Medicines & Healthcare products Regulatory Agency

PBPK Modelling in Regulatory Submissions to the MHRA

Andrew Butler

Clinical pharmacology assessor

29 September 2025

What is PBPK used for in MAAs?

- Quantifying the extent of potential drug-drug interactions
  - Metabolic enzymes, drug transporters, proton pump inhibitors
- Understanding differences in pharmacokinetics between different populations
  - Paediatrics, obesity, disease states
- Demonstrating mechanistic understanding to support formulation
  - Mechanistic absorption models, dissolution, food effects
- Dose selection
  - First-in-human, paediatrics

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Reduce the clinical trial burden in order to facilitate the development of, and access to, new medicines

Regulatory guidance

EMA guidelines

- On the reporting of physiologically based pharmacokinetic modelling and simulation
- On the investigation of drug interactions
- On the use of pharmacogenetic methodologies in the pharmacokinetic evaluation of medicinal products

ICH guidelines

- E11A: Paediatric extrapolation
- M12: Drug interaction studies
- M15: Model-Informed Drug Development General Principles Guideline

Other perspectives

- PBPK Modeling to Support Pediatric Clinical Development: An IQ Working Group Perspective on the Current Status and Challenges
- PBPK Modeling in Renal and Hepatic Impairment Populations: A Pharmaceutical Industry Perspective

Model qualification

- If PBPK modelling is intended to support a regulatory decision, the model needs to be sufficiently qualified for the intended use.
- The extent of qualification required depends on the regulatory impact of the modelling.
- The regulatory impact is directly linked to the risk to the patient in case the modelling predictions or assumptions lead to erroneous regulatory decisions.

Table 1: Guideline Overview: Sequence of MIDD in Relation to the Relevant Guideline Sections

Stages	Planning and Regulatory Interaction		Implementation, Reporting, and Submission		
Sequence of Activities	**Key Assessment Elements**	**Additional Considerations for Interaction with Regulator and to Inform Decision-Making**	**Model Evaluation**	**Model Analysis Reporting**	**Documentation for Regulatory Interactions and Submissions**
	• Question of Interest • Context of Use • Model Influence • Consequence of Wrong Decision • Model Risk • Model Impact	• Appropriateness of Proposed MIDD • Technical Criteria for model evaluation and model outcomes[1] These should be documented (e.g., in a Model Analysis Plan [MAP]).	• Verification • Validation • Applicability assessment	• Model Analysis Report(s) (MAR)	• Regulatory documents, including + Outcome of MIDD Evidence Assessment + References to all relevant MAPs and MARs
Relevant Guideline Section	Section 2.1 and Appendix 1	Sections 2.2 and 4.1 and Appendix 1	Section 3	Section 4.2 and Appendix 2	Sections 2 and 4.3 and Appendix 1

Note: Terms used in this table are defined in relevant guideline sections.
[1] Results derived from M&S (i.e., via model-based predictions or simulations) and associated conclusions that are typically aligned to a Question of Interest.

Inform Decision-Making

ICH M15 guideline on general principles for model-informed drug development

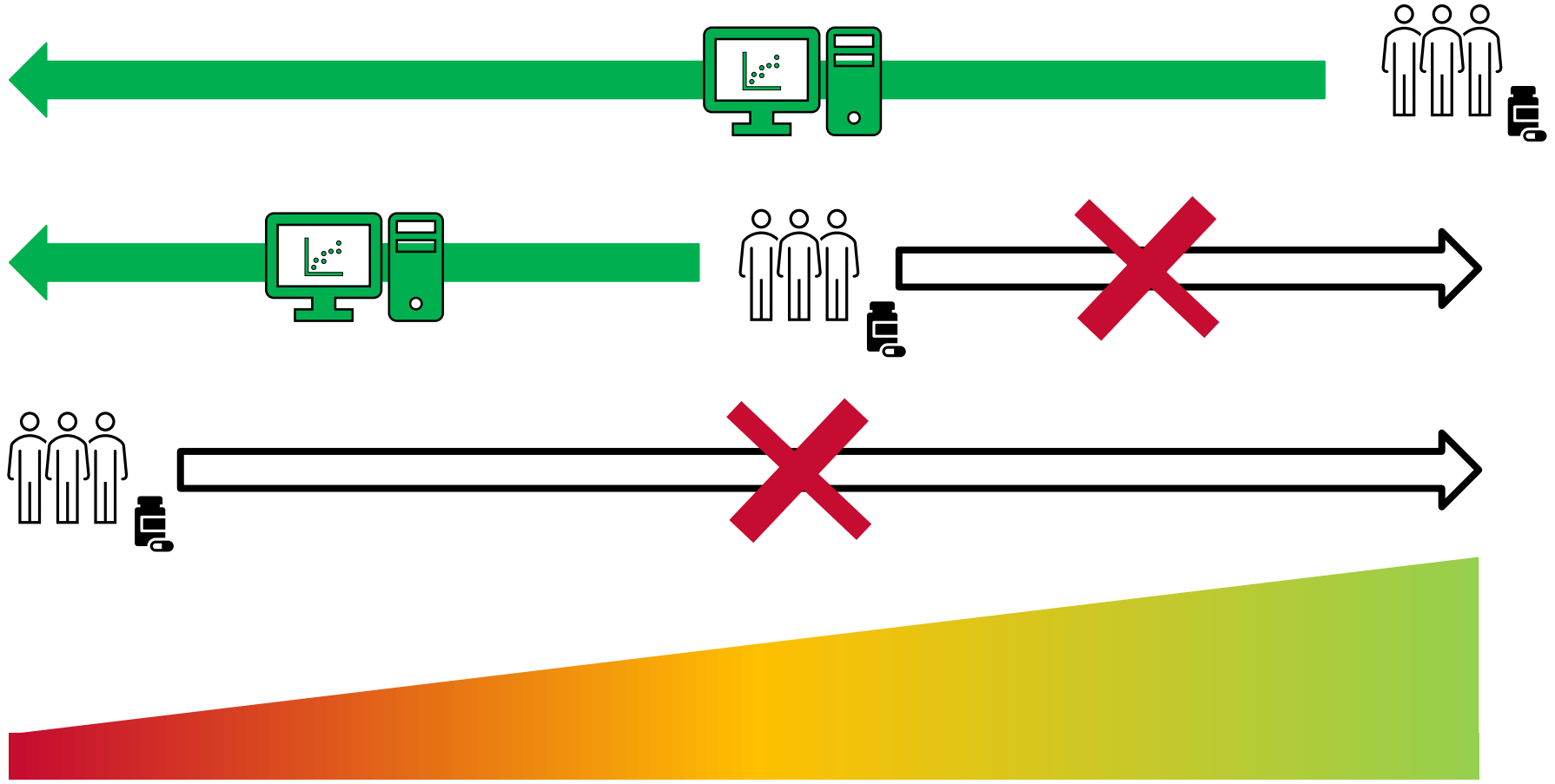
Model qualification (2)

- If PBPK modelling is intended to support a regulatory decision, the model needs to be sufficiently qualified for the intended use.
- The extent of qualification required depends on the regulatory impact of the modelling.
- The regulatory impact is directly linked to the risk to the patient in case the modelling predictions or assumptions lead to erroneous regulatory decisions.

- Qualification can be assessed within a MAA or on a platform level
- A qualification issued within the context of a specific regulatory submission should be considered only valid for that particular submission
- It is considered that e.g. eight to ten compounds is indicative of a sufficient number and this should cover a range of pharmacokinetic characteristics that could influence the outcome

EMA Guideline on the reporting of physiologically based pharmacokinetic modelling and simulation

Interpolations versus extrapolation



Case studies

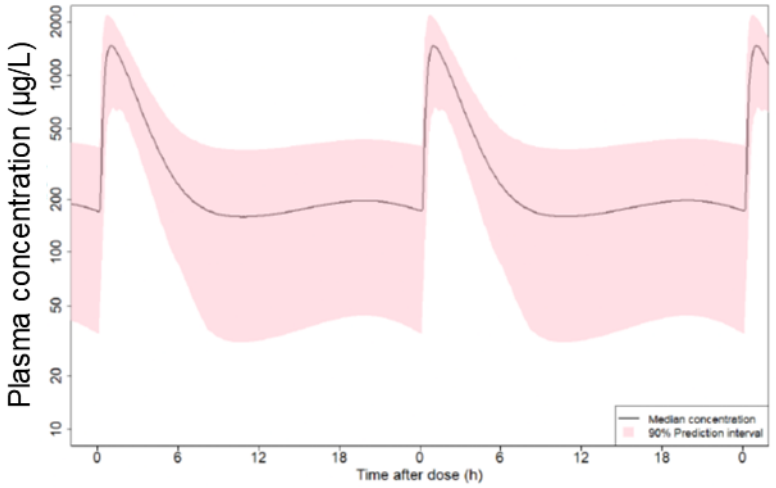
- Drug-drug interactions
- Hepatic Impairment
- Paediatric
- Stomach pH sensitivity
- Nasal absorption

Drug-drug interactions

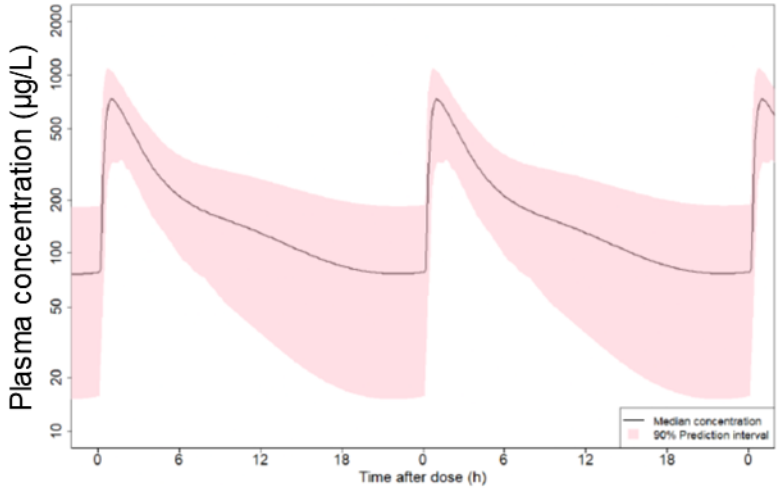
Predicting the effect of co-administration with weak and moderate CYP3A4 inhibitors

