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Applications of Virtual Patients in Pharmaceutical Development

Dr. Britta Wagenhuber

Head Translational Disease Modeling I&I,
Sanofi R&D

DGRA Annual Congress
June 20th, 2024

Imagine

We explore treatment efficacy & safety of **all** drug candidates in **virtual patients** to gate the best ones into the clinic with the right dose & patients in clinical trials

Comparator

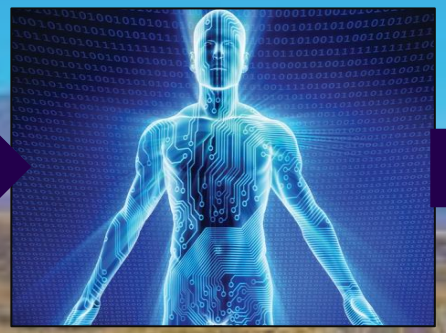
Drug candidate

In-vitro & ex-vivo data

Predicted human exposure

input

Virtual Patients



output

- Best in disease?
- In which patients?
- Biomarker for patients with better response?

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Translational Disease Modeling

Home of “virtual patients”
Driving in-silico drug development at Sanofi

Translational Disease Modeling **integrates multi-modal data** in computational models to build digital twins and **virtual patients**.

In-silico clinical trials in virtual patients created to explore the clinical benefit of drug candidates as novel treatment options for patients.

Main Impact Areas ….

1. **Move right asset into clinic “Clinical Translation"**
2. **Move right asset into next clinical phase “Differentation"**
3. **Replace need for clinical trials** in pediatric & vulnerable patients
4. **Optimize Clinical Trial Design*** * dose, patient, combination
5. **Impact Regulatory Decisions**

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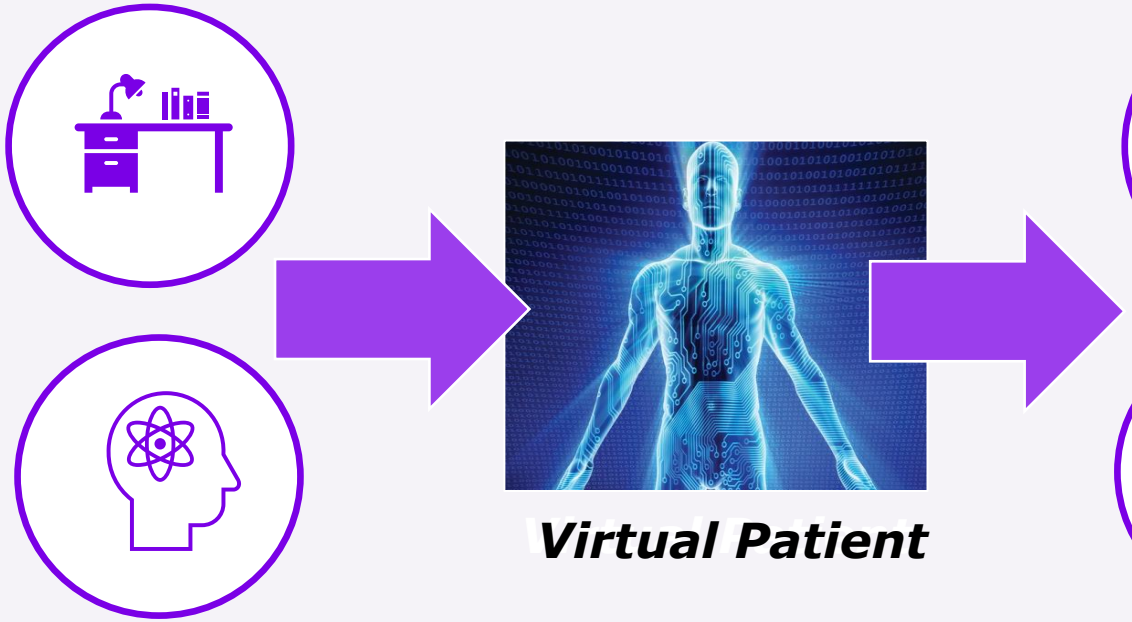
Quantitative Systems Pharmacology (QSP) Modeling

Integrating available data on physiology, pathophysiology, pharmacology

Capturing current knowledge



Virtual Patient

*Allowing to simulate dynamic reponse to therapeutic treatment**

*Providing causal connection of all underlying processes from drug binding up to treatment response***

* at molecular, cellular, and organ level up to relevant clinical endpoint

** in a QSP model all relevant processes are captured in ordinary differential equations, allowing the simulation of time-series data and providing a causal connection of all model components

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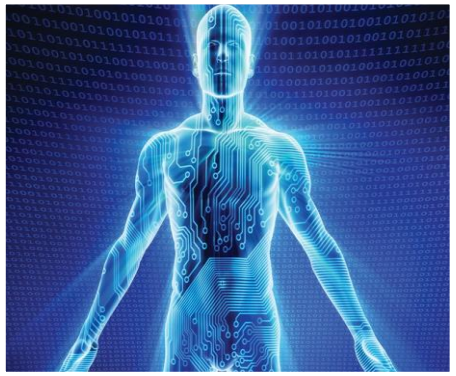
Proof-Points for Digital Twinning Empowered by QSP



Simulating novel drug assets **vs marketed drugs in virtual patient to predict** clinical efficacy	Gating **best-in-disease** drug candidates into clinic/next phase	**Improve Decision**
Simulating **different scenarios of clinical trial settings** (dose, patient) in virtual patients	Optimizing **clinical trial design – right** drug dosing and **right** patient	**Increase PoS**
Simulating treatment response in virtual patients of **vulnerable patient subgroup**	**Replacing need for clinical trials** in vulnerable patients	**Accelerate Development**

