

Opportunities for application of PBPK models in special populations and different modalities

Loeckie de Zwart, Johnson & Johnson,
on behalf of EFPIA and a pharma industry PBPK expert team

A presentation in session 3: Mechanistic models for the future

Introduction

EFPIA pharma industry PBPK expert team
Pradeep Sharma (AstraZeneca), Kunal Taskar(GSK); Neil Parrott (Roche); Ivana Tomic (Novartis); Caroline Sychterz(BMS); Theunis Goosen (Pfizer); Gareth Lewis (GSK), Priyanka Kulkarni (Takeda); Mary Choules (Astellas); Ryota Kikuchi (Abbvie); Maria Posada, Sonya Chapman and Ivelina Gueorguieva (Lilly); Jialin Mao (Genentech) and Loeckiede Zwart (Johnson & Johnson)

The presentation represents the collected experience and opinions of multiple Pharmaceutical Industry experts in PBPK modelling who have united efforts for the purpose of delivering optimal input to this meeting.

The discussions were facilitated by the Simcyp Consortium Members Discussion Group (SMDG)

Final application and coordination was facilitated via EFPIA

We appreciate the opportunity to participate in this EMA multi-stakeholder workshop and thank the organizers for their work

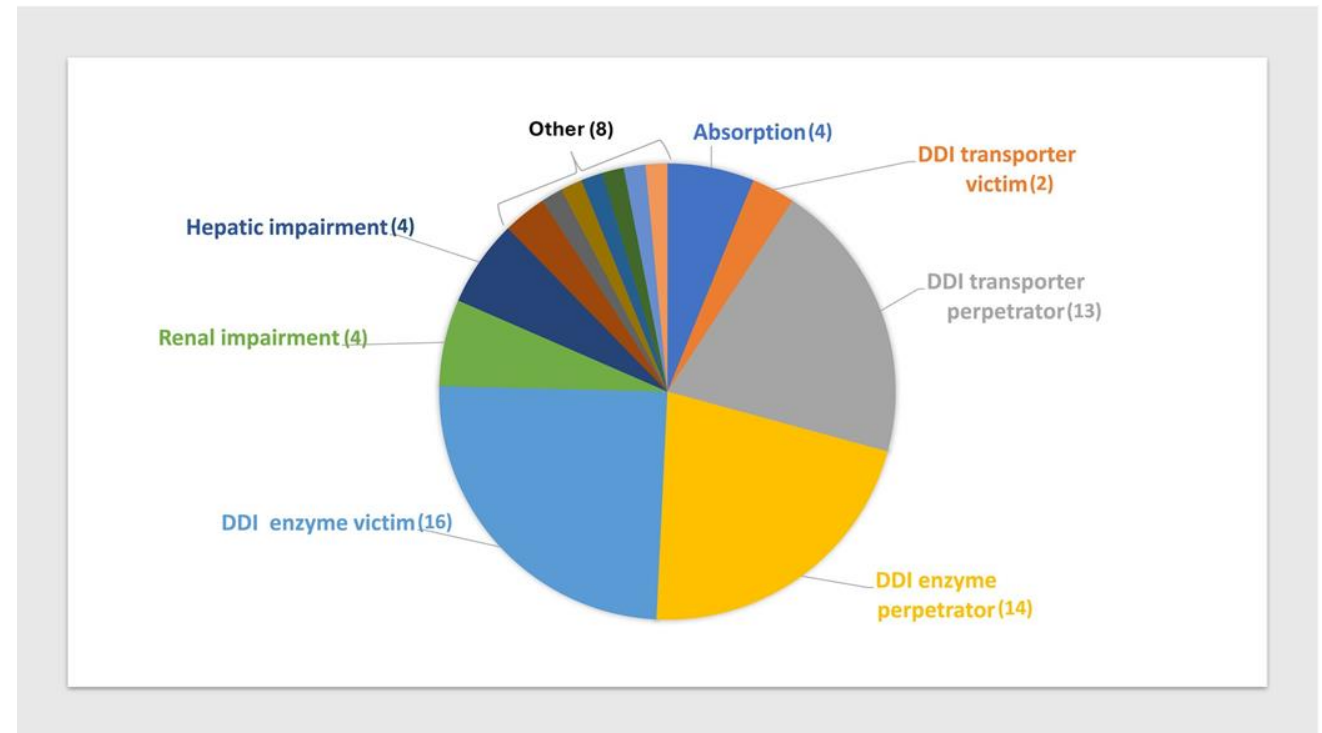
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Current Use of PBPK modeling in New Medicinal Product Approvals at EMA

- Highest rate of qualification in the three most common general areas of use, models predicting DDIs with enzymes (including all pathways, i.e., CYP and UGT enzymes)
 - Drug as a perpetrator (5/14, 36%)
 - DDIs with enzymes with the drug as a victim (3/16, 19%)
 - DDIs with transporters with the drug as a perpetrator (1/13, 8%)