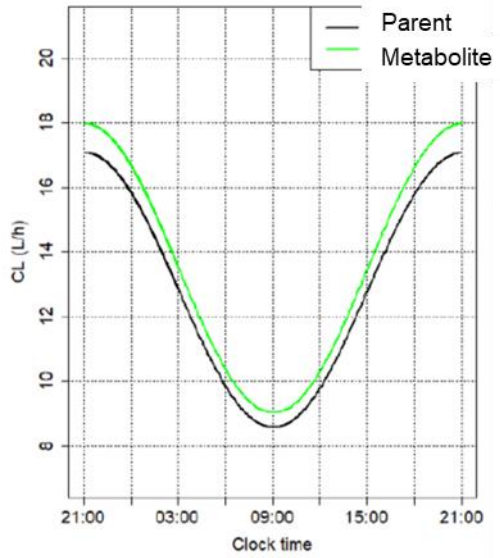
DDI: Model development

Morning dose

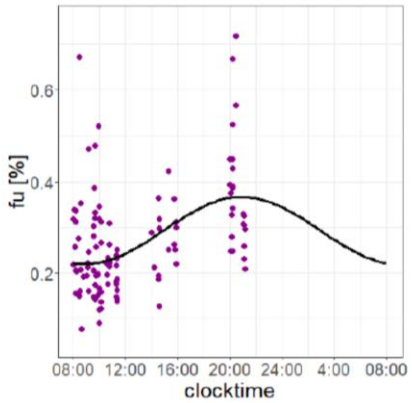


Evening dose

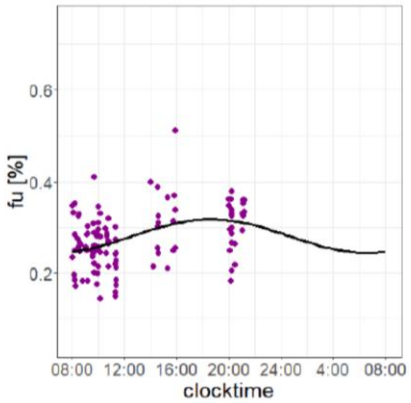




Parent

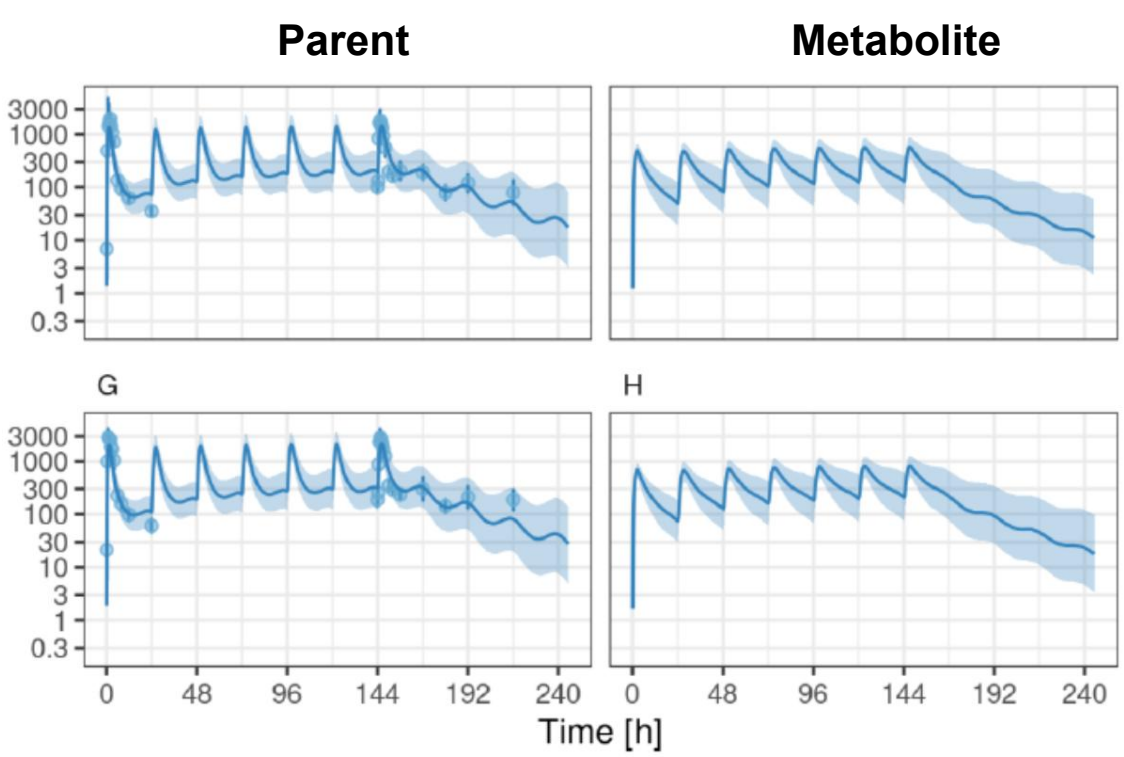


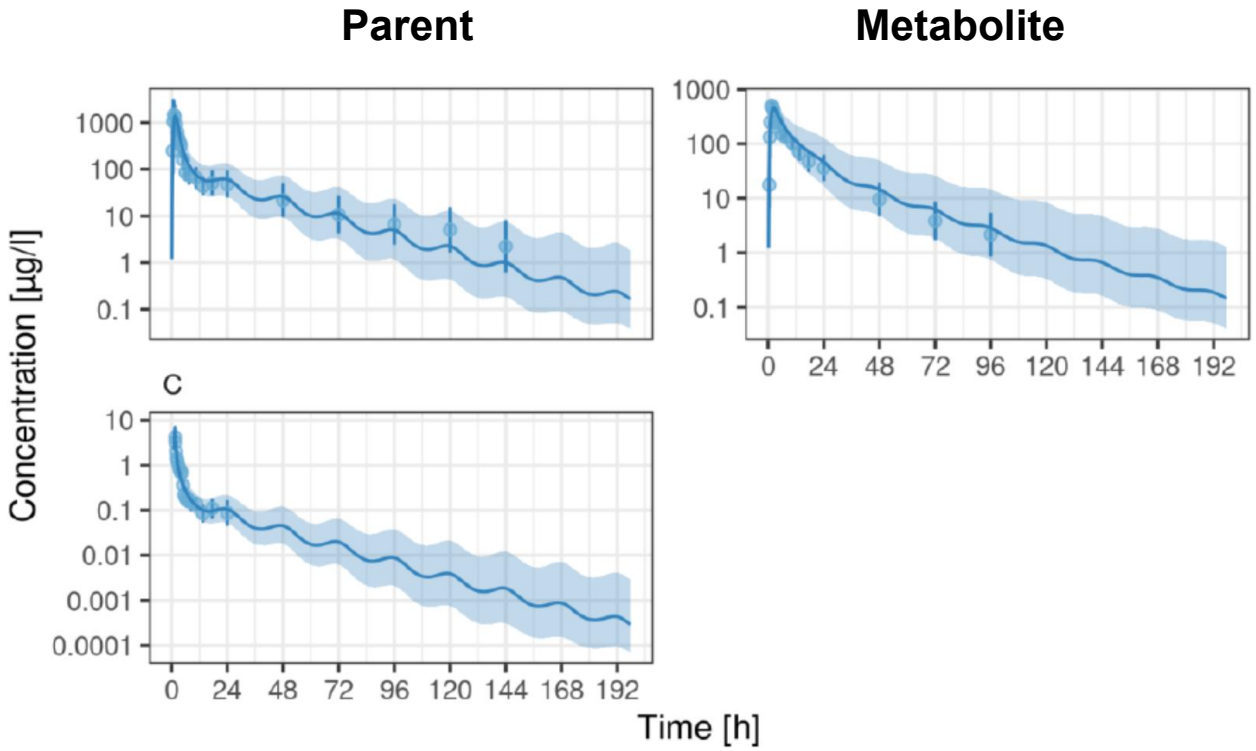
Metabolite



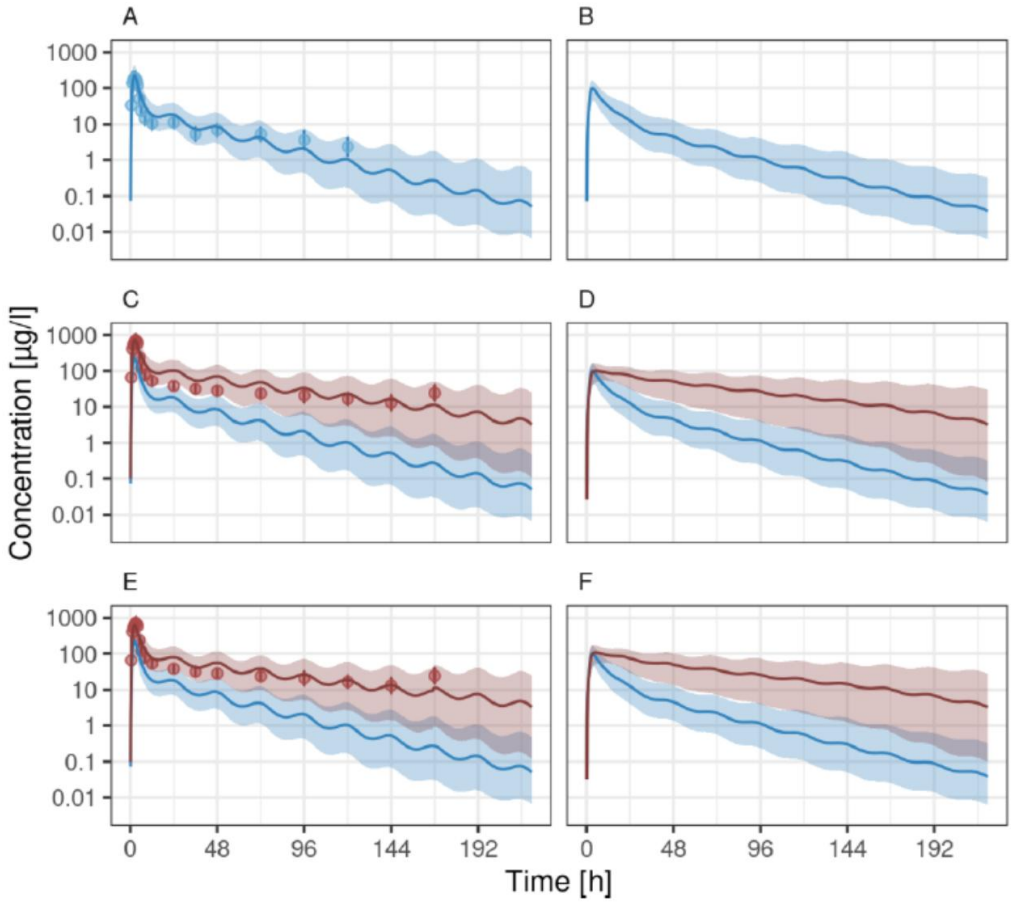
$$f_u(clocktime) = f_{u,base} \times (1 + amplitude \times \cos\left(2\pi \times \frac{shift + clocktime}{24h}\right))$$