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Accelerating Development & Optimizing Clinical Trial Design through Virtual Asthma Patients

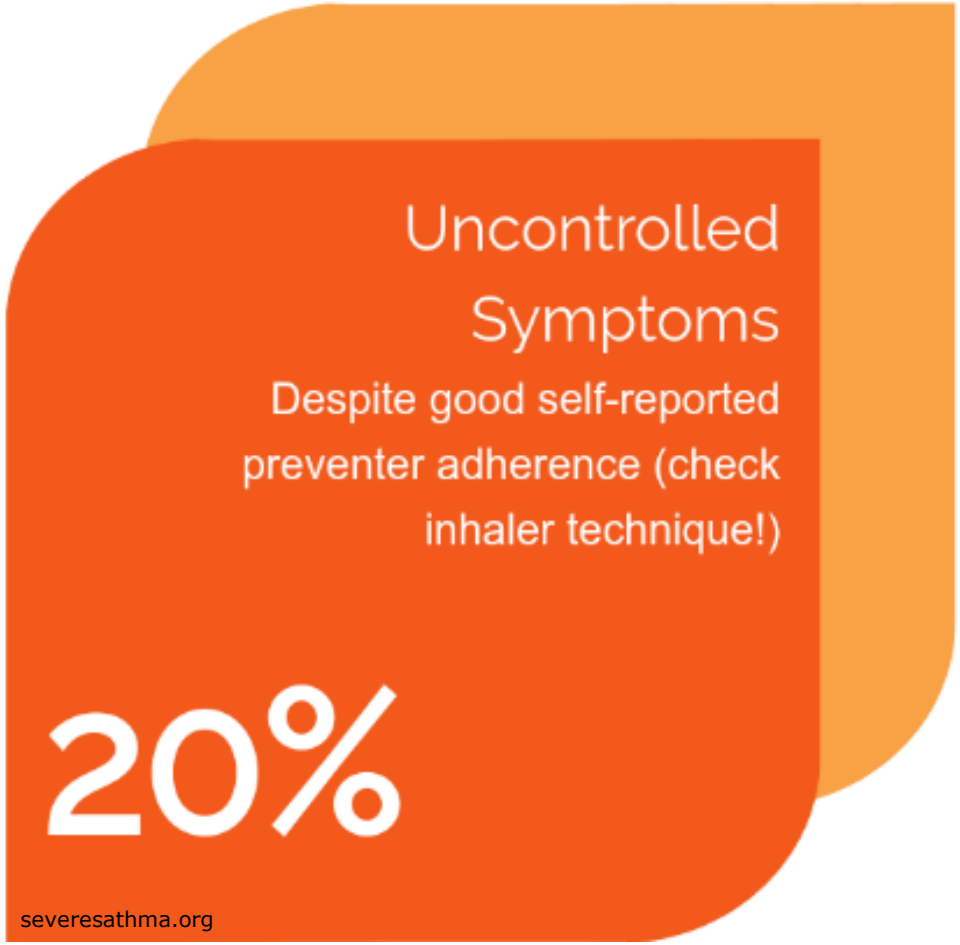
Britta Wagenhuber, Anastasios Siokis, Lieselot Bontinck, Annemie Deiteren, Benjamin Surratt, Heribert Staudinger

Sanofi R&D

Background & Challenge

- Asthma is a chronic respiratory condition that affects 262m patients with 461k deaths (WHO 2019)
- 20% (>52m) of Asthmatics require add-on therapies
- Biologics are common add-on therapies
- Still many patients do not respond
- Need for new drugs/modes of action

- **QSP modeling support for**
  - **new drug candidates**
  - **first- or best-in-class drugs**
  - **clinical trial design and optimization**
  - **optimization for dose and regimen selection**



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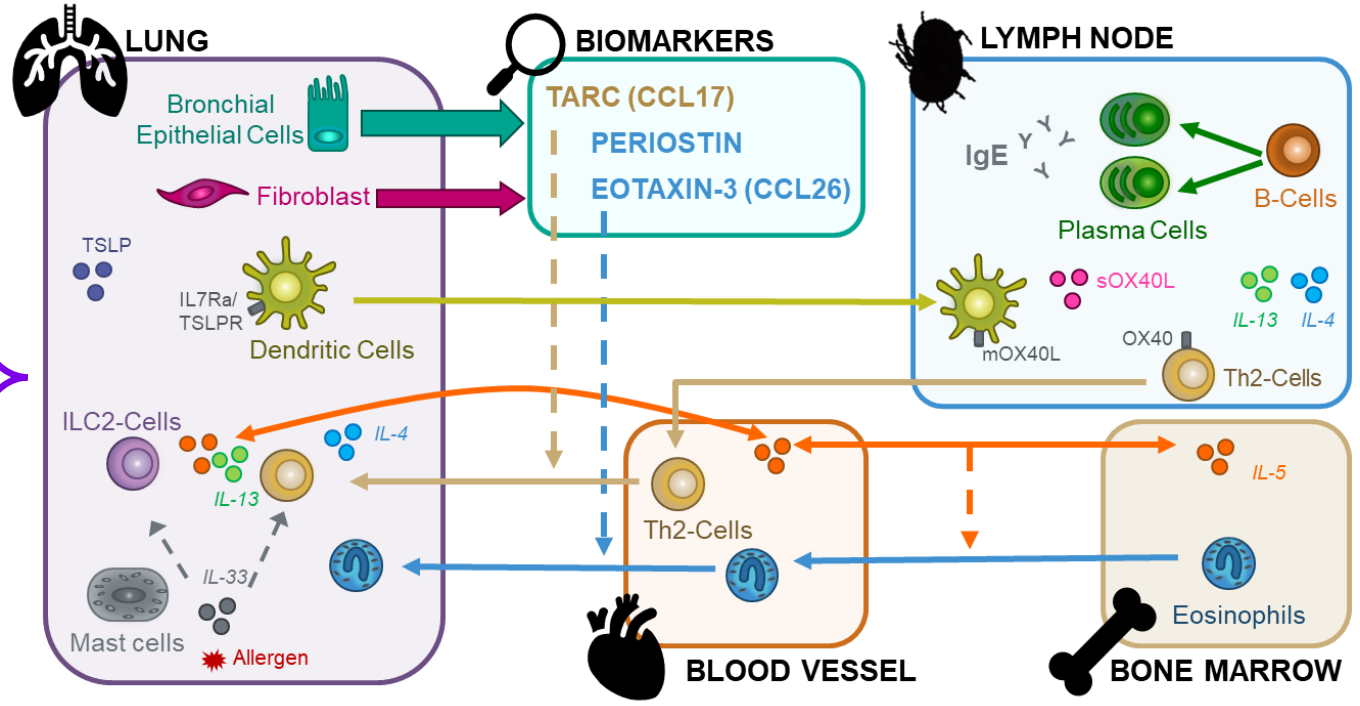
Virtual Asthma Patients – Underlying QSP Framework