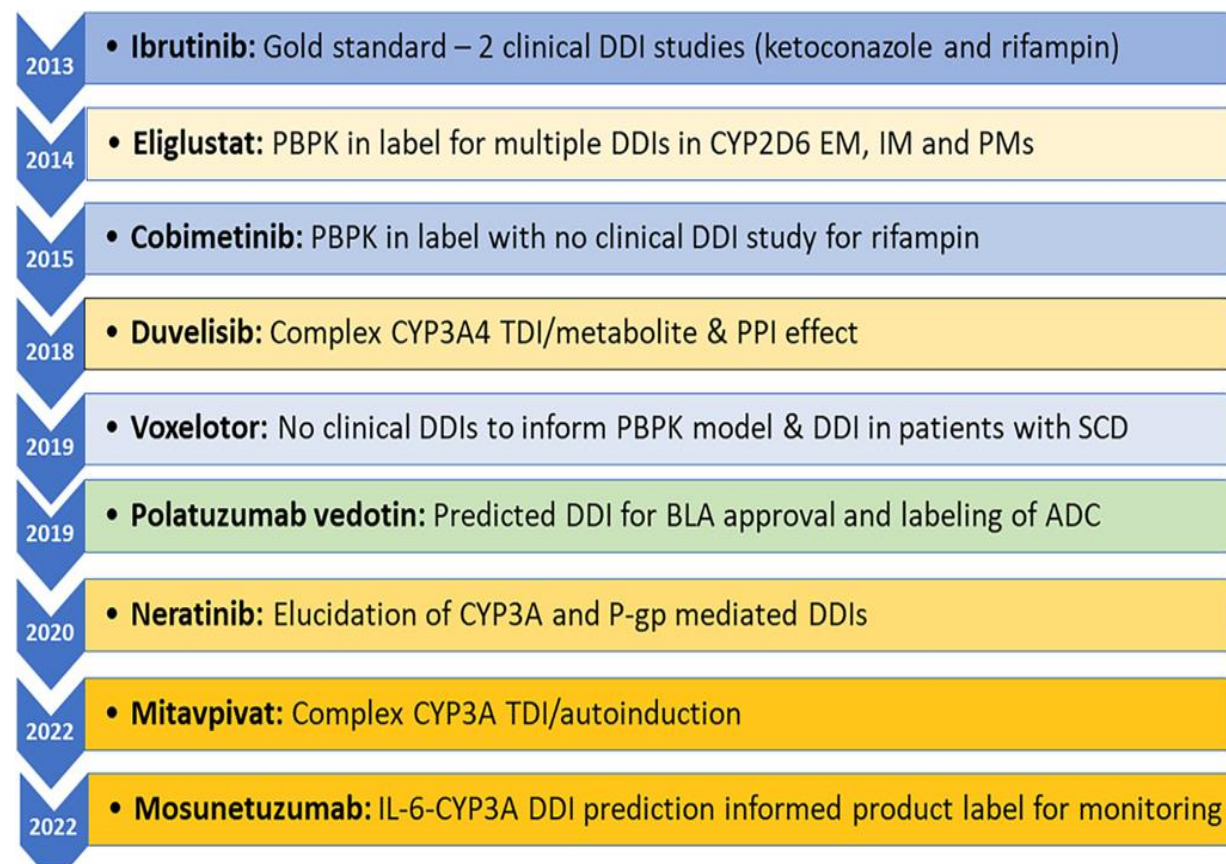
General areas of proposed intended uses of PBPK models in approved "full" MAAs in 2022 and 2023 ($n = 65$)