DDI: Model verification

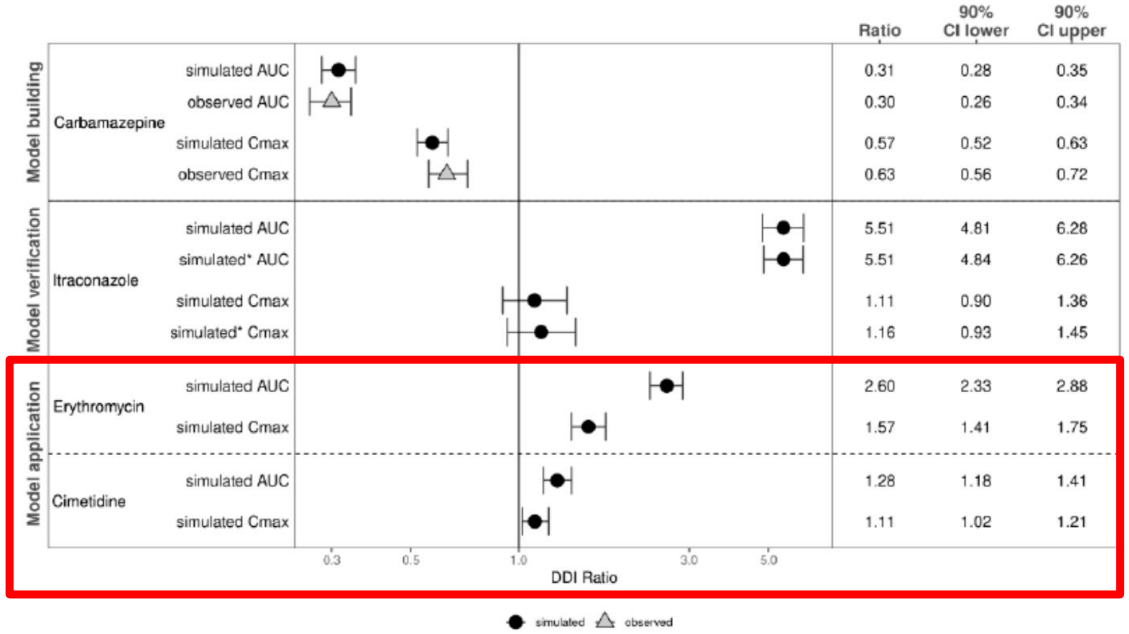




DDI: Prediction of liability

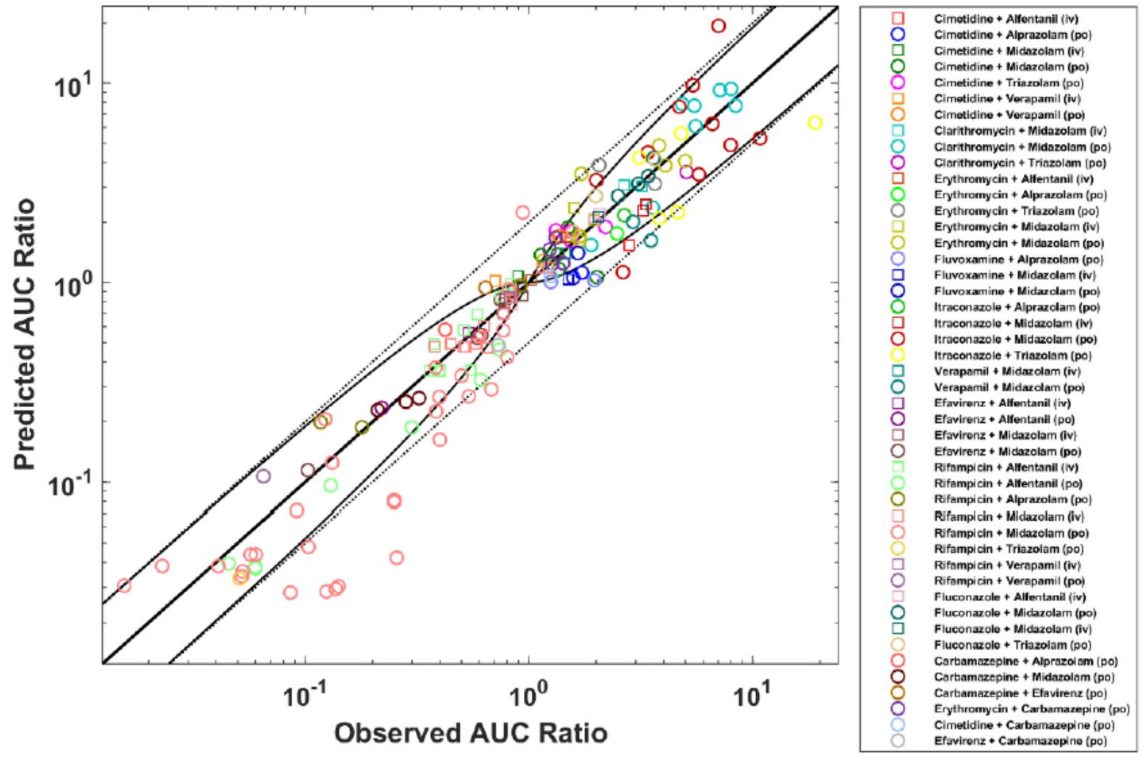


Itraconazole



Subsequently, adjusted dosing regimen were indicated within the SmPC for co-administration with *moderate* CYP3A4 inhibitors whilst *strong* inhibitors were contraindicated

DDI: Model qualification



Disease models

Predicting the effect of moderate and/or severe hepatic impairment

Hepatic impairment: Model qualification

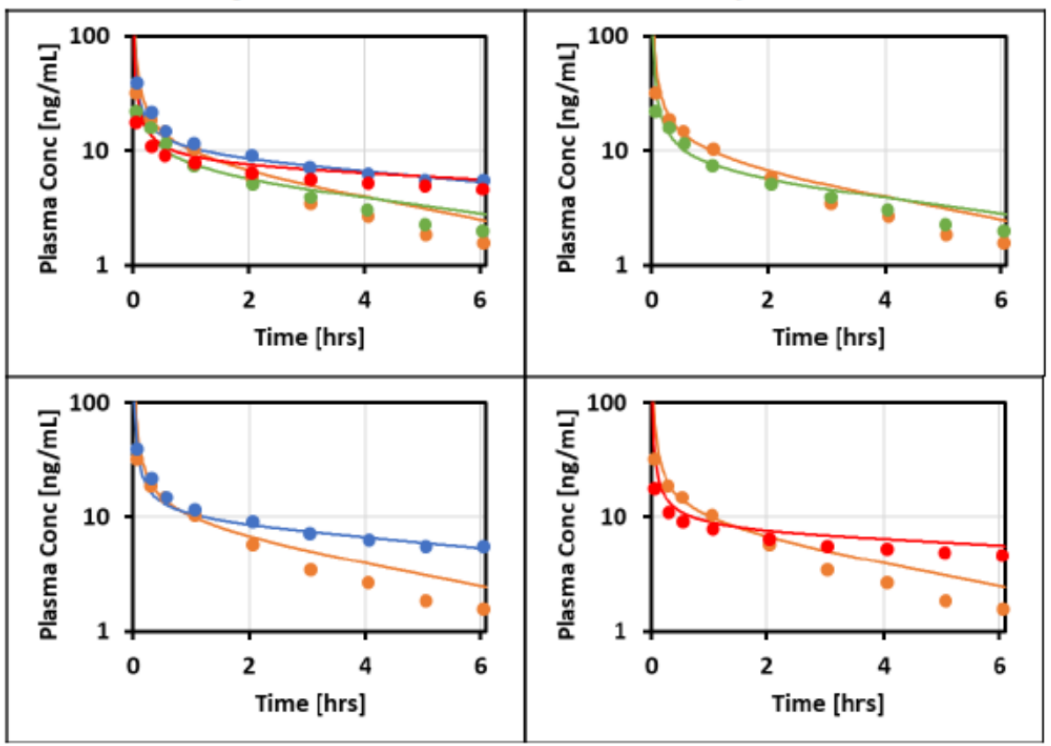


Figure A.1. Observed (points) and predicted (lines) PK profiles after 1 mg intravenous administration of midazolam in healthy subjects (orange), and subjects with different degrees of hepatic impairment: Child-Pugh A (green), Child-Pugh B (blue), Child-Pugh C (red) [6].