Providing a multiscale view of asthma by integrating key processes of Th2 biology and connecting mode of action of Th2 biologics to key biomarkers and clinical endpoints***

Integrate available data on
Biology
Pathophysiology
Pharmacology

Capturing current **knowledge**



THERAPIES

- ❑ Itepekimab (a-IL33)
- ❑ Dupilumab (a-IL4R)
- ❑ Mepolizumab (a-IL5)
- ❑ Benralizumab (a-IL5R)
- ❑ Lebrikizumab (a-IL13)
- ❑ Oxelumab (a-OX40L)
- ❑ Tezepelumab (a-TSLP)
- ❑ Amlitelimab (a-OX40L)
- ❑ Lunsekimig (a-IL13/TSLP)

* *Calibrated and validated with preclinical data and data from Dupilumab, Mepolizumab, Lebrikizumab and Tezepelumab clinical trials*
** *AAER, FEV1, FeNO, Eosinophils, Immunoglobulin E (IgE), TARC, Periostin, Eotaxin-3*

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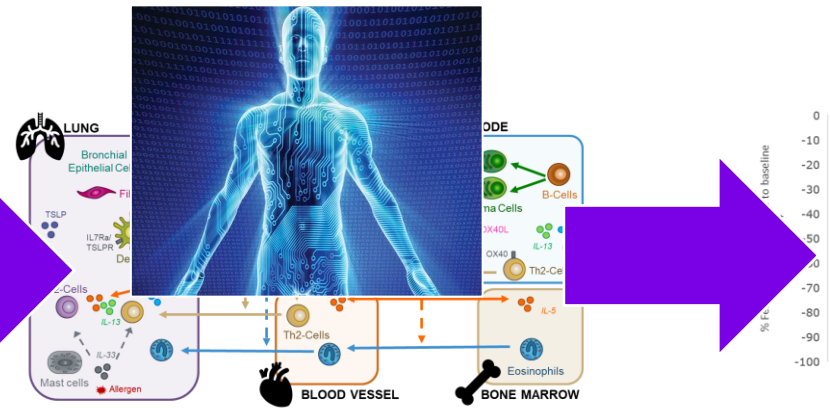
QSP: Quantitative Systems Pharmacology
AAER: Annualized Asthma Exacerbation Rate
FEV1: Forced Expiratory Volume in 1 second
FeNO: Fractional Exhaled Nitric Oxide

Building Confidence in Predictions in Virtual Asthma Patients

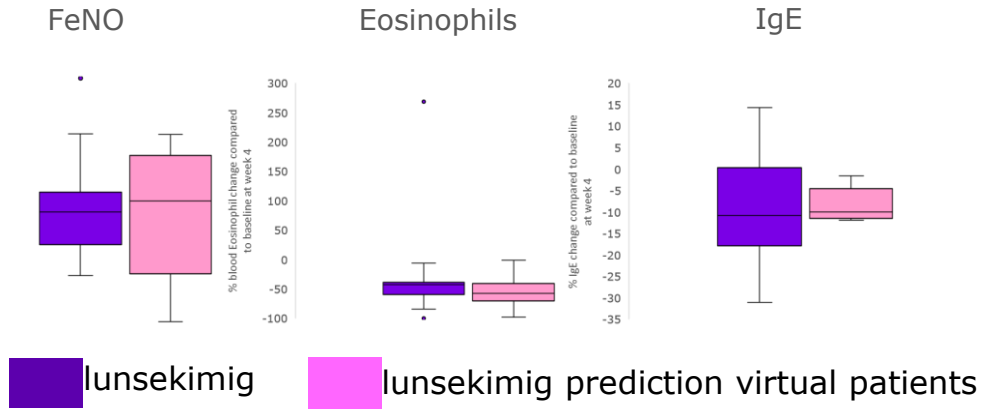
Binding affinities

Human PK model

Lunsekimig



Virtual Asthma Patients



Prediction of POM Biomarker Data (400 mg SC Single Dose)

