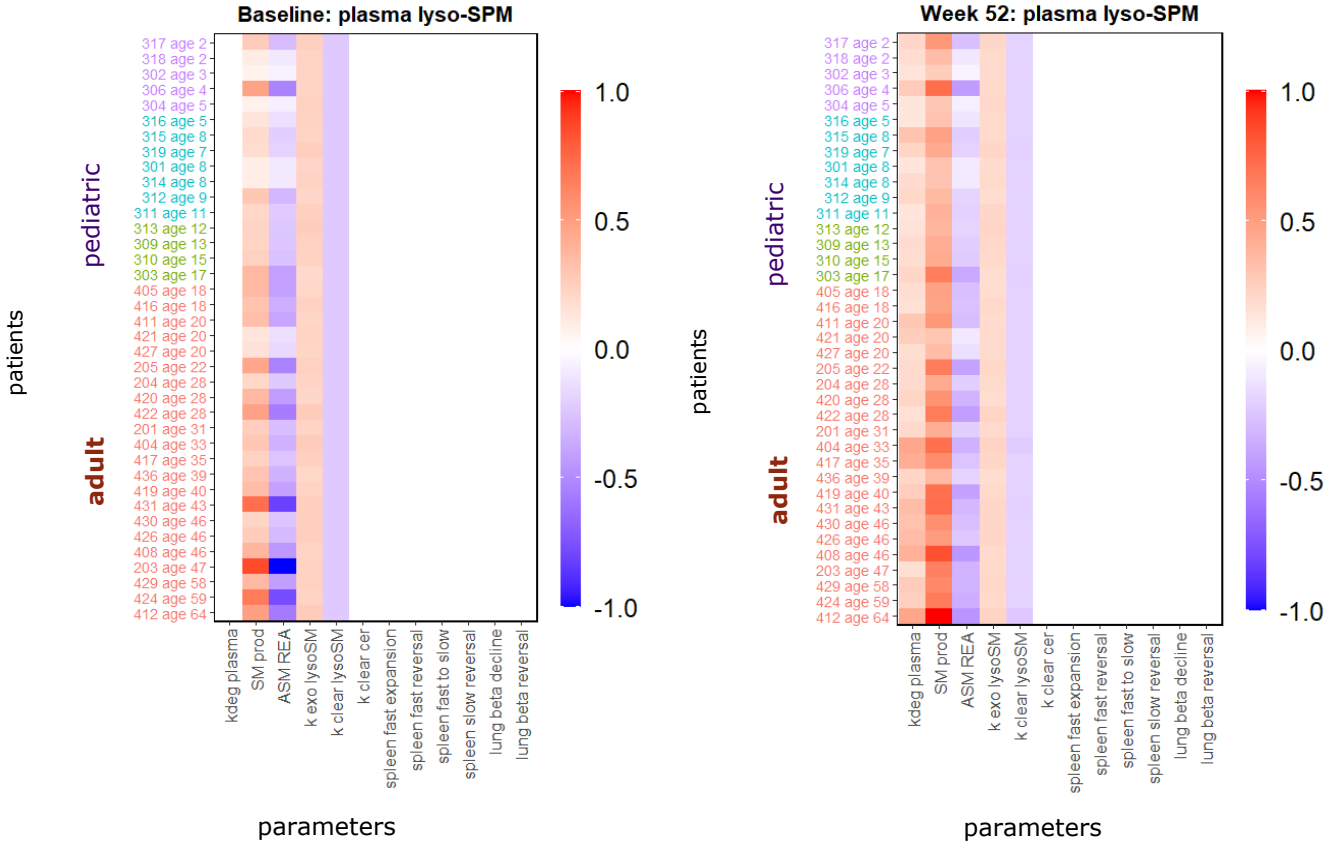
Virtual patient population of ASMD patients simulated from birth predicts a continuum of disease burden

- Vpop derived from sampling parameter distributions from virtual twins
- Highlights continuum of disease burden between pediatric and adult patients
  - Observed treatment naïve data shown as scatter overlay
  - Any differences interpreted by survivor/ diagnosis differences reported in data [1,2, 3]



1. McGovern MM, Wasserstein MP, Bembi B, Giugliani R, Mengel KE, Vanier MT, et al. Prospective study of the natural history of chronic acid sphingomyelinase deficiency in children and adults: eleven years of observation. Orphanet J Rare Dis. 2021;16(1):212. 2. Cassiman D, Packman S, Bembi B, Turkia HB, Al-Sayed M, Schiff M, et al. Cause of death in patients with chronic visceral and chronic neurovisceral acid sphingomyelinase deficiency (Niemann-Pick disease type B and B variant): Literature review and report of new cases. Mol Genet Metab. 2016;118(3):206-13. 3. McGovern MM, Lippa N, Bagiella E, Schuchman EH, Desnick RJ, Wasserstein MP. Morbidity and mortality in type B Niemann–Pick disease. Genetics in Medicine. 2013;15(8):618-23.

Parameters sensitivities values were similar in pediatric and adult virtual twins



QSP Analysis Conclusions

Same pathophysiology described in model can capture both pediatric and adult datasets in a similar manner supporting mechanistic similarity of disease and response

The QSP analysis supports the view that there are no distinct patient sub-populations defined by age but a continuum of disease burden due to variability in disease severity

Impact

*"Review team conclude that the submitted QSP model provides **insight on mechanism of ASMD progression and response to olipudase alfa treatment** in pediatric and adult ASMD patients. The simulation results supported the **mechanistic similarity of disease and response to olipudase alfa** between pediatric and adult ASMD patients. These results **support the approval of olipudase in pediatric patients**, in addition to the observations from clinical trials in pediatric and adult patients"*

FDA integrated review Aug 2022: feedback on QSP model

"The safety and effectiveness of XENPOZYME for the treatment of non-central nervous system manifestations of acid sphingomyelinase deficiency (ASMD) have been established in pediatric patients down to birth."

FDA label

https://www.accessdata.fda.gov/drugsatfda_docs/nda/2022/761261Orig1s000IntegratedR.pdf

Acknowledgments

DDS/TDM
- RJ Leiser
- Mengdi Tao
- Chanchala Kaddi
- Bradley Niesner
- Thomas Klabunde

PKDM
- Jing Li
- Gilles Tiraboschi
- Jean-Marie Martinez
- David Fabre
- Raj Macha
- Vanaja Kanamaluru

Olipudase/Xenpozyme project team
- Monica Kumar
- Andreas Jessel
- Catherine Ortemann-Renon
- Federica Albissola
- Vanessa Davidson
- John Salcedo
- Qi Zhang
- Yong Kim
- Atef Zaher
- Rachel Palmer
- Kelly George
- Mario Aguilar
- Joyce Tay

Sanofi R&D Digital team
- Daniel Biehle
- Quan Wan
- Tuan Nguyen
- Bruno Vareilles

Past Colleagues
- Ruth Abrams
- Karim Azer
- Sourish Chakravarty
- Spyros Stamatelos
- Jeff Barrett

KOL Mount Sinai
Ed Schuchman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Q&A

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