# Physiologically Based Pharmacokinetic Modeling to Evaluate Hepatic and Intestinal CYP3A4 Ontogeny

## Insights from Elexacaftor/Tezacaftor/Ivacaftor in Children with Cystic Fibrosis

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# Disclosures

Femke Elzinga and Paola Mian have no conflicts of interest to declare.

Paul Malik is a full-time employee of Ionis Pharmaceuticals and may hold stock or stock options.

The perspectives shared are those of Femke Elzinga and not the position of the UMCG or Ionis Pharmaceuticals.

# Getting the first pediatric dose right



**Simple dose extrapolation**
(body weight or body surface area)



# Children are not small adults!

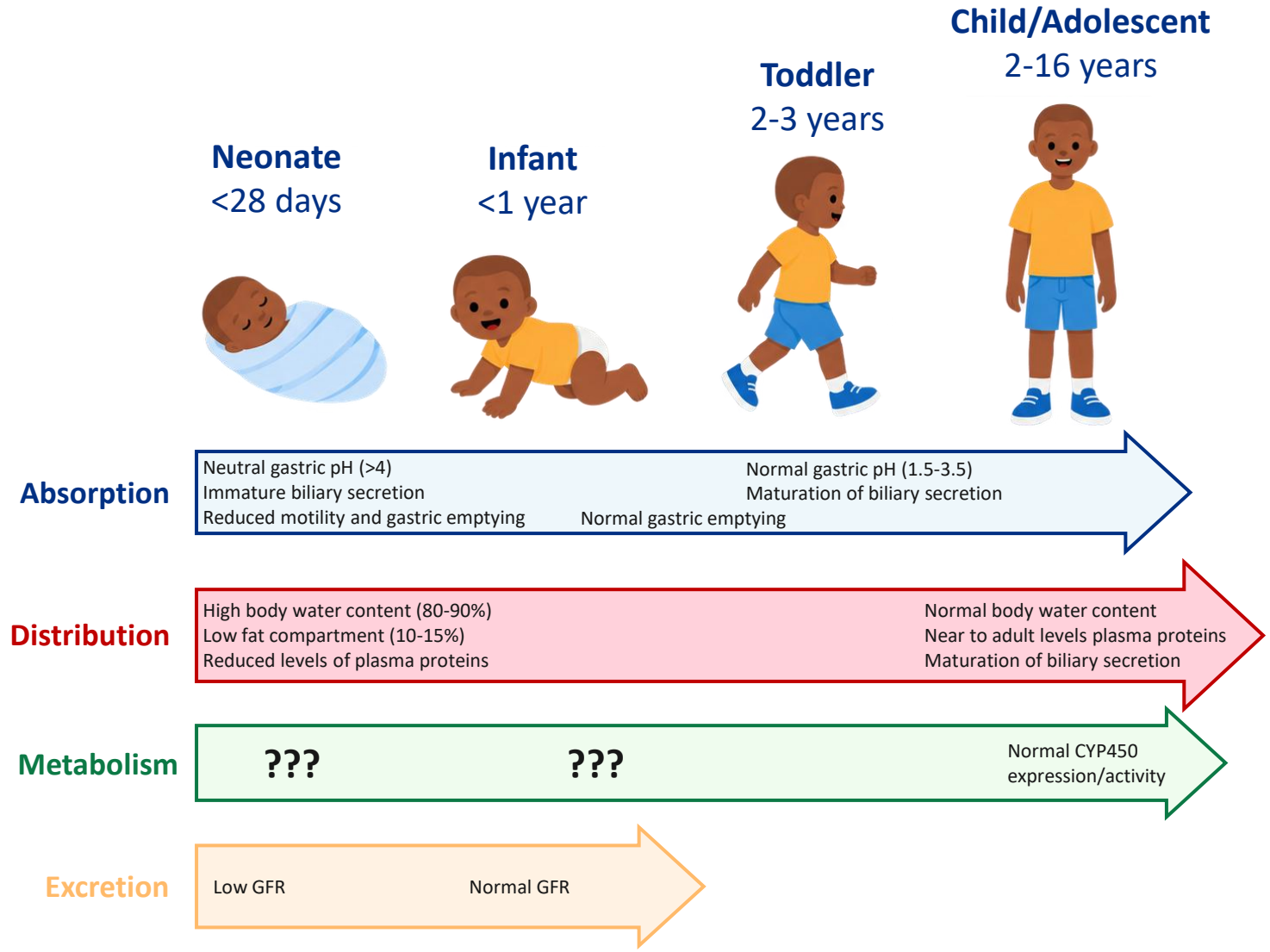
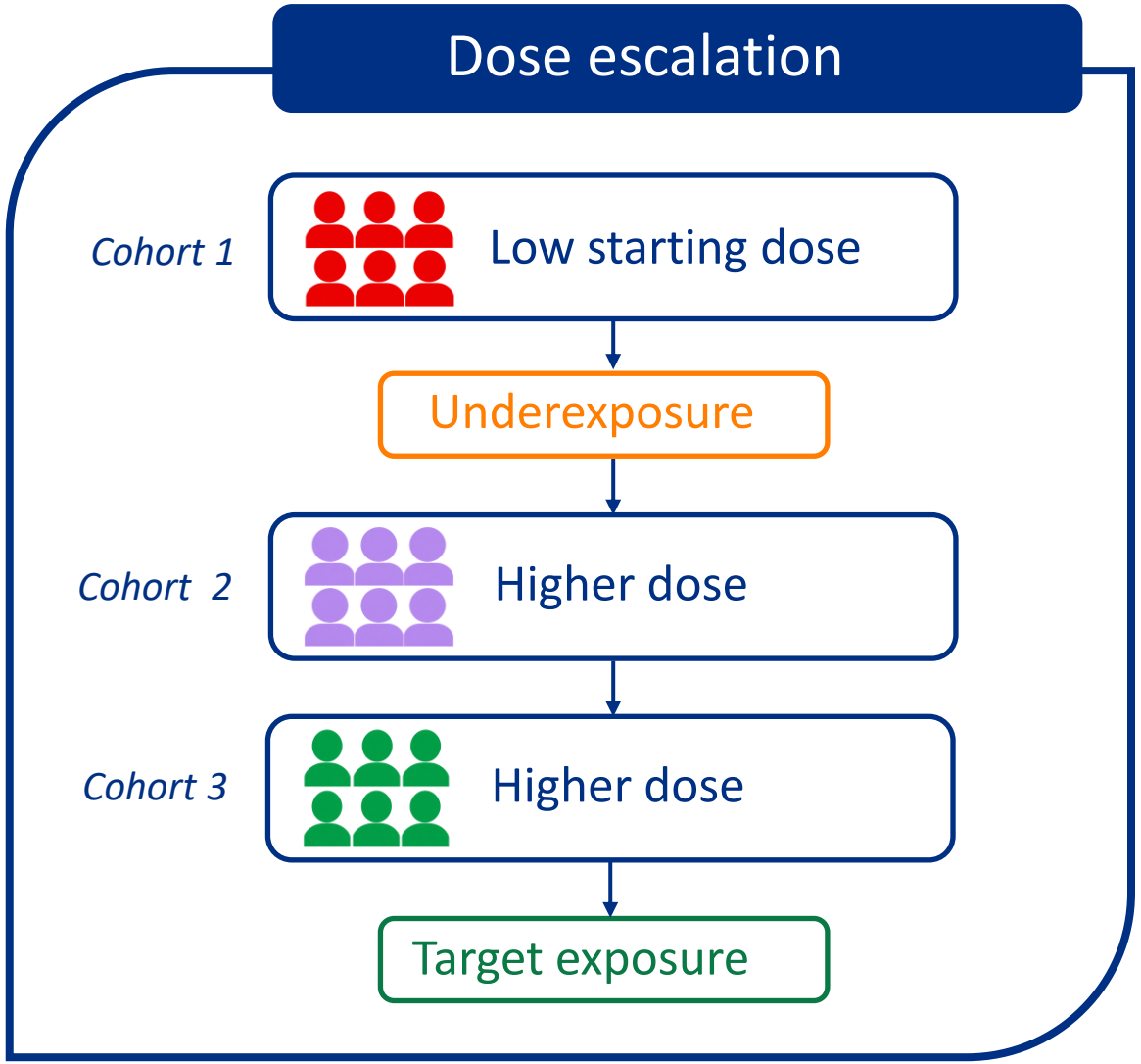
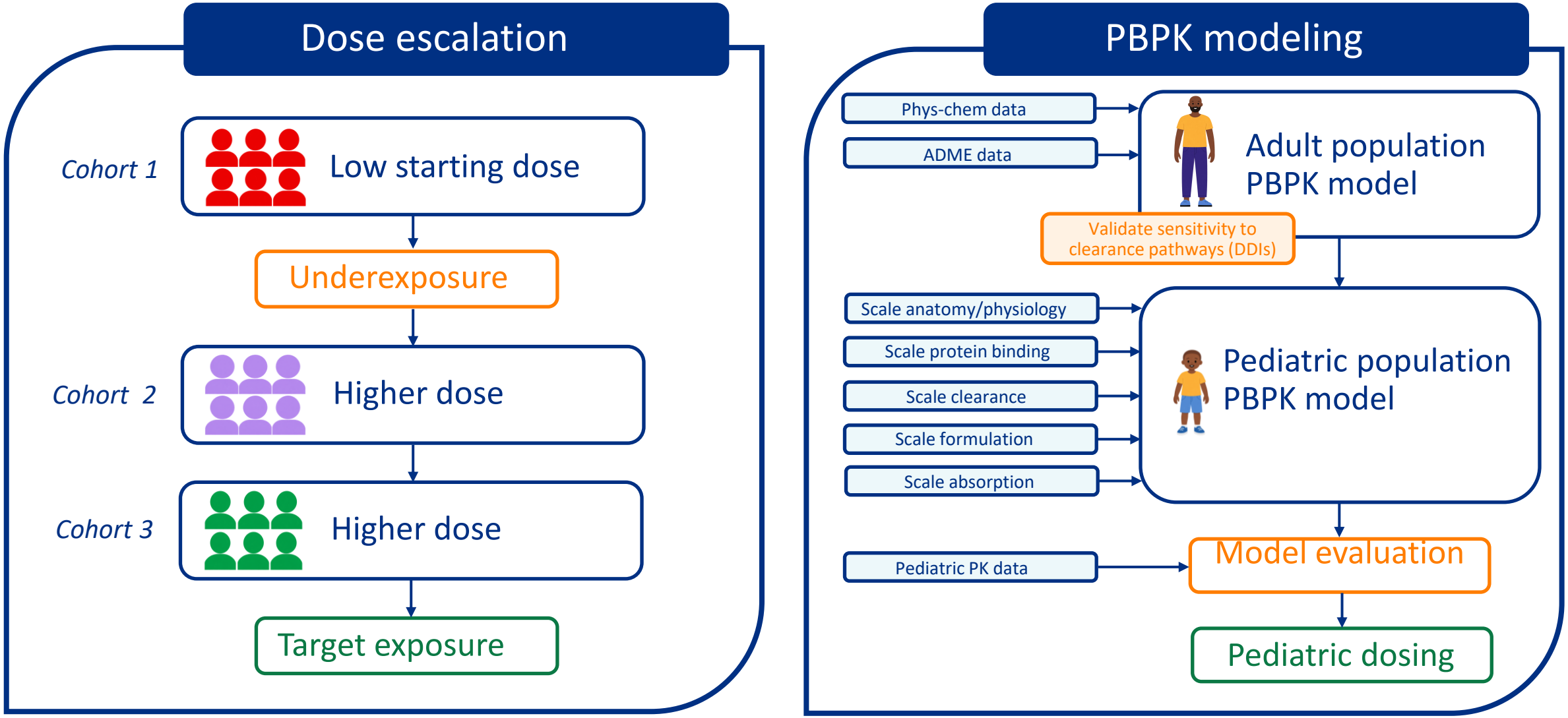