Succesful blind prediction of phase 1b clinical endpoint & biomarker data

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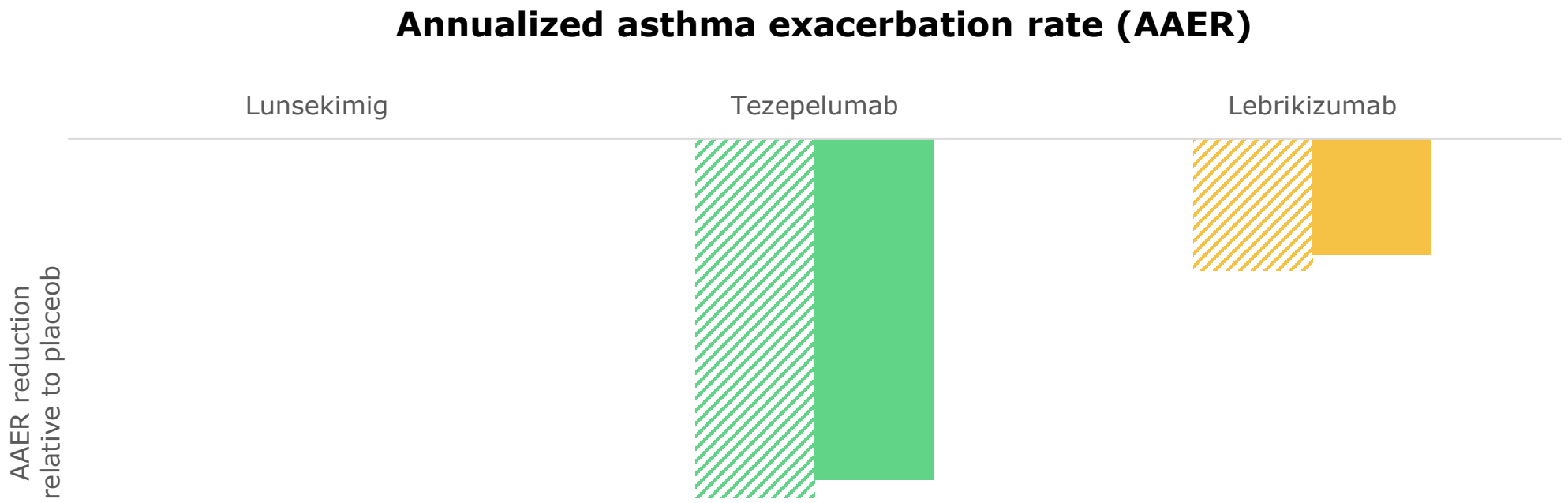
POM: Proof of Mechanism
SC: subcutaneous

Head-to-Head Comparison in Virtual Asthma Patients



Differentiation in virtual asthma patients

- 1000 virtual asthma patients
- Variability in physiological parameters, e.g. TSLP, IL-5 synthesis rates
- PK variability and uncertainty from affinity measurements

QSP Virtual Patients

Data

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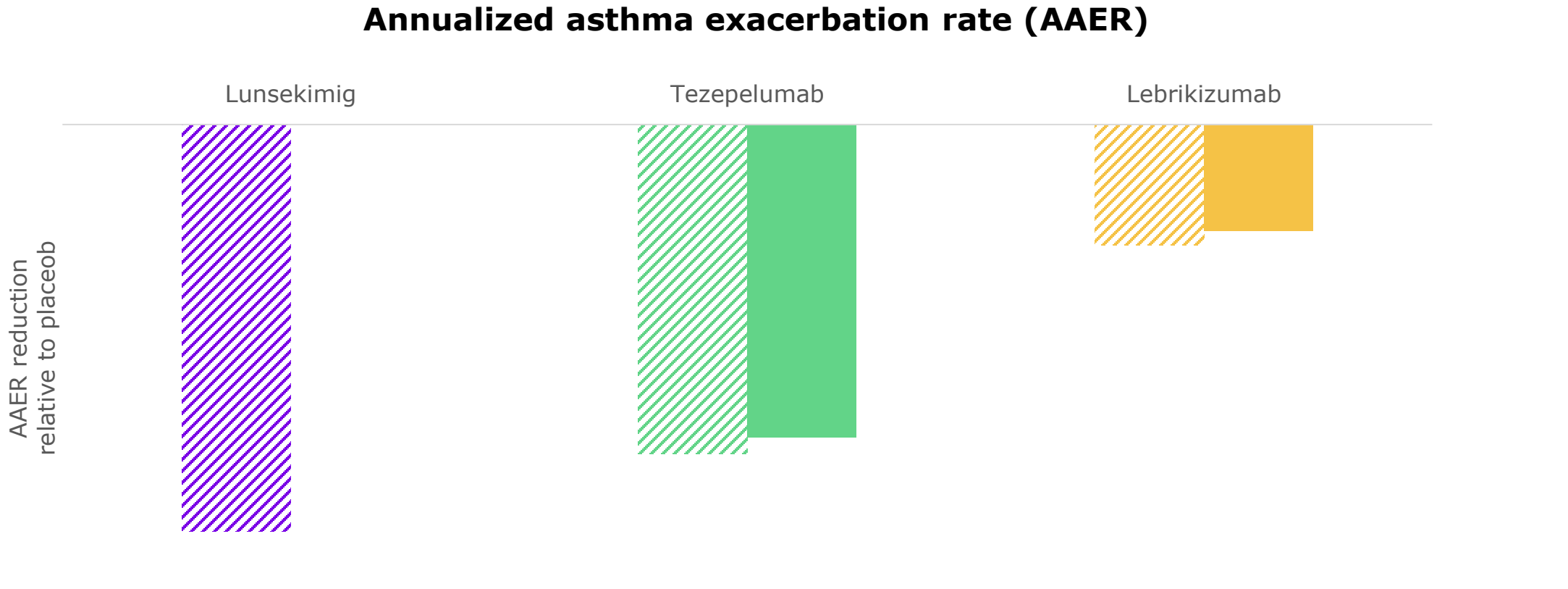
! Lebrikizumab (a-IL13 mAb) is not marketed but contains part of the MoA of Lunsekimig

Head-to-Head Comparison in Virtual Asthma Patients

*lunsekimig is predicted to be **most efficacious drug in asthma** based on QSP model predicted **AAER reduction***