Paul et al. CPT, Volume: 117, Issue: 3, Pages: 808-817, 2025,

Dose Optimization Informed by PBPK Modeling: State-of-the Art

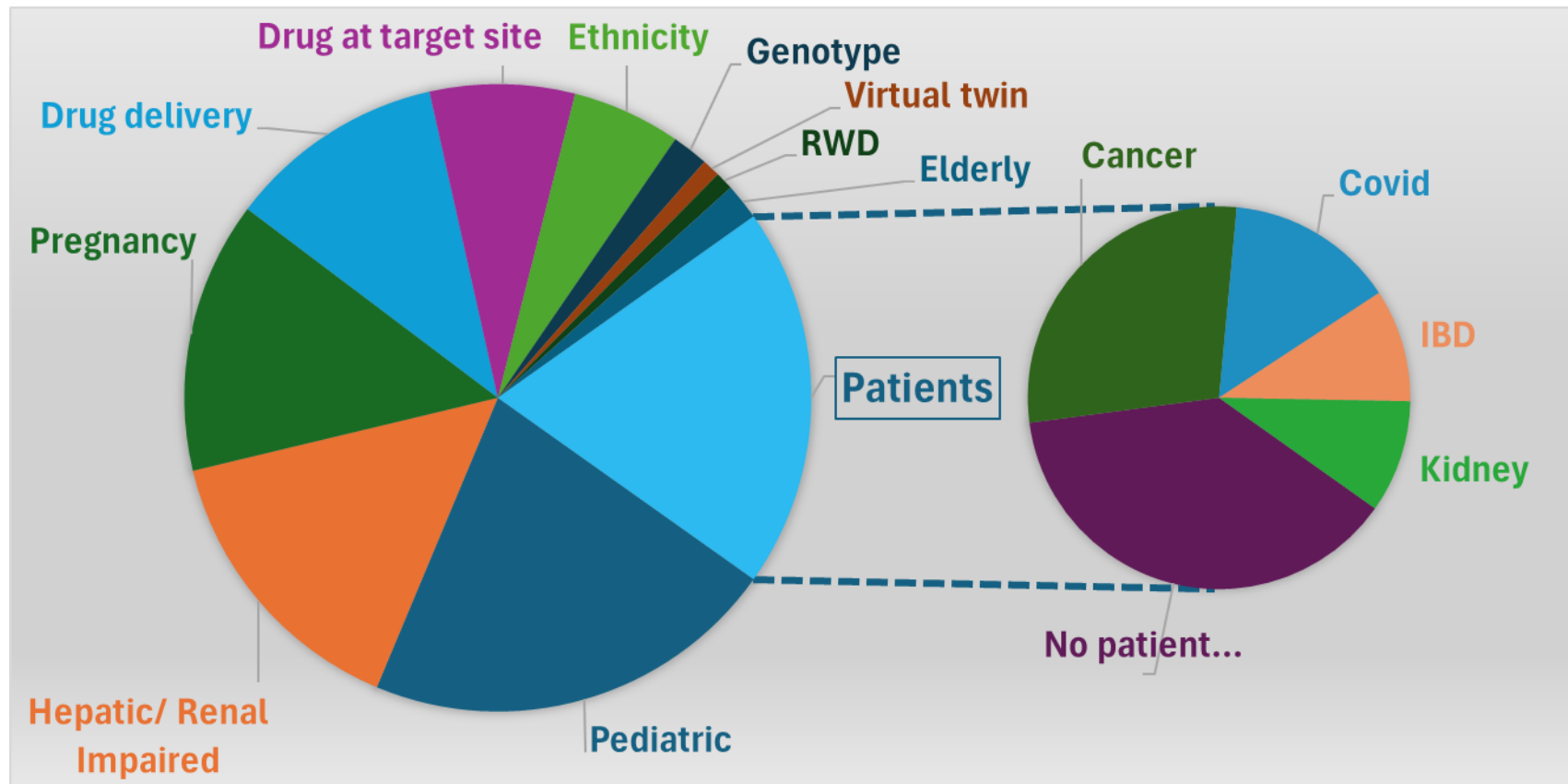
- Utility in PBPK modeling has expanded over the last decade
- From initial example of a high CI, CYP3A4 substrate based on 2 clinical DDI studies, towards more complex cases
- Ranging from multiple inhibition mechanisms, multiple enzymes, to enzyme/transporter interactions; other modalities like siRNAs and mAbs; Specific patient populations and combinations of these areas.
- Focus for this presentation will be on extended applications in **special populations** and for **other modalities** and combinations of those, based on literature examples



Rowland-Yeo et al. CPT 2024 Volume: 116, Pages: 563-576, 2024

Special populations: from healthy subjects to patients

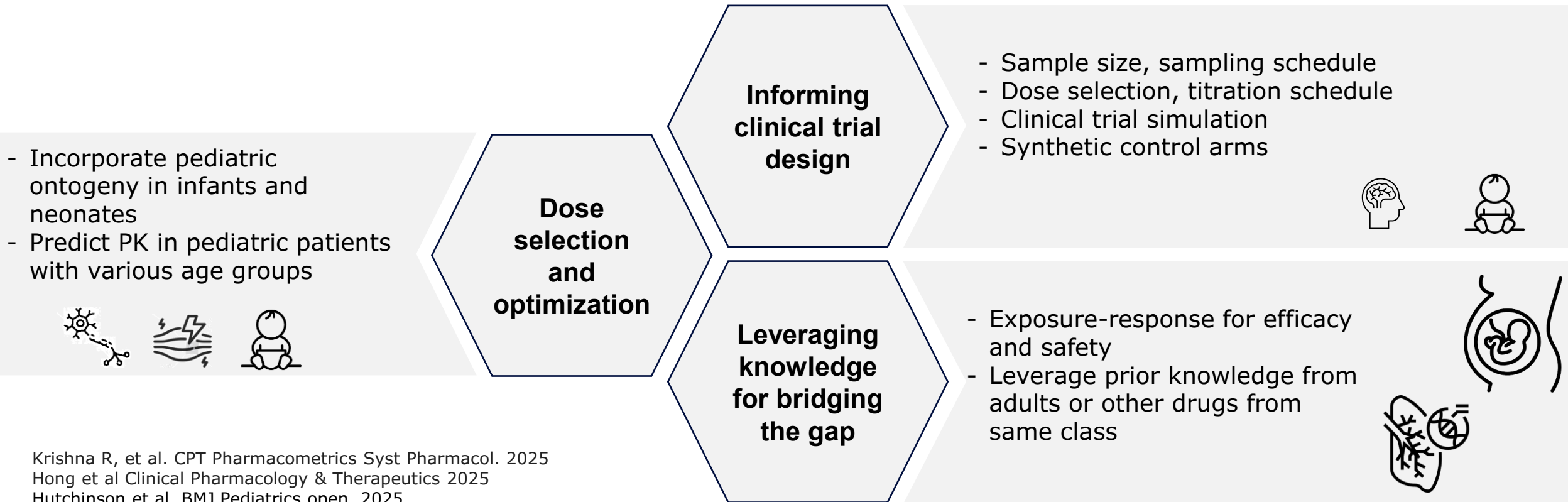
- Pubmed publications in 2025 (“PBPK” or “PBPK and Patients”): 102 results