*Figure created with data from: Kearns et al. N Engl J Med. 349, 2003*

# Better accuracy for the first-in-pediatric dose yields greater learning from our clinical trials



# Better accuracy for the first-in-pediatric dose yields greater learning from our clinical trials



# CYP3A4 ontogeny introduces uncertainty in pediatric dose selection



Adult dose = 1 mg/kg

**One-year-old infant**



**Allometric scaling**

$$CL_{child} = CL_{adult} \times \left(\frac{10\ kg}{75\ kg}\right)^{0.75}$$

Pediatric dose = 1.66 mg/kg

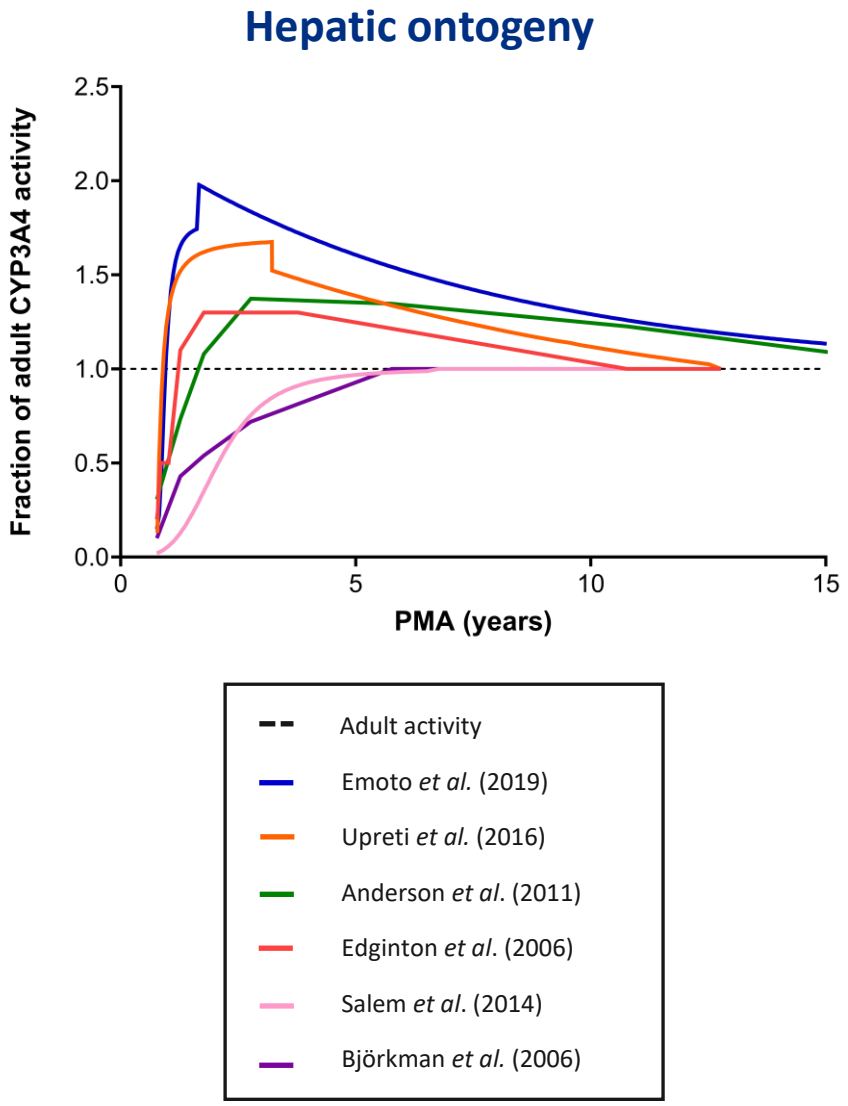
**CYP3A4 scaling methods**

| | Dose ∝ CL/kg<br>Ontogeny fold = Dose fold |
|---|---|
| Emoto *et al.* (2019) | 1.96 mg/kg |
| Upreti *et al.* (2016) | 1.62 mg/kg |
| Edginton *et al.* (2006) | 1.30 mg/kg |
| Anderson *et al*. (2011) | 1.08 mg/kg |
| Salem *et al*. (2014) | 0.74 mg/kg |
| Johnson *et al*. (2001) | 0.56 mg/kg |
| Björkman *et al*. (2006) | 0.54 mg/kg |

Picking the right ontogeny function matters!