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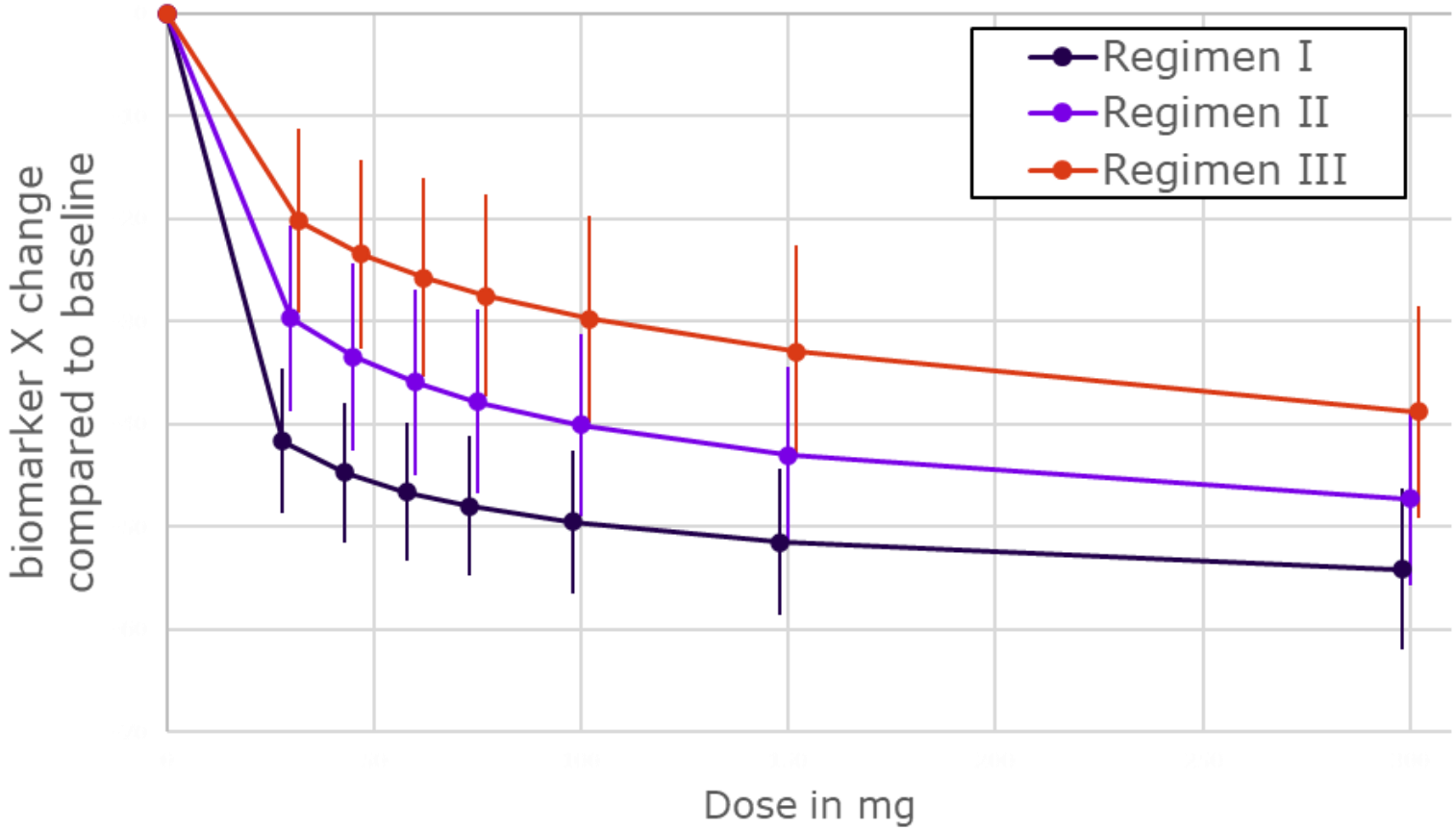
Exploring Efficacy of Various Dosing Regimens in Virtual Asthma Patients

*Simulations of **biomarker** and **clinical endpoint** change for various potential dosing regimens of **lunsekimig** allows to optimize dose selection for phase 2b trial*



Optimized phase 2b dose regimen selection increasing its Probability of Success

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Conclusion

- Lunsekimig is a novel, bispecific anti-TSLP/anti-IL-13 NANOBODY® compound that has the **potential** to be **the most efficacious biologic** for the treatment of asthma
- **In-silico head-to-head comparisons** in virtual asthma patients complemented phase 1b data to support early **Proof of Concept**
- Based on modeling approaches, the program **accelerated** from phase 1b to phase 2b, a Sanofi-first approach that was **accepted by the FDA**

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Presented at Sanofi R&D Day in Dec 2023

Replacing Need for Clinical Trial in Vulnerable Patients by Partial Pediatric Extrapolation

Susana Zaph, Chanchala Kaddi, Randolph Leiser, Mengdi Tao

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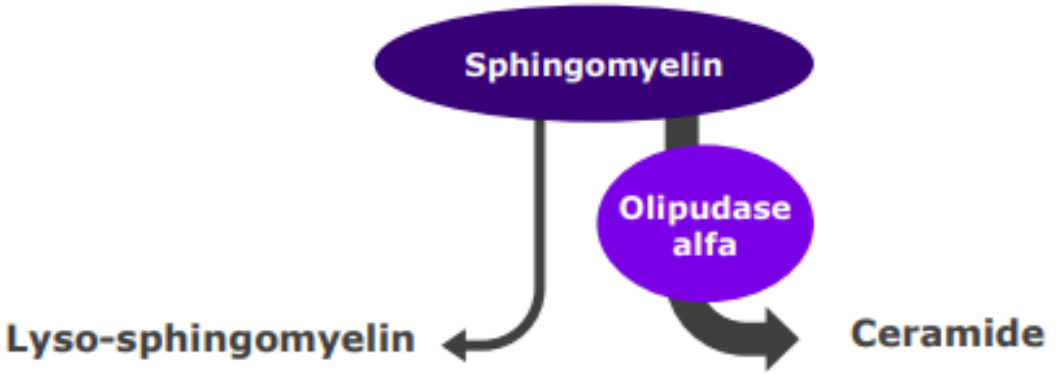
Olipudase alfa (Xenpozyme) is the first treatment for ASMD