PBPK in pediatrics.. and for pediatric (rare) diseases

Challenging for drug development

- Small patient populations
- Ethical constraints on clinical trial design
- Limited prospectively defined natural history data



Krishna R, et al. CPT Pharmacometrics Syst Pharmacol. 2025
Hong et al Clinical Pharmacology & Therapeutics 2025
Hutchinson et al. BMJ Pediatrics open. 2025.

Dose
selection
and
optimization

DDI studies unethical in vulnerable very young population Can PBPK modeling help evaluating the dose of comeds in pediatric population?

Spinal Muscular Atrophy



Risdiplam/metabolite TDI of CYP3A4



Pediatric dose + comeds

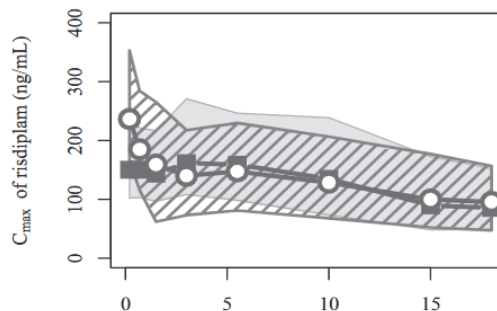
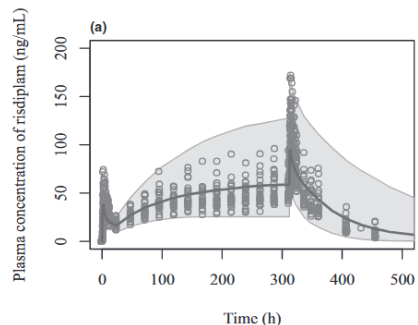


Adult population

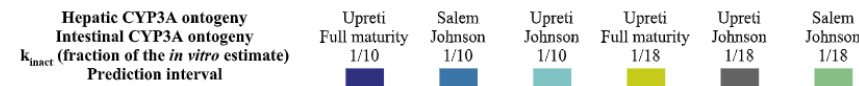
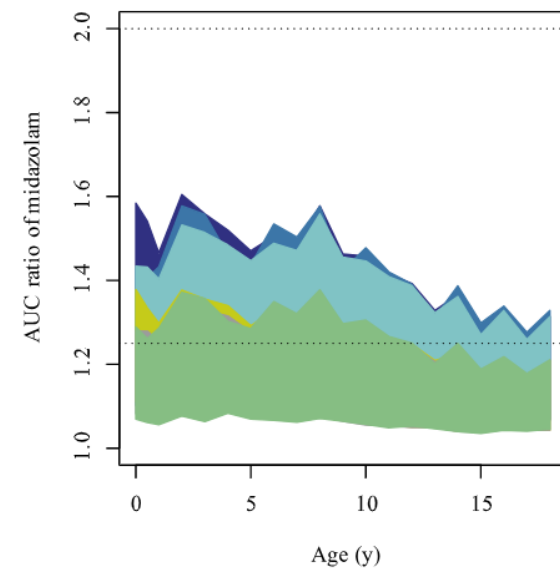
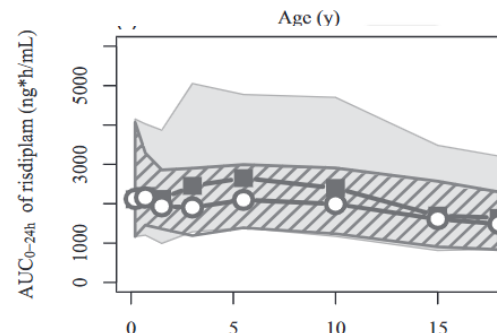
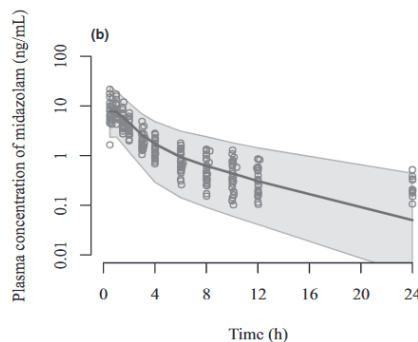
Pediatric population