Healthy volunteers

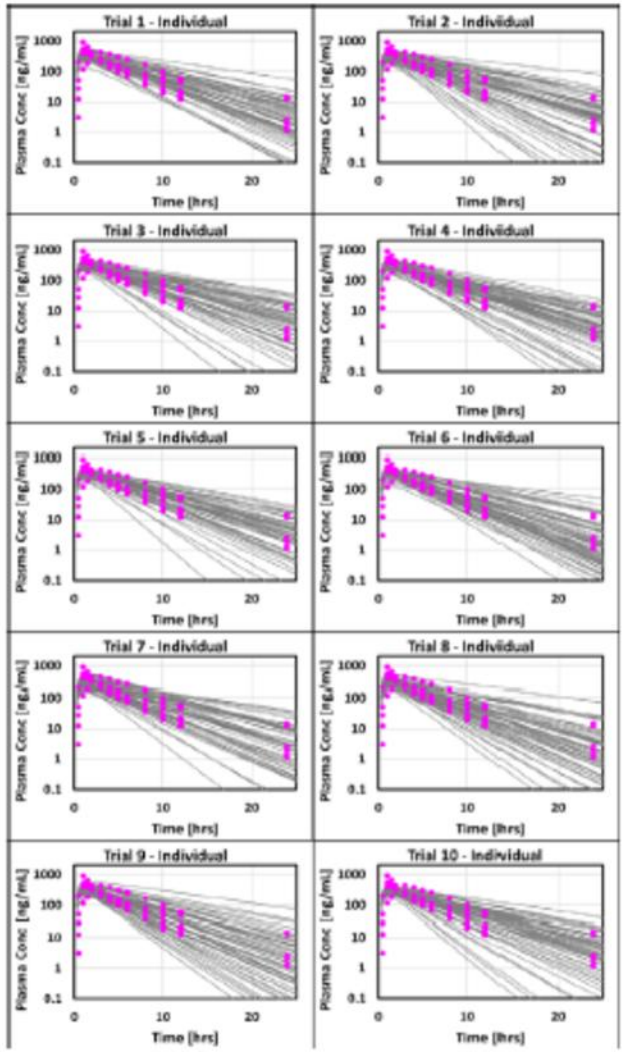
Child-Pugh A

Child-Pugh B

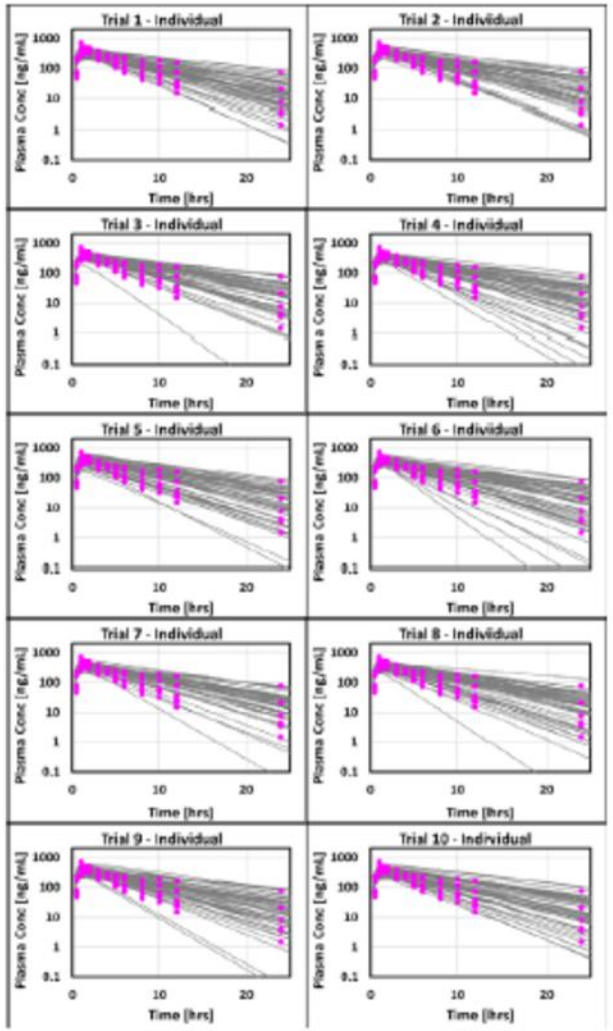
Child-Pugh C

Mild hepatic impairment

Healthy volunteers

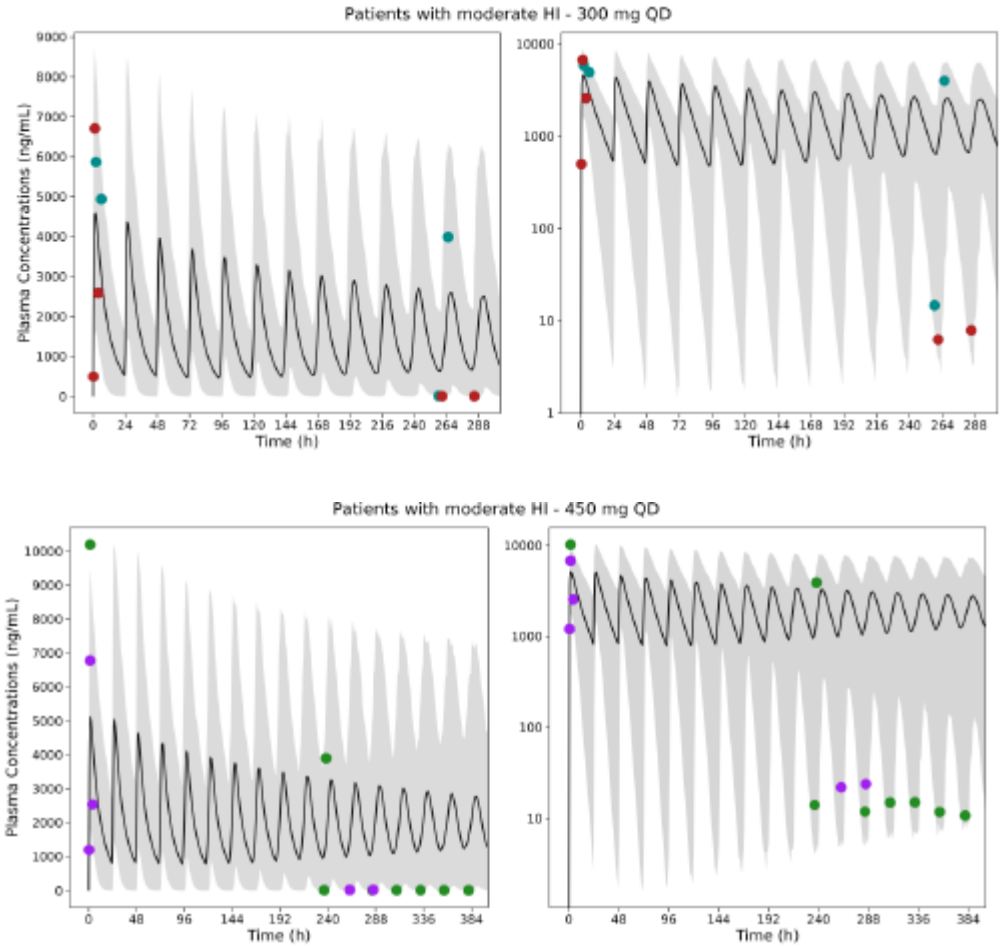


Mild HI



Observed	Mild HI
AUC0-inf (fold change)	1.55
Cmax (fold change)	1.21

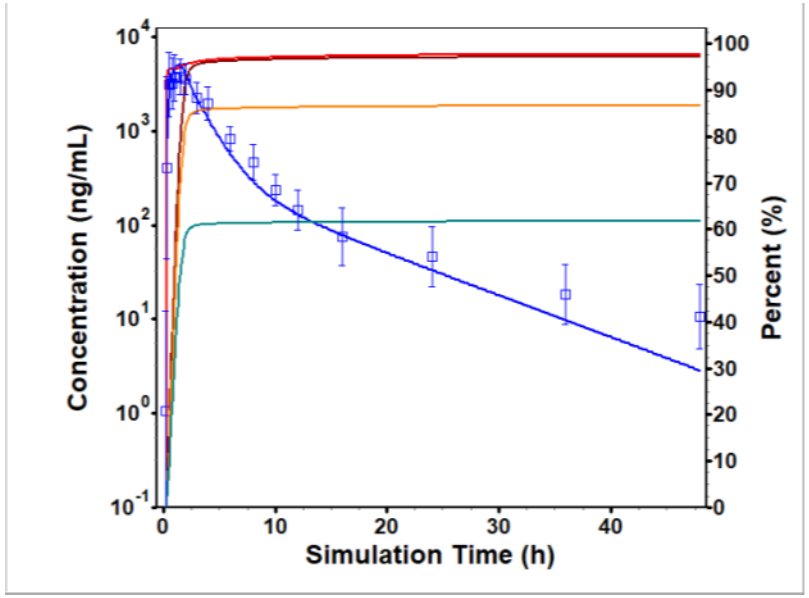
Moderate hepatic impairment

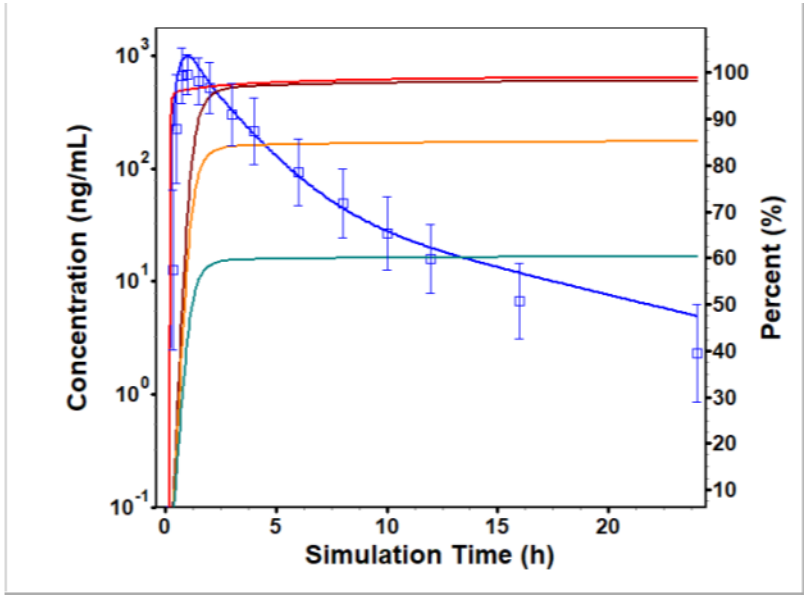


Based on these simulations, the applicant proposed alternative dosing regimen for patients with moderate hepatic impairment, however this was rejected in favour of the existing SmPC wording:

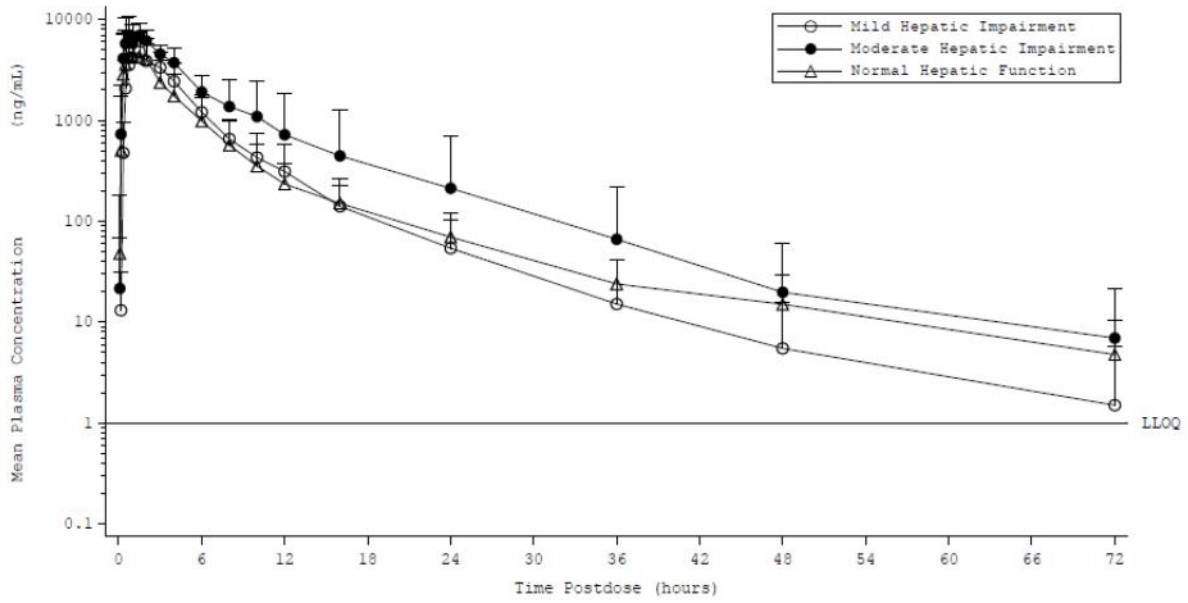
In the absence of clinical data, this drug is not recommended in patients with moderate or severe hepatic impairment.