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]

Alfie ASDM (UK)

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



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Simulation of olipudase alfa treatment effect in virtual ASMD patients to enable partial pediatric extrapolation and broad label

BACKGROUND & CHALLENGE

- **Pediatric ASMD patients** have a more **severe presentation of disease** than adult patients
- **Same** disease biology and Olipudase alfa response **in adults and children?**
- Can we bridge from adults to children allowing us to **avoid additional clinical trials** in children?

APPROACH

1. **Build** mechanistic multiscale QSP model of ASMD to connect enzyme deficiency to observed biomarkers, clinical endpoints and response to Olipudase alfa
2. **Quantify** QSP model parameters describing disease biology and Olipudase treatment effects to evaluate similarity of both in adults and children

ASMD = Acid Sphingomyelinase Deficiency

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

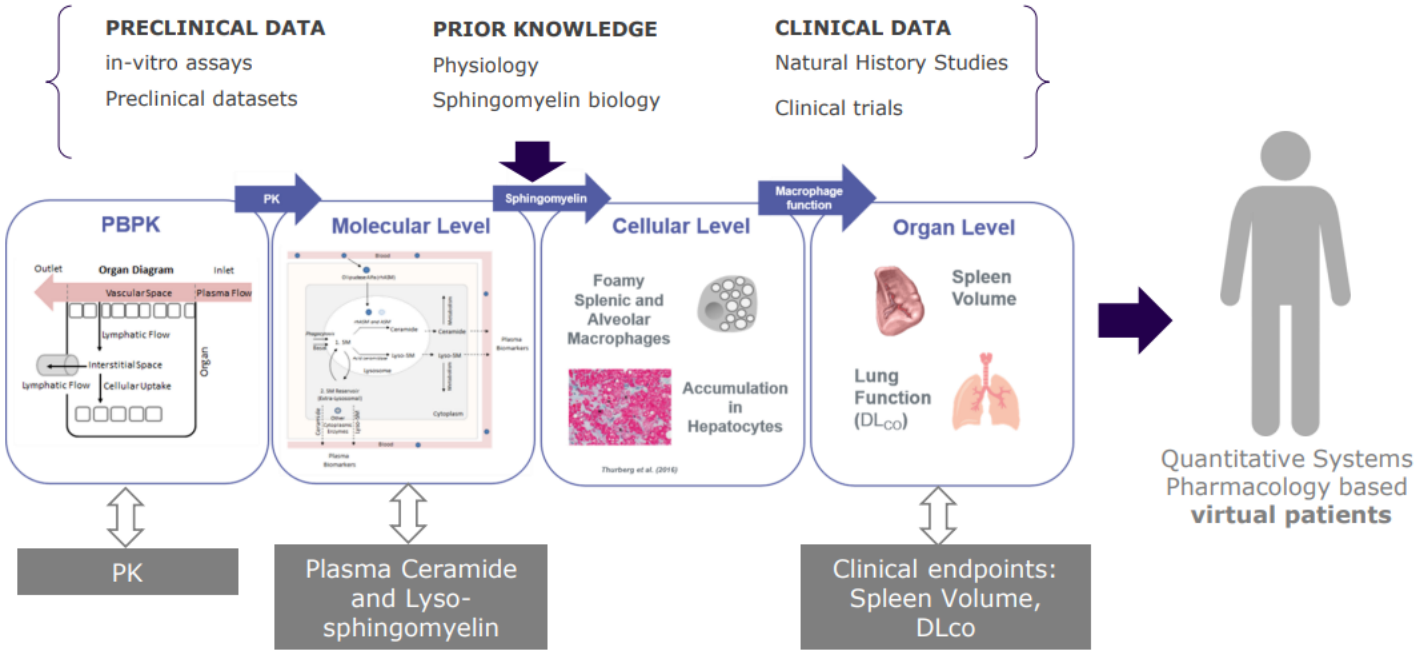
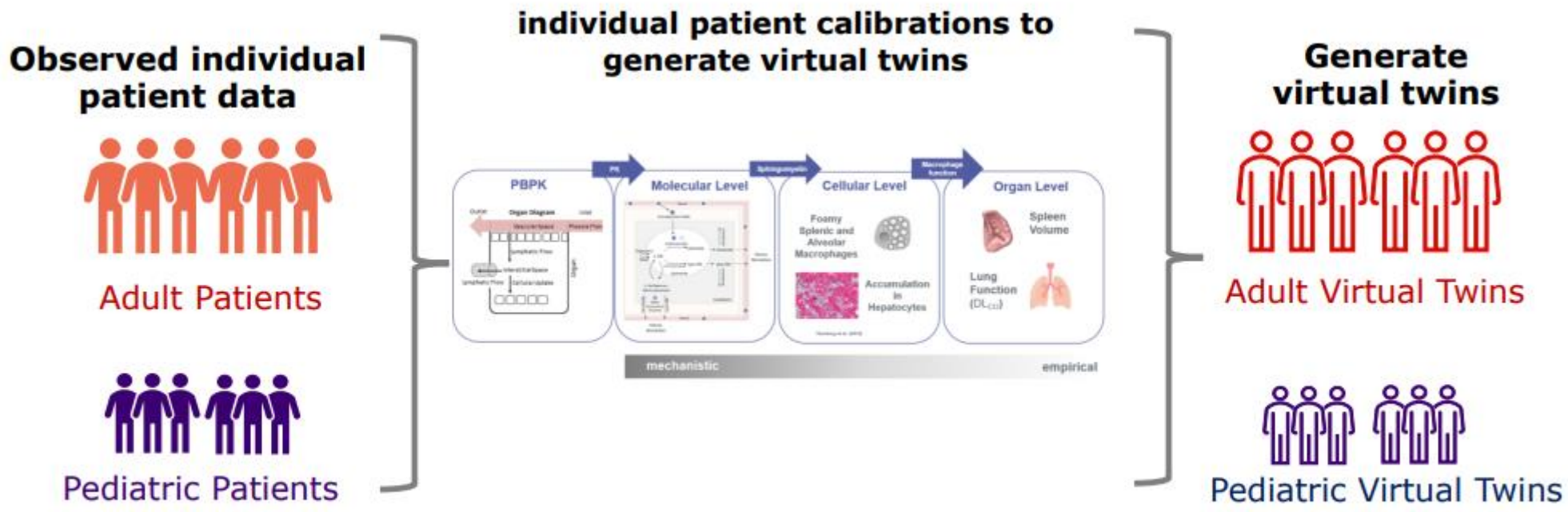