Model application DDI in pediatric population

risdiplam



midazolam
+
risdiplam



Cleary 2021 CPT

Johnson&Johnson

Opportunities for application of PBPK models in special populations and different modalities

Leveraging
knowledge
for bridging
the gap

Knowledge gap due to exclusion of pregnant populations from clinical trials Can PBPK modeling help bridging this gap?

Cystic fibrosis



Maternal dose



Non-pregnant population

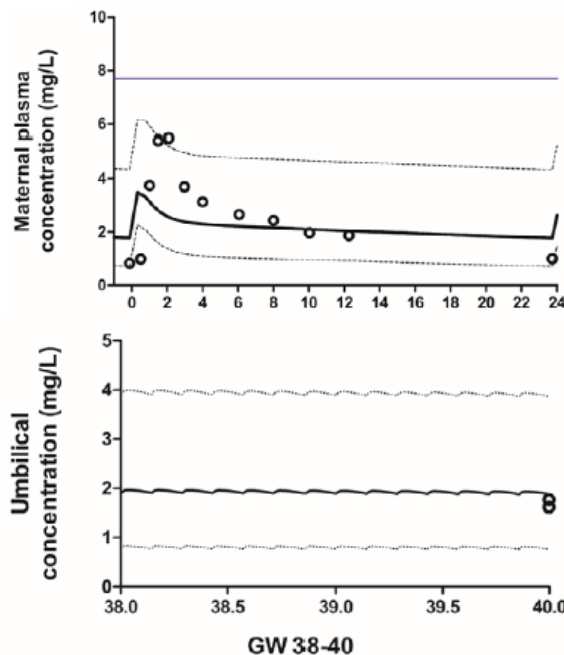
Tezacaftor 100 mg qd Steady-state PK parameters

	Simulated		Observed	
	C _{max} (mg/L)	AUC (mg·h/L)	C _{max} (mg/L)	AUC (mg·h/L)
Mean	5.9	109.7	6.7	92.4
CV (%)	36.5	44.5	20.8	25.8
Sim/ Obs	0.9	1.2		

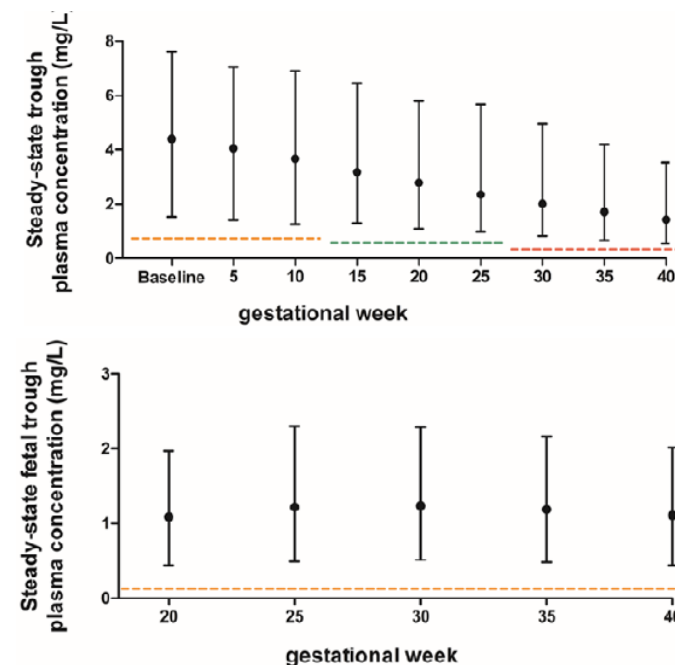
Hong E et al. Pharmacotherapy. 2023

Data only shown for Tezacaftor
Other results also available in Hong et al. 2025

Pregnant population + umbilical cord



Pregnant population + fetus



Informing clinical trial design

Unmet needs of patients with HIE: feasibility and safety of metformin in infants. Can PBPK help to determine the correct dose, frequency and duration of metformin?