Drug model verification





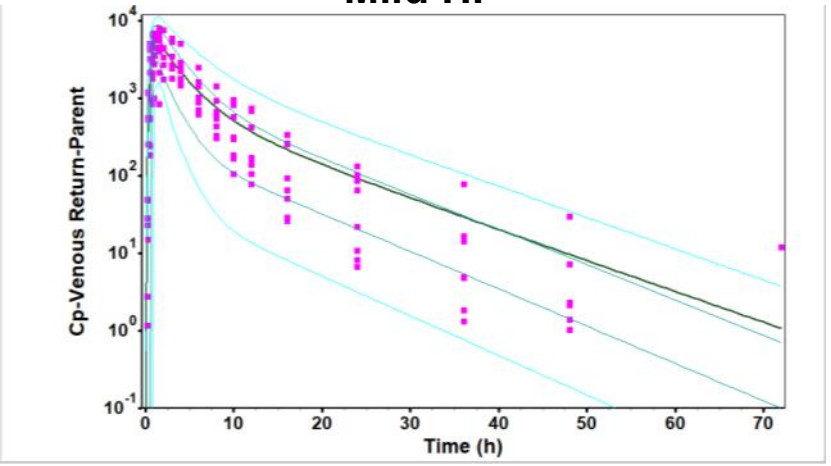
Hepatic impairment: Observed data



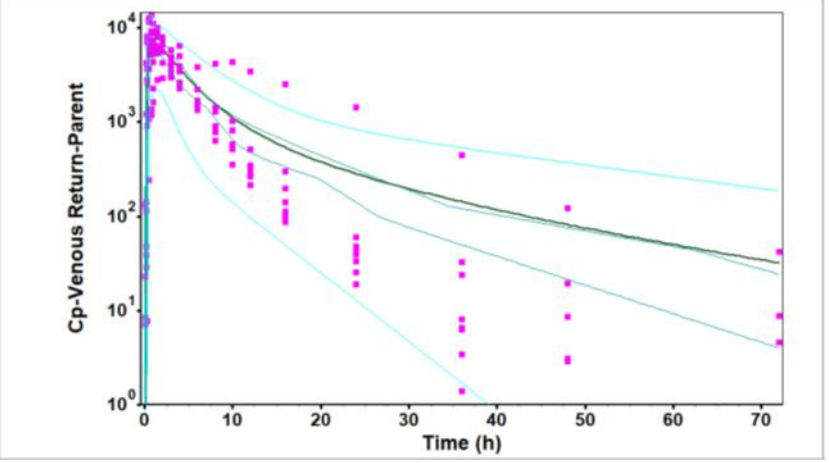
Observed	Mild HI	Moderate HI
AUC0-inf (fold change)	1.16	1.99
Cmax (fold change)	1.07	1.6

Hepatic impairment: Predicted data

Mild HI



Moderate HI



Predicted	Mild HI	Moderate HI
AUC0-inf (fold change)	1.40	2.63
Cmax (fold change)	1.35	1.34

Observed	Mild HI	Moderate HI
AUC0-inf (fold change)	1.16	1.99
Cmax (fold change)	1.07	1.6

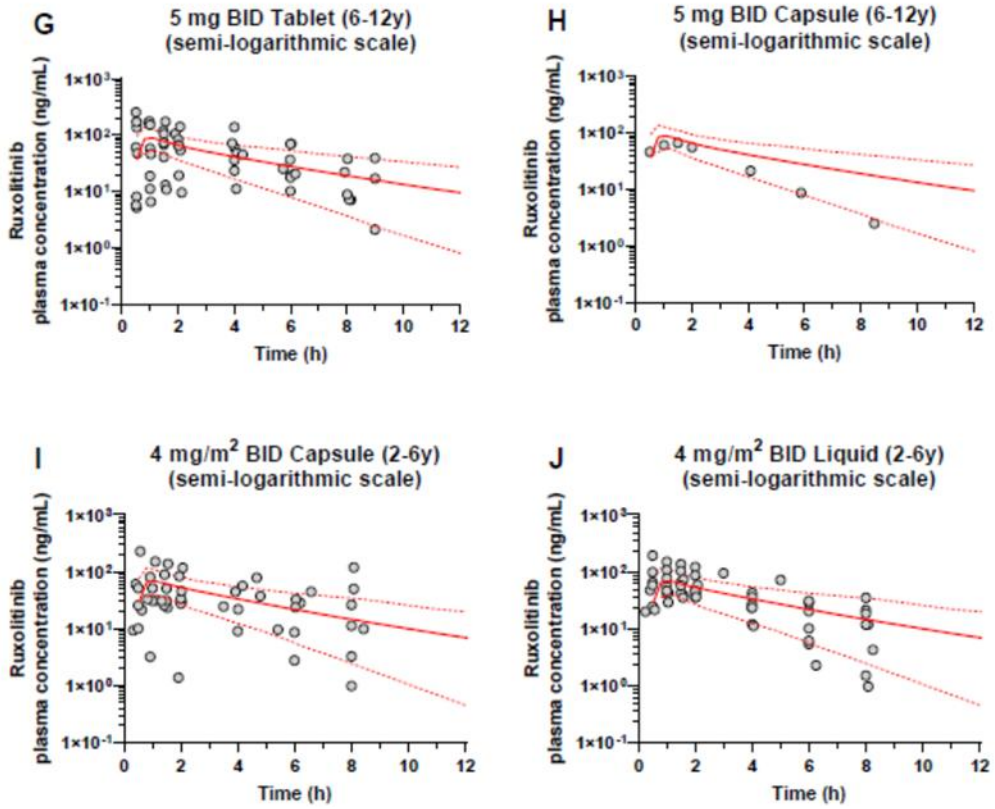
Applicant wanted to include the predicted HI predictions within the SmPC, however this was rejected in favour of the clinically observed data

Paediatrics

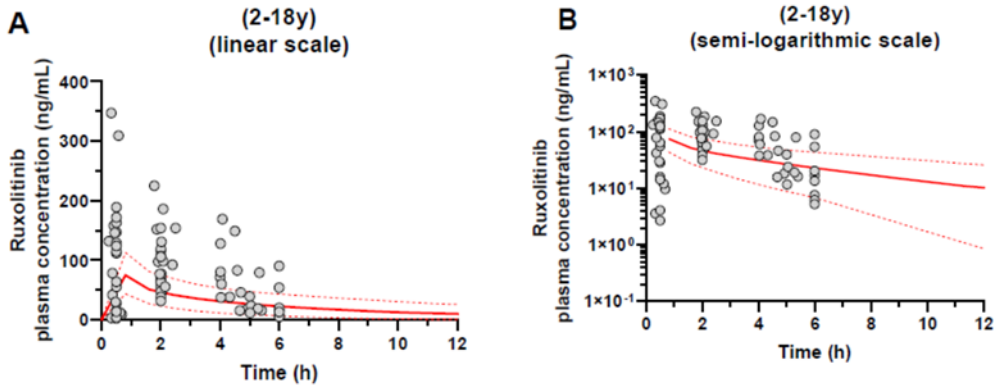
Predicting exposure in infants <2 years of age

Modelling of paediatric exposure (2 – 18 years)

Acute patients

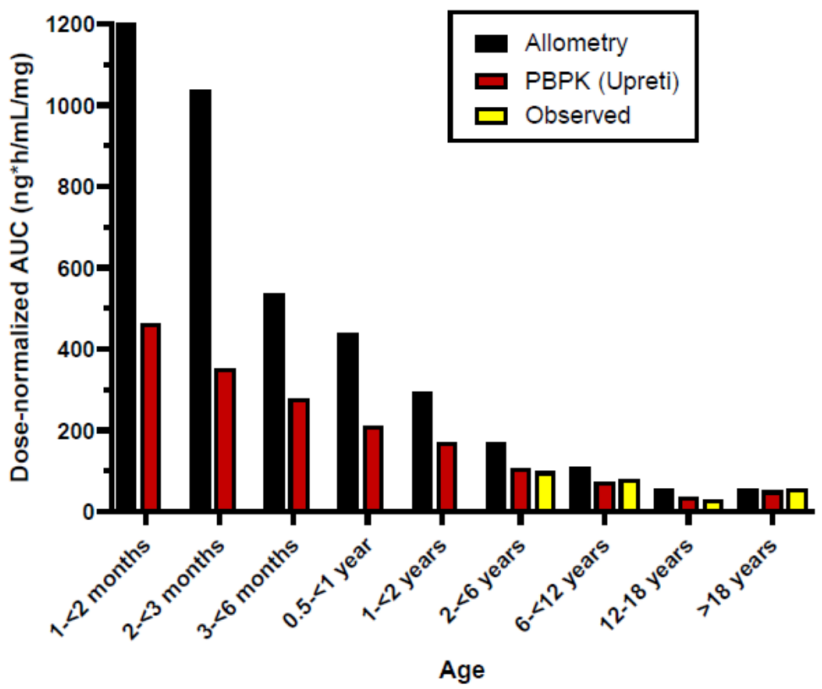


Chronic patients

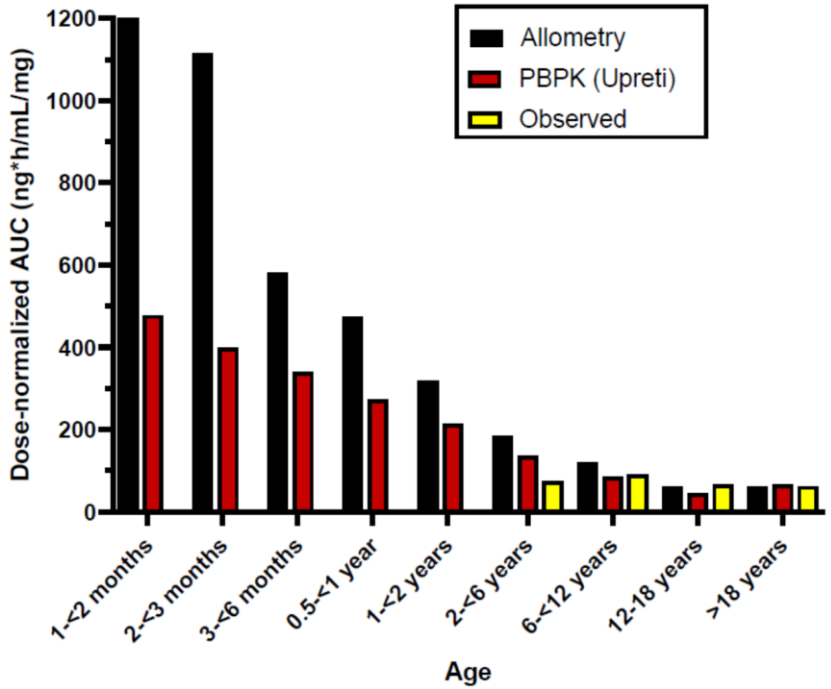


Extrapolation of paediatric exposure (1 – 24 months)