Table 1 Overview of data sources used to develop and calibrate the QSP model

Data source	Model level
Preclinical studies (ASMKO mouse)[22]	PBPK
Natural history study (59 adult and pediatric patients, from 1 year to up to 11 years of assessment)[20]	Organ
Phase Ia (11 adult patients)[21]	PBPK
Phase Ib (5 adult patients)[8]	PBPK, molecular, organ
Literature	Molecular, cellular, organ

Kaddi, C. D. et al. (2018). 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 & Systems Pharmacology, 7(7), 442–452.

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



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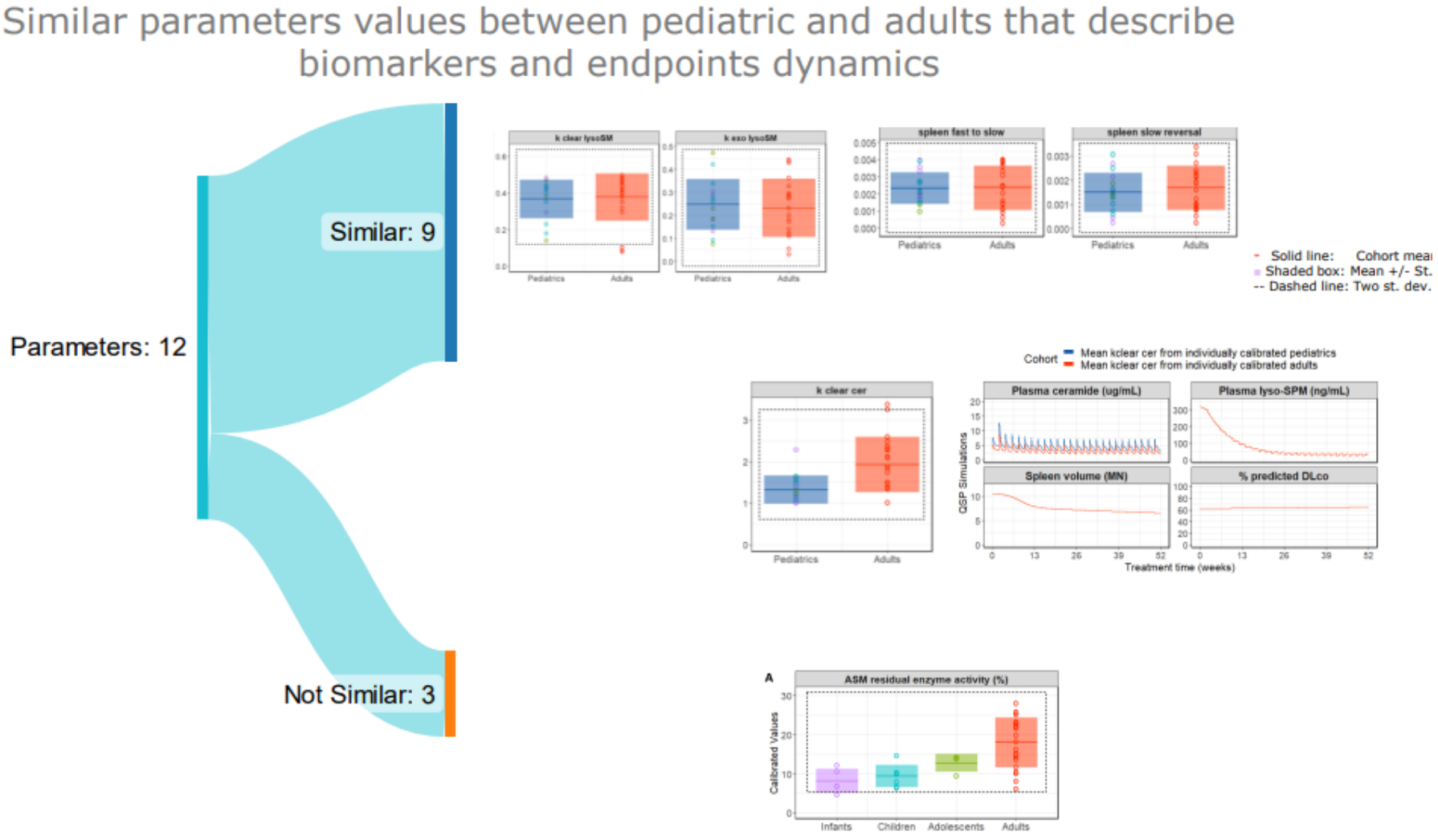
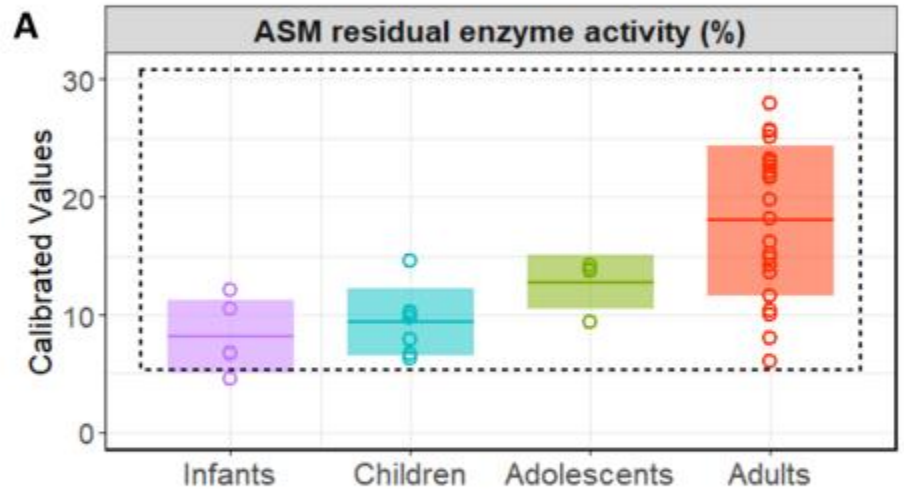
Most model parameter values that defined virtual twins were similar in pediatric and adult cohorts