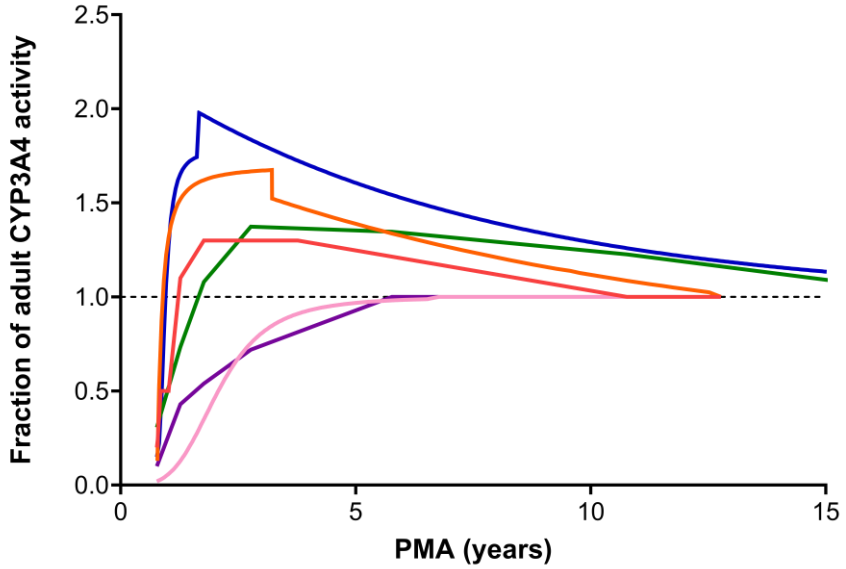
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# CYP3A4 ontogeny functions



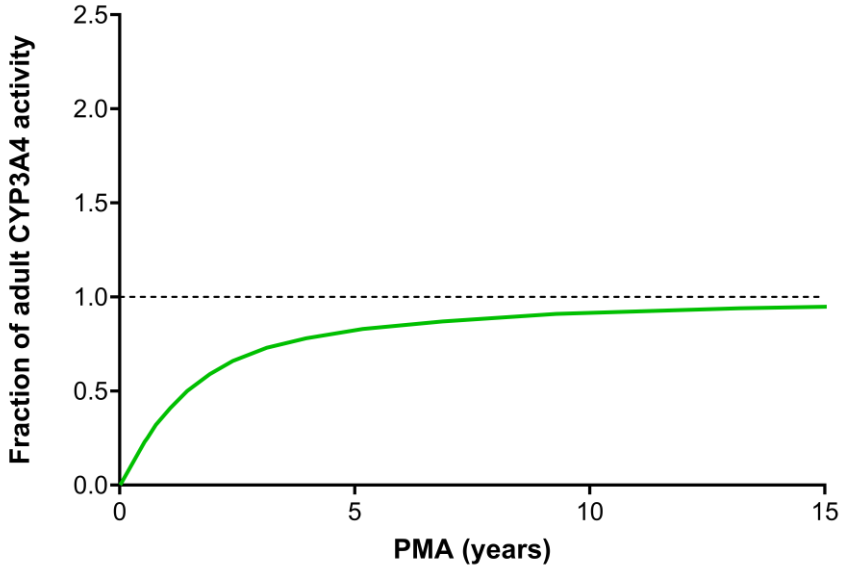
# CYP3A4 ontogeny functions

## Hepatic ontogeny




- Adult activity
- Emoto *et al.* (2019)
- Upreti *et al.* (2016)
- Anderson *et al*. (2011)
- Edginton *et al*. (2006)
- Salem *et al*. (2014)
- Björkman *et al.* (2006)