Acute patients



Chronic patients



Proposed paediatric dosing (1 – 24 months)

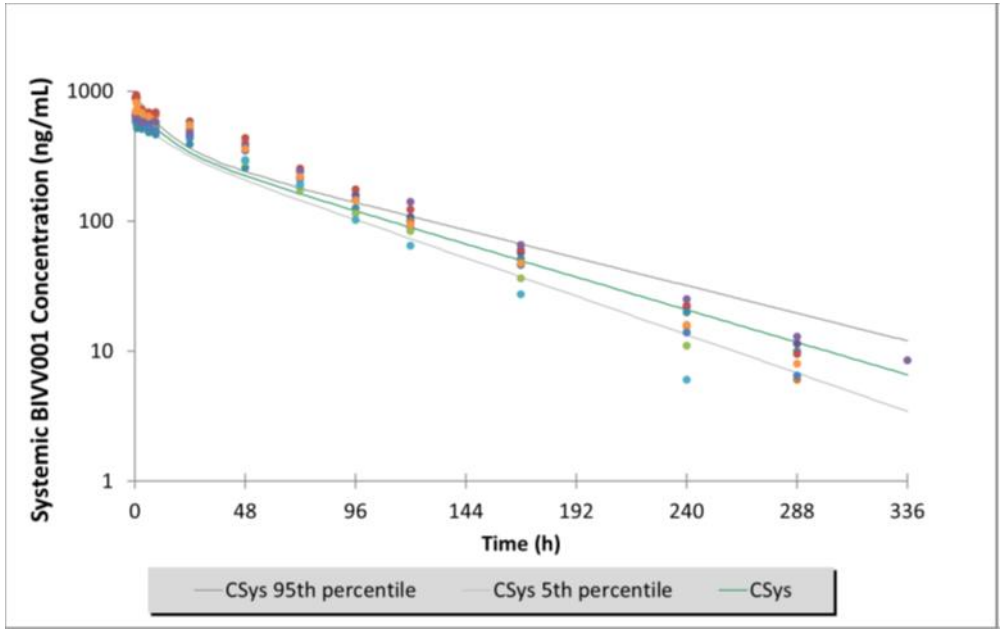
Table 7-8 Recommended dose normalized to BSA values of [redacted] based upon PBPK simulations in [redacted] pediatric patients aged from 28 days to <2 years old applying Strategy 1, 2 or 3

Age group (year) [month]	Final round dose of [redacted] (mg)[2]			Final volume of [redacted] using liquid formulation (mL)[3]			Final calculated dose normalized to BSA of [redacted] (range) (mg/m² BID)[4]			Recommended round dose normalized to BSA of [redacted] (mg/m² BID)[5]			Recommended round dose normalized to BW of [redacted] (mg/kg BID)[6]		
Strategy[1]	1	2	3	1	2	3	1	2	3	1	2	3	1	2	3
0.084 to <1.67 [1 to <2]	1.0	1.0	0.5	0.2	0.2	0.1	3.85 (3.03-5.00)	3.85 (3.03-5.00)	1.92 (1.52-2.50)	4.0	4.0	2.0	0.24	0.24	0.12
1.67 to <0.25 [2 to <3]	1.5	1.0	1.0	0.3	0.2	0.2	5.17 (4.17-6.52)	3.45 (2.78-4.35)	3.45 (2.78-4.35)	5.0	3.5	3.5	0.30	0.20	0.20
0.25 to <0.5 [3 to <6]	1.5	1.0	1.0	0.3	0.2	0.2	4.55 (3.49-6.00)	3.03 (2.33-4.00)	3.03 (2.33-4.00)	4.5	3.0	3.0	0.24	0.16	0.16
0.5 to <1 [6 to <12]	2.0	1.5	1.5	0.4	0.3	0.3	4.76 (3.28-6.45)	3.57 (2.46-4.84)	3.57 (2.46-4.84)	4.5	3.5	3.5	0.23	0.18	0.18
1 to <2 [12 to <24]	2.0	2.0	1.5	0.4	0.4	0.3	3.92 (2.74-5.13)	3.92 (2.74-5.13)	2.94 (2.06-3.85)	4.0	4.0	3.0	0.18	0.18	0.14

PBPK modelling was considered supportive of the proposed posology for 2 – 12 years old, and this was accepted by the agency.

Extrapolation into patients <2 years of age was considered a high-risk application for which the model was not sufficiently qualified, and this indication was therefore rejected.

Modelling adult exposure



Parameters		25 IU/kg		65 IU/kg	
		C_{max} (ng/mL)	AUC [a] (ng.h/mL)	C_{max} (ng/mL)	AUC [a] (ng.h/mL)
Observed [b]	Mean	282	14 950	735	43 300
	CV (%)	22.0	29.0	17.0	15.0
Predicted [c]	Mean	288	13 726	749	35 687
	CV (%)	13.9	6.32	13.9	6.32
Predicted to Observed Ratio		**1.02**	**0.92**	**1.02**	**0.82**

[a] Predicted $AUC_{0\text{-}360h}$ values were used to approximate the predicted AUC values.

[b] N = 6 for 25 IU/kg and N = 8 for 65 IU/kg

[c] N = 100

Functions for FcRn and extravasation

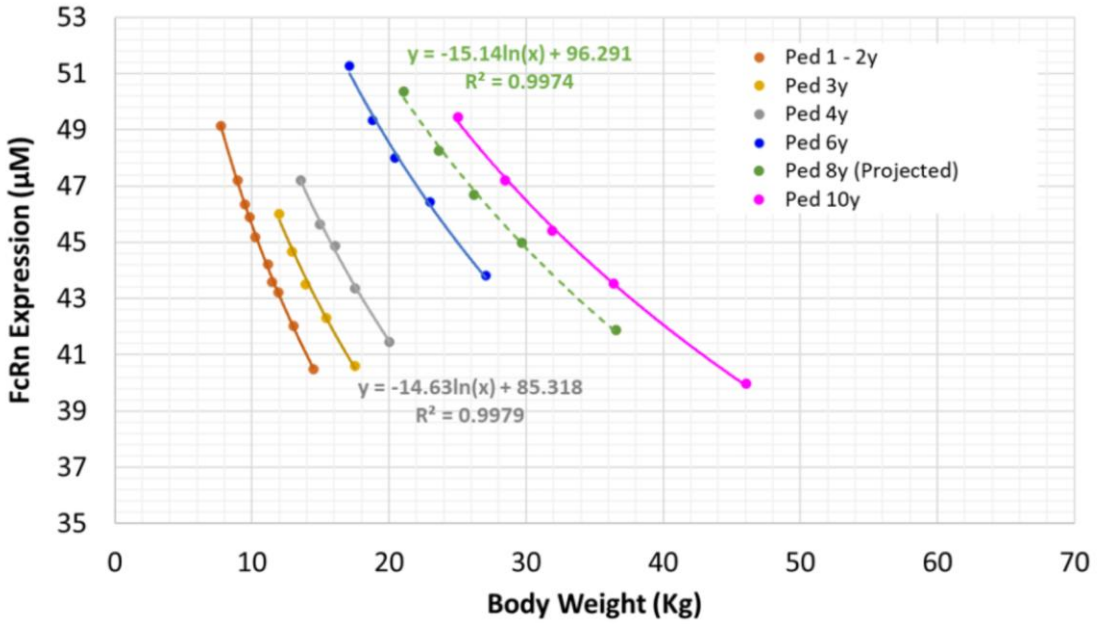
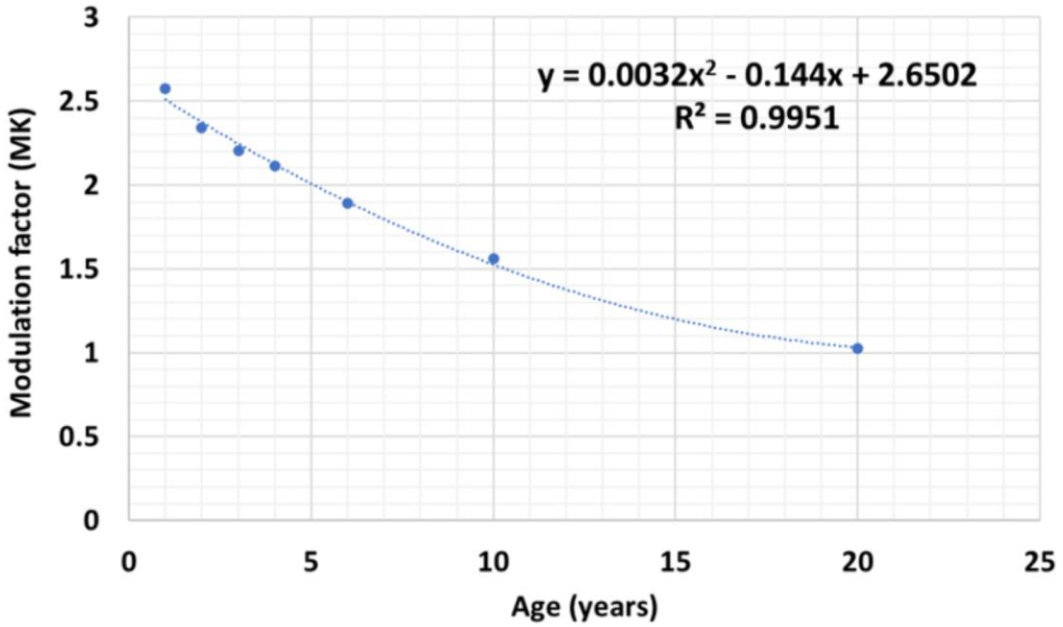


Figure 3 - Modulation factor (MK) of extravasation rate of the median participants.