HIE: hypoxic-ischaemic encephalopathy



metformin



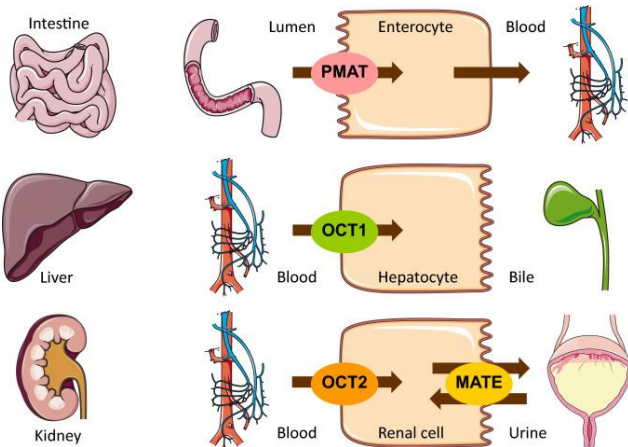
Clinical trial design in < 3-months



Adult population

9 yrs old infants

Optimised dose for future efficacy-targeted clinical trials

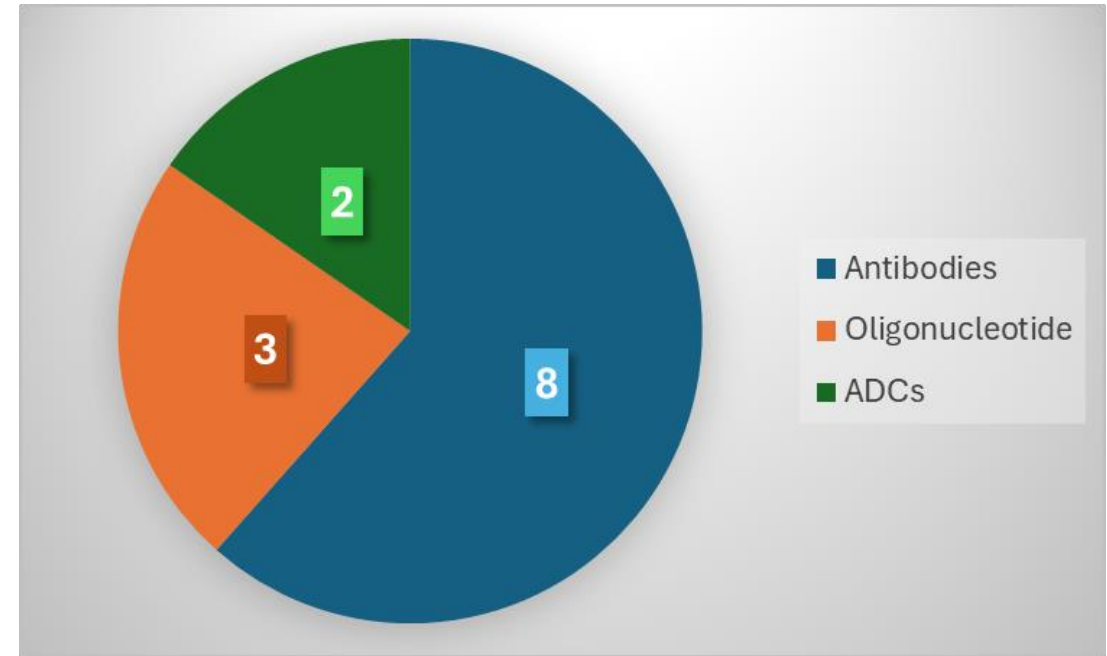


- Scaling of the adult PBPK model to an infant population of 3-months old.
- Virtual children created using appropriate anatomy and physiology
- Ontogeny of transporters, MATE1, PMAT, OCT1 and OCT2.
- PK of metformin within the 90th prediction interval in 4 infants of 9 year of age were

- Exposure matching to derive a weight-normalized metformin dose in 3 month old patients using PBPK model results in a dose of 32 mg/kg
- Results of this trial can serve as foundation for future trials to study the efficacy of metformin in improving neurodevelopmental outcomes in children with HIE.

Other modalities: from synthetics to biologics

- Emerging therapies: Oligonucleotide, siRNAs, monoclonal antibodies, bi- and tri-specific antibodies, ADCs
- Unique properties to include and account for in mechanistic models, PBPK models:
 - lymphatic flow as extravasation pathway
 - Modeling tissue level processes (TMDD)
 - FcRn-mediated recycling
- Pubmed publications in 2025 (“PBPK and oligonucleotide or siRNA or antibody or ADC”): 13 results



PBPK across modalities and populations

Challenging for drug development

- Small patient populations
- Ethical constraints on clinical trial design
- Limited prospectively defined natural history data



- Incorporate transcriptomics for tissue distribution for target expression
- Optimise route of administration
- Evaluate new indications



**Dose
selection
and
optimization**

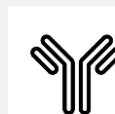
**Informing
clinical trial
design**

- Tissue distribution and efficacy
- Dose selection, titration schedule
- Clinical trial simulation
- Route of administration



**Leveraging
knowledge
for bridging
the gap**

- Exposure-response for efficacy and safety
- Leverage prior knowledge from adults or other drugs from same class



Pradeep Sharma et al. CPT PSP 2025
Kardouh et al. CPT 2025

**Dose
selection
and
optimization**

Unmet need of efficacy of IFN-diseases affecting different organs Can PBPK modeling help evaluating efficacy in tissues?