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

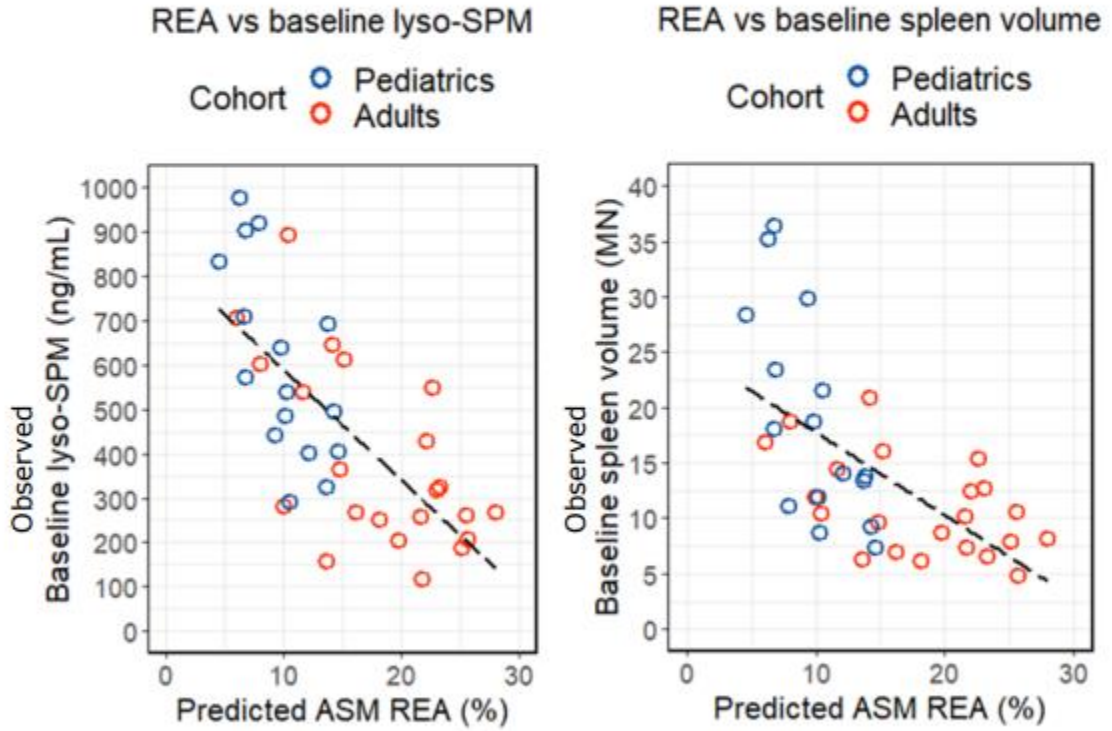
Percent of ASM enzyme activity compared to healthy value

Represents the severity of enzyme deficiency



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

REA parameter values correlate with observed endpoint severity



RESULTS & CONCLUSIONS

- QSP model provides **insight on mechanism of ASMD progression and response to olipudase alfa treatment** in pediatric and adult ASMD patients
- Same pathophysiology described in model can capture both pediatric and adult datasets in a similar manner **supporting mechanistic similarity of disease and treatment response**
- 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**
- QSP results enabled **partial pediatric extrapolation** from adults to children
- QSP-model based analysis and simulations helped to get enzyme replacement **therapy faster to ASMD patients**

Presented at FDA Workshop "Creating a roadmap to QSP-informed rare disease drug development" in May 2023

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Summary & Conclusion

Take Home Messages

- Integrate data and knowledge on physiology and pharmacology into computational **disease models** and **virtual patients**
- Run **in-silico clinical trials** in **virtual patient populations** for smarter decision-making in research & clinical development
  1. Gating the best drug candidates into the clinic or into the next clinical phase
  2. Optimizing clinical trial design (e.g., right dosing and patients)
  3. Replacing need for clinical trial in vulnerable patients
- **Virtual patient engine** contributes to increased probability of success and accelerated development of innovative medication to improve people's lives

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… to all my wonderful colleagues in Translational Disease Modeling

… to all our collaborators and partners within Sanofi

… to you for your attention !!

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