## Intestinal ontogeny




- Adult activity
- Johnson *et al.* (2001)

Alternative intestinal CYP3A4 ontogenies showed no meaningful differences or lacked sufficient precedent

# And it gets even more complicated…

**$F_{m,CYP3A4}$ ≥95%**

Midazolam PO

Ibrutinib PO

Buspirone PO

**+ Itraconazole**

Strong CYP3A4 inhibitor

**=**

**DDI ratios**

Midazolam: ↑ 6-fold [1]

Ibrutinib: ↑ 10-fold [2]

Buspirone: ↑ 14.5-fold [3]

**Differential DDI effects of the same strong inhibitor indicate that CYP3A4 substrate drugs can be uniquely sensitive to intestinal metabolism and first-pass extraction.**

**Before scaling these processes to children, we MUST demonstrate that our model can adequately describe what happens when CYP3A4 expression/activity is modulated in adults.**

[1] *Hanke et al. CPT Pharmacometrics Syst Pharmacol. 7, 2018*
[2] *Tapaninen et al. Clin Transl Sci. 13, 2020*
[3] *Kivistö et al. Pharmcol Toxicol. 84, 1999*

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# Objective

To evaluate which hepatic and intestinal CYP3A4 ontogeny functions best predict drug exposure in young children

*This workflow recapitulates one that was performed by these authors on a similar compound for first in pediatric dose selection which earned regulatory acceptance by FDA, EMA and PMDA, and was considered acceptable pediatric dose justification for an NDA submission*