IFN- α -receptor



IV and SC administration



IV



SC



New indications



**Informing
clinical trial
design**

Plasma ->Tissue

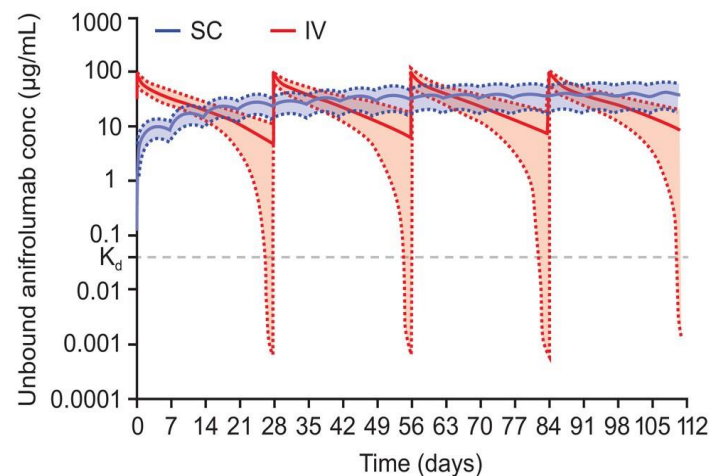
Novel relative transcriptomics approach for IFNAR1 expression in tissues using mRNA abundances from bioinformatic databases in:

- Blood
- Skin
- gastrointestinal tract
- Lungs
- Muscle

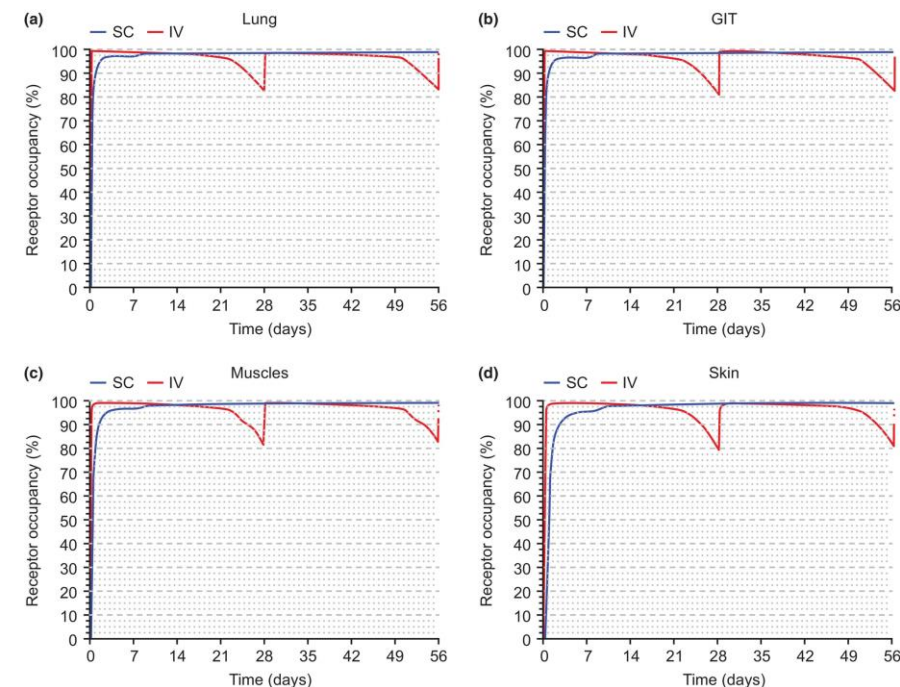
External validation: absolute serum IFNAR1 receptor expression data in clinical studies

Pradeep Sharma et al. CPT PSP 2025

IV and SC dosing



Application for new indication



Leveraging
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Knowledge gap due to exclusion of pregnant populations from clinical trials Can PBPK modeling help bridging this gap?

Therapeutic antibodies



FcRn ontogeny



Maternal dose

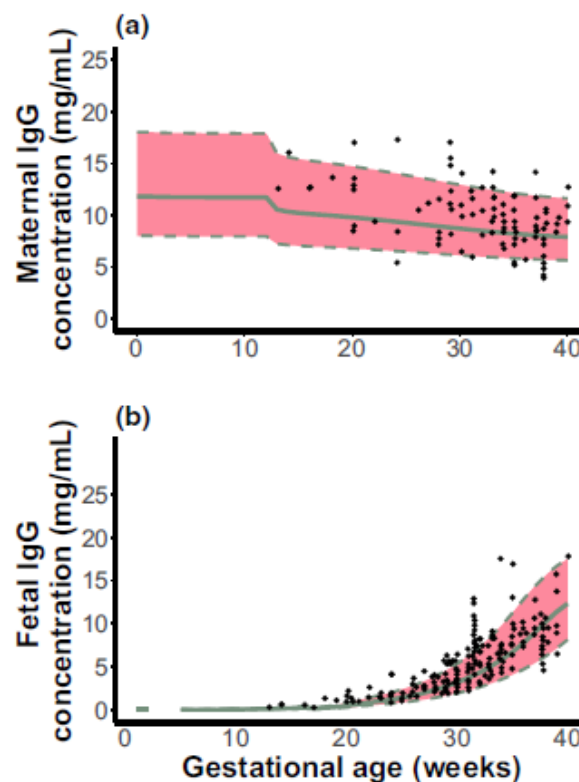


Non-pregnant population

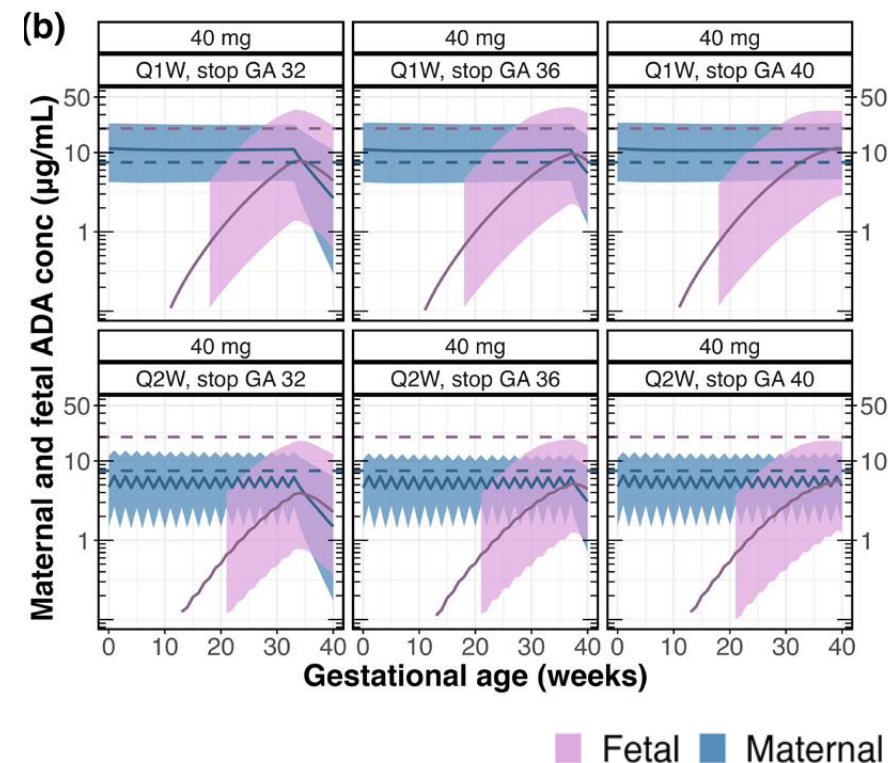
PBPK models for 5 different antibodies:

Infliximab
Adalimumab
Etanercept
Ustekinumab
vedolizumab

Maternal and fetal blood



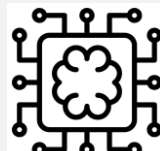
Pregnant population + fetus



**Leveraging
knowledge
for bridging
the gap**

Leverage RWD/AI/ML in PBPK models: The future?

Artificial Intelligence



Real World DATA



Value added for PBPK models

- Lack of parameters or estimation of unknown parameters is one of the main problems affecting PBPK model building and accuracy
- AI may be valuable to improve the identification and summary of all available PK data in published literature as well as assist in evaluating different model structures
- RWD in combination with ML has been put forward as a potential powerful tool to deconvolute some key characteristics of a drug.

Challenges (for qualification)

- RWD can be inaccurate, incomplete, and less structured in comparison to data collected from well-controlled clinical trials, therefore come with a higher risk of bias
- ML algorithms are data-driven and consequently prone to bias
- The credibility of the outcome from models and the ability to explain the generated rules can be questioned, as the rules from ML algorithms are not usually explicitly expressed in models

Chou et al. 2023; Isoherranen 2025; Deepika et al 2023; Huang et al. 2024;

Qualification in emerging context of use

- Context of use of PBPK models is evolving from DDIs of synthetics in healthy patients towards dose predictions for a wide range of modalities in “special” populations
- “Special” population inclusion in clinical trial, use of RWD, ML etc will emerge in the future applications of PBPK models
- Qualification of models is often not at same level
 - Lack of data to fully validate models and assumptions
 - Driven by unmet medical need
 - Based on off label use
- Do we need additional consideration for COUs in cases of unmet medical need?

Thank you