Paediatric exposure

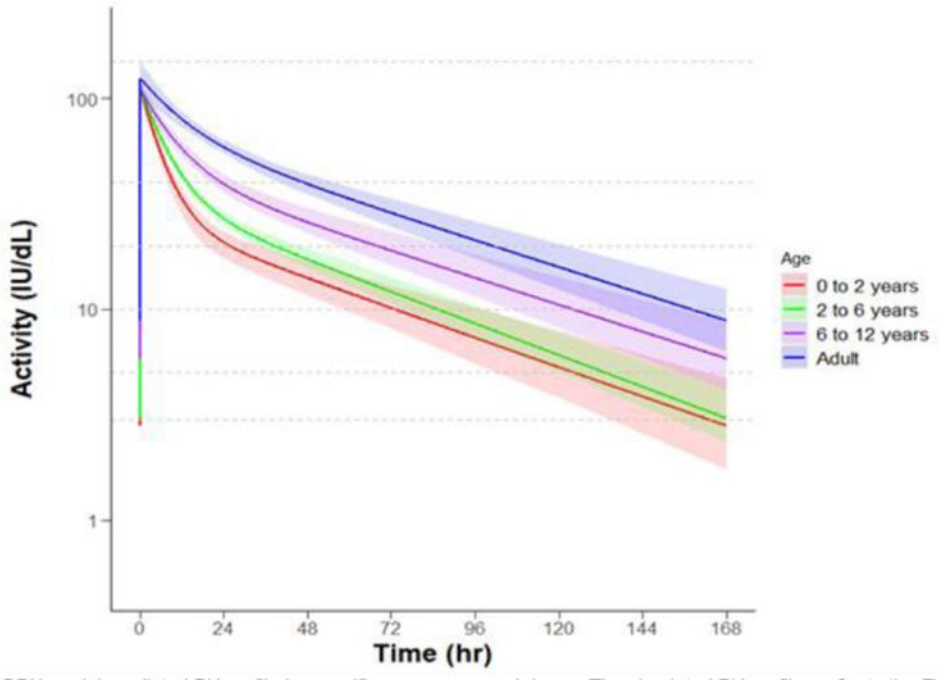


Table 12 - PBPK model simulated geometric mean [90% confidence intervals] PK parameters of [redacted] at steady state after once weekly dosing in the pediatric population

Age cohort (years)	Dose (IU/kg)	C_{max} (IU/dL)	C_{trough} (IU/dL)	C_{avg} (IU/dL)
0 to <2	50	110 [109,111]	2.64 [2.50,2.79]	13.4 [13.1,13.6]
	65	143 [141,145]	3.43 [3.25,3.62]	17.4 [17.1,17.7]
	80	175 [173, 177]	3.58 [3.42, 3.74]	20.4 [20.1, 20.7]
≥2 to <6	50	110 [109,111]	2.97 [2.88,3.07]	16.1 [15.9,16.2]
	65	143 [141,144]	3.86 [3.74,3.99]	20.9 [20.7,21.1]
	80	176 [174,177]	4.76 [4.60,4.91]	25.7 [25.5,26.0]
≥6 to <12	50	109 [107,110]	5.63 [5.40,5.87]	22.9 [22.5,23.2]
	65	141 [140,143]	7.32 [7.02,7.63]	29.7 [29.2,30.2]
	80	174 [172,176]	9.01 [8.65,9.38]	36.6 [36.0,37.2]

Abbreviations: C_{max} – maximum concentration at steady state, C_{trough} - predose concentration during repeated dosing, C_{avg} – average concentration at steady state.

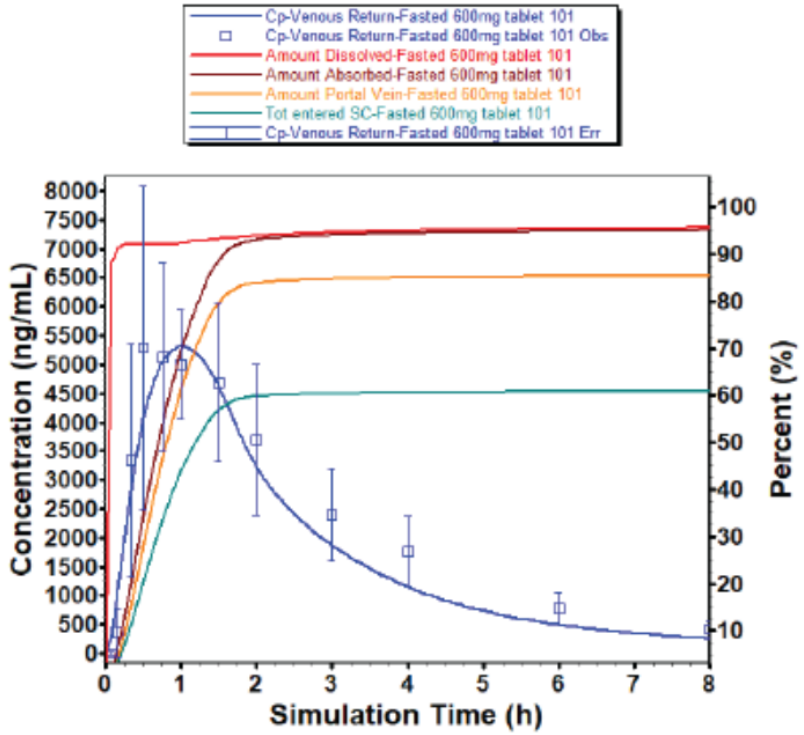
PBPK modelling was considered supportive of the proposed posology for 2 – 18 years old, and this was accepted by the agency.

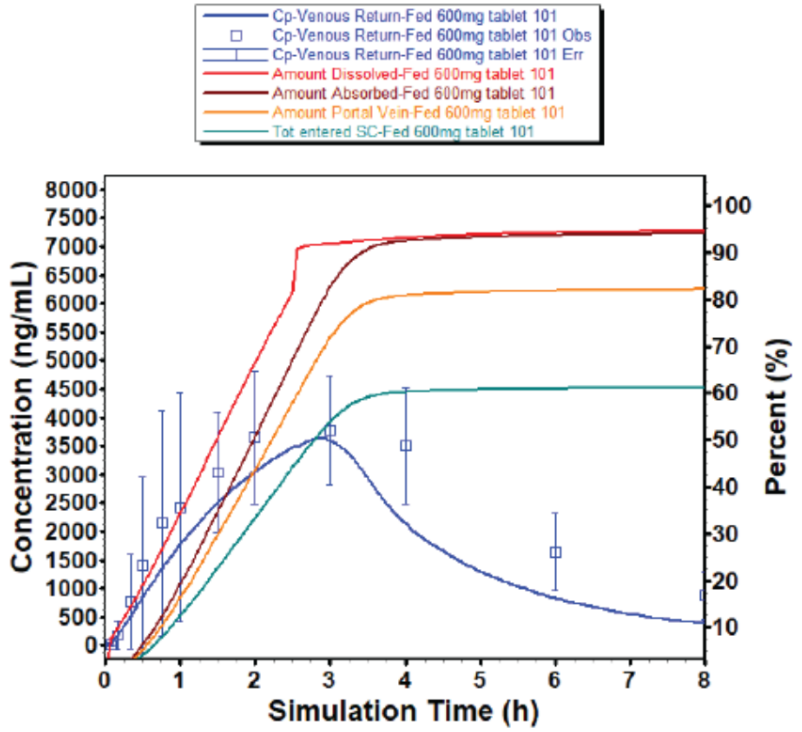
Extrapolation into patients <2 years of age was considered a high-risk application for which the model was not sufficiently qualified, and this indication was therefore rejected.

Absorption

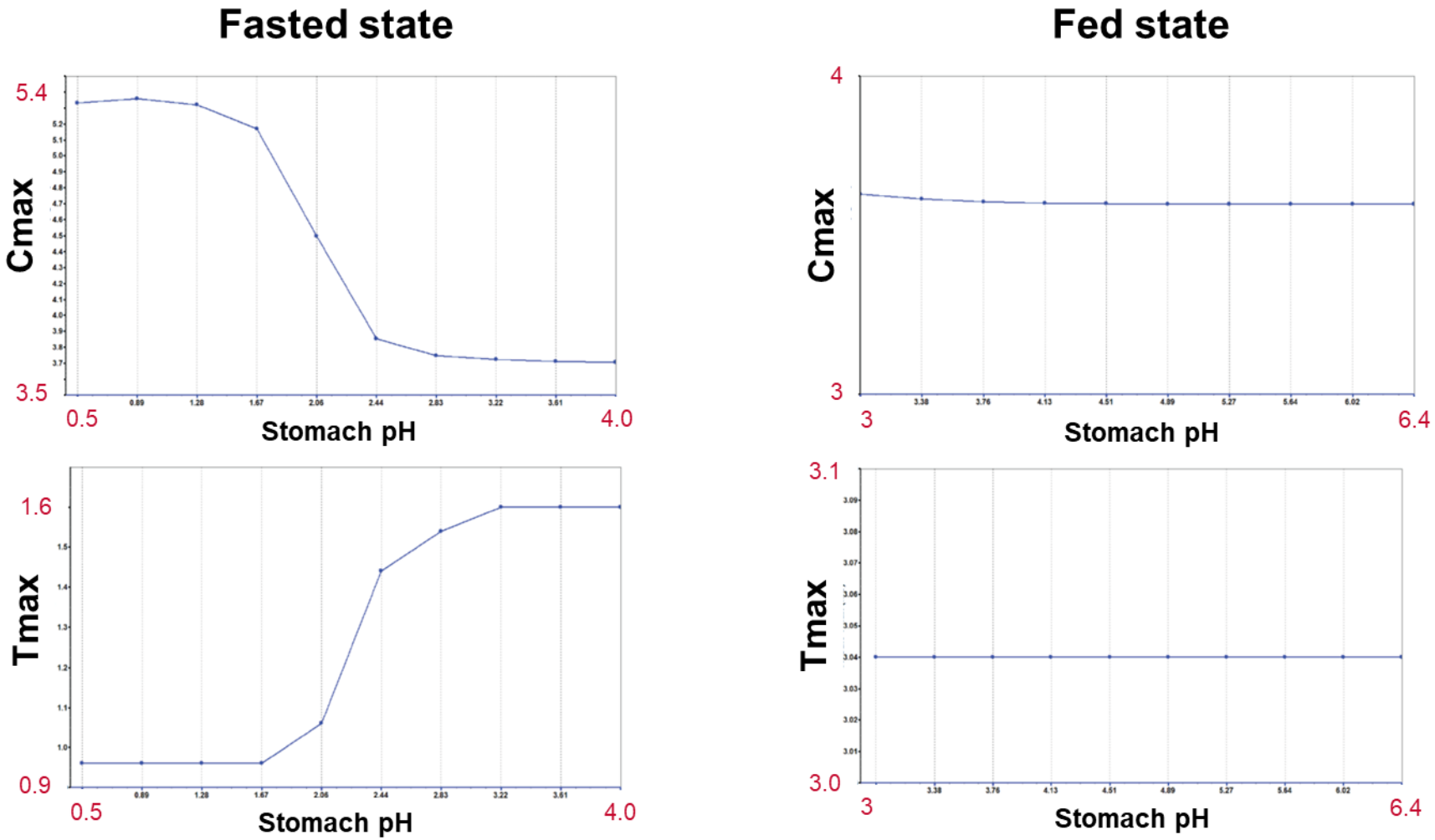
Predicting the effect of changing stomach pH on drug exposure

Mechanistic model to recapitulate the food effect





Sensitivity analysis for stomach pH



MHRA response

“Given the pH dependent solubility, an effect of drugs that modify gastric pH may be expected. A PBPK model was included but no qualification was provided. This will need to be addressed further”

Applicant responses

Additional data provided regarding the model robustness (food effect, interactions with quinidine).