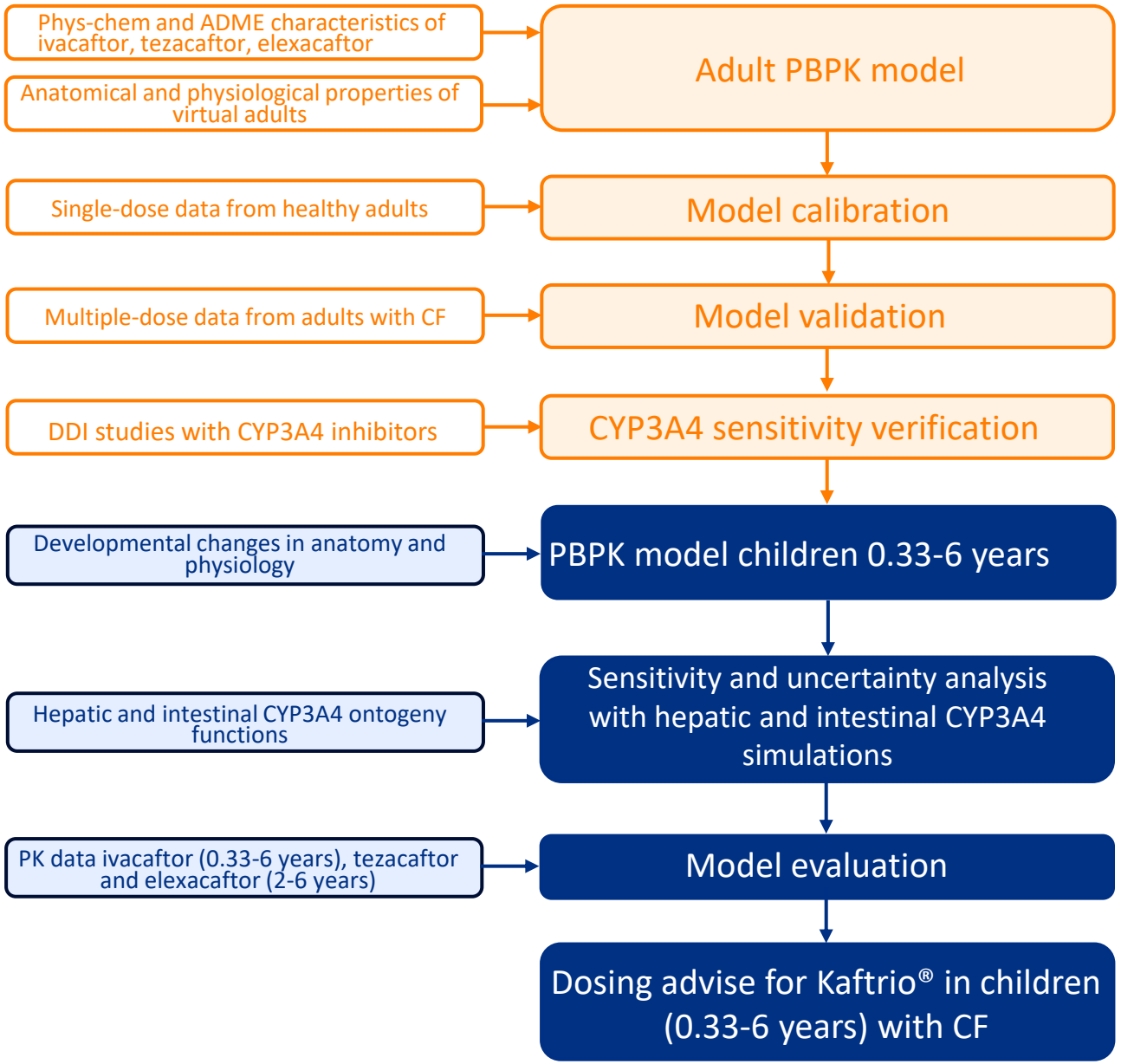
# Clinical pharmacokinetics

| | Ivacaftor | Tezacaftor | Elexacaftor |
|---|---|---|---|
| Molecular weight | 392.49 g/mol | 520.50 g/mol | 597.66 g/mol |
| Acid-base status | $pK_a$ 9.4 (acid)<br>$pK_a$ 11.6 (base) | $pK_a$ 11.54 | $pK_a$ 5.02 |
| Lipophilicity (logP) | 4.6 | 2.9 | 5.6 |
| Fraction unbound | 0.0013 | 0.009 | 0.00704 |
| Main plasma protein | Albumin | Albumin | Albumin |
| Fraction absorbed | 100% | 82% | 92% |
| Fraction of absorbed drug metabolized by CYP3A4 | ~100% | 74% | 82% |
| Fraction of absorbed drug excreted unchanged in | | | |
| feces | ~0% | 26% | 18% |
| urine | <LLOQ | <1% | <LLOQ |
| Substrates for transporters | - | P-gp<br>BCRP | P-gp<br>BCRP |
| | *Not modelled* | → OATP1B1 | |

# Oral absorption characteristics

| | Ivacaftor | Tezacaftor | Elexacaftor |
|---|---|---|---|
| Formulated as amorphous solid dispersion | ✓ | ✓ | ✓ |
| Food effect | | No | |
| $AUC_{inf}$ | 3.08 | | 1.89 |
| $C_{max}$ | 4.32 | | 3.87 |
| Gut metabolism | ✓ | ✓ | ✗ |
| Specific intestinal permeability | 1.19E-3 cm/s | 1.41E-5 cm/s | 3.08E-6 cm/s |
| Source | Hong *et al*. 2022 (Table S1); SimCyp Peff model | Hong *et al*. 2022 (Table S2); Caco-2 x Scalar of 2.997 | Hong *et al*. 2022 (Table S3); Caco-2 |

# Model building philosophy




**Parameters that are optimized with parameter identification tool**

| Compound | Optimized parameters |
|---|---|
| Ivacaftor | CYP3A4 specific clearance |
| Tezacaftor | CYP3A4 specific clearance<br>Biliary transporter maximum rate ($V_{max}$)<br>Cell permeability (global) |
| Elexacaftor | CYP3A4 specific clearance<br>Biliary transporter maximum rate ($V_{max}$) |

Parameter identifiability was confirmed by multiple global estimations from randomized start values arriving at a consistent solution

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