Further arguments made regarding the clinical relevance of the anticipated changes in drug exposure.

Applicant provided further model qualification showing that the model was able to recapitulate (or over-estimate) the effect of changes in gastric pH for most medications in a dataset of 39 drugs.

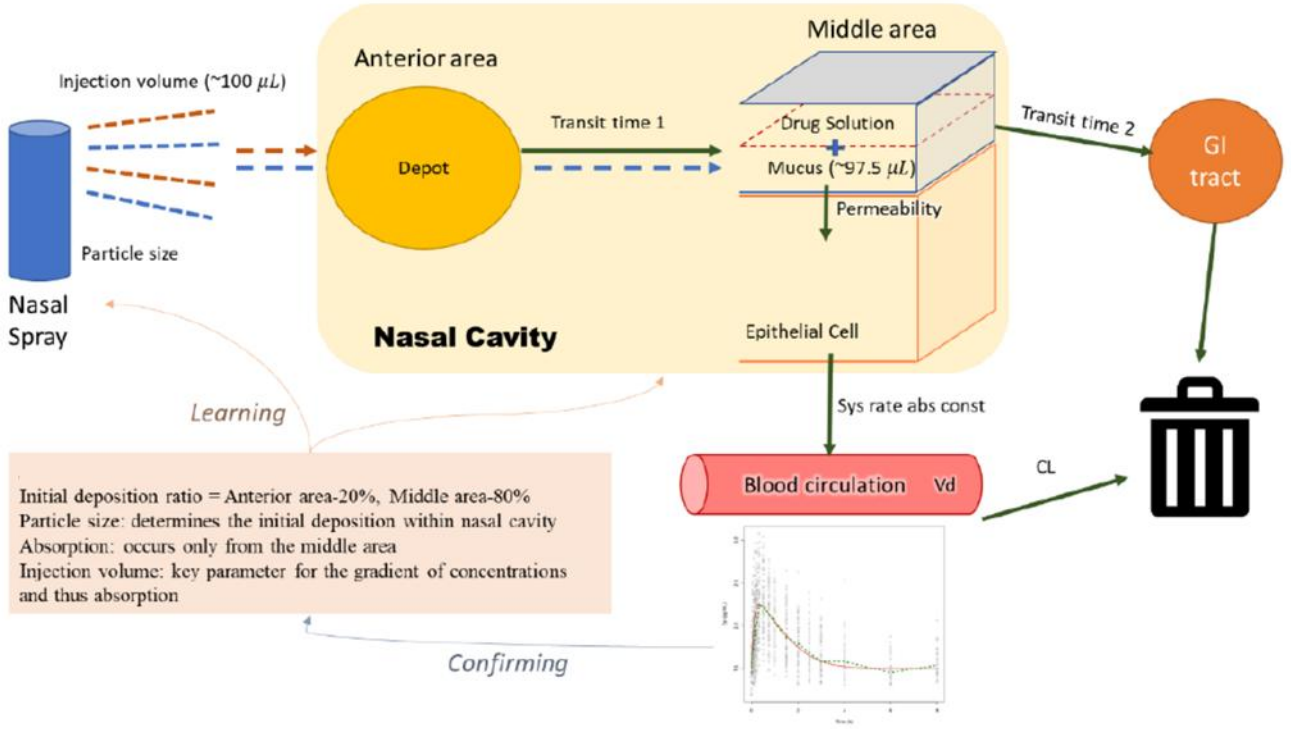
Overall, the agency felt that the *totality* of evidence supported the applicant's claim that there would be little clinical effect of changes in stomach acid pH.

As such, despite initial concerns, it was deemed that no clinical trial investigating DDIs with ARAs was required.

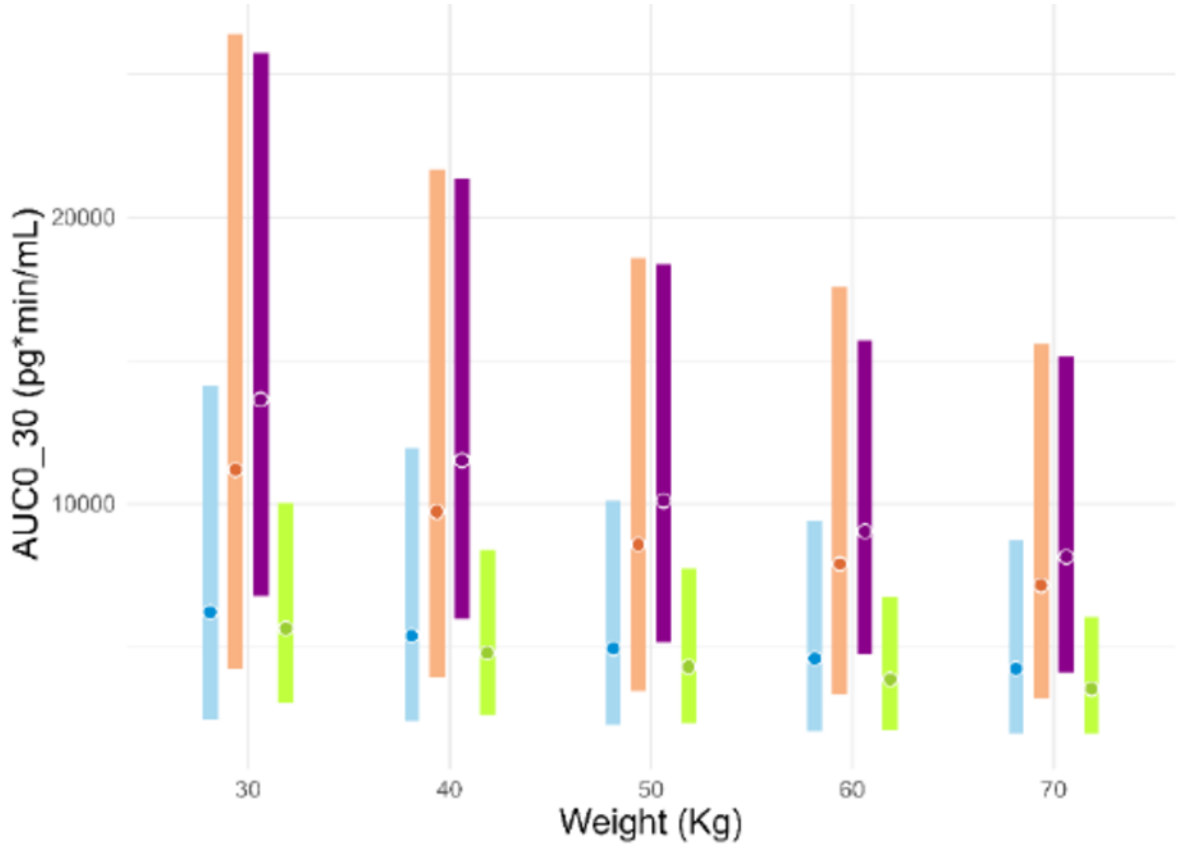
Absorption

Utilising a mechanistic model for nasal absorption to predict paediatric exposure

Mechanistic model of nasal absorption



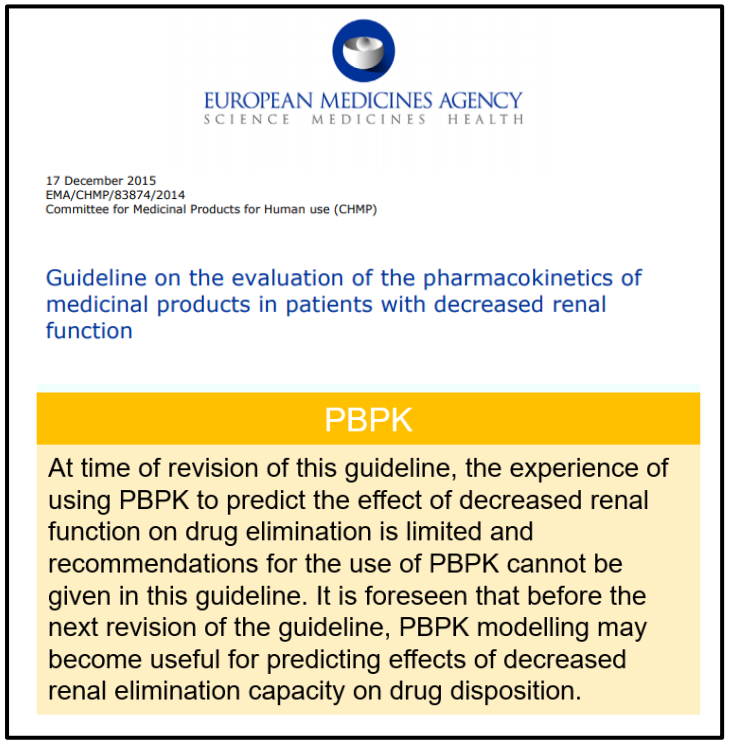
Similar exposure following intake of nasal and existing formulations



PBPK model with nasal absorption supported the clinical data in showing that exposure to the 2 mg nasal formulation was similar to that of the existing formulation across a range of weight classes, supporting the paediatric indication that the applicant applied for.

Future directions

- Transporter DDIs
- Qualification of disease states
  - Cancer, hepatic impairment, renal impairment, etc
- Predictions for pregnant or breastfeeding individuals
  - PBPK mentioned in ICH E21
- Physiologically Based Biopharmaceutics Modelling (PBBM)
- More data needed for qualification!



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

17 December 2015
EMA/CHMP/83874/2014
Committee for Medicinal Products for Human use (CHMP)

Guideline on the evaluation of the pharmacokinetics of medicinal products in patients with decreased renal function

PBPK

At time of revision of this guideline, the experience of using PBPK to predict the effect of decreased renal function on drug elimination is limited and recommendations for the use of PBPK cannot be given in this guideline. It is foreseen that before the next revision of the guideline, PBPK modelling may become useful for predicting effects of decreased renal elimination capacity on drug disposition.

Conclusions

- The MHRA encourages the use of PBPK modelling to reduce the clinical trial burden during drug development
- PBPK models can be used for a range of applications throughout drug development
- Model evaluation by the MHRA is commensurate with model risk
- Qualification of model performance is critical for model acceptance
- Where limited model qualification is available, models may be accepted as supportive
  - **We want to see your data!**

With thanks to

Susan Cole
Essam Kerwash
Mary Malamatari
Dany Bozadzhieva
Nisha Kanwar

Medicines & Healthcare products Regulatory Agency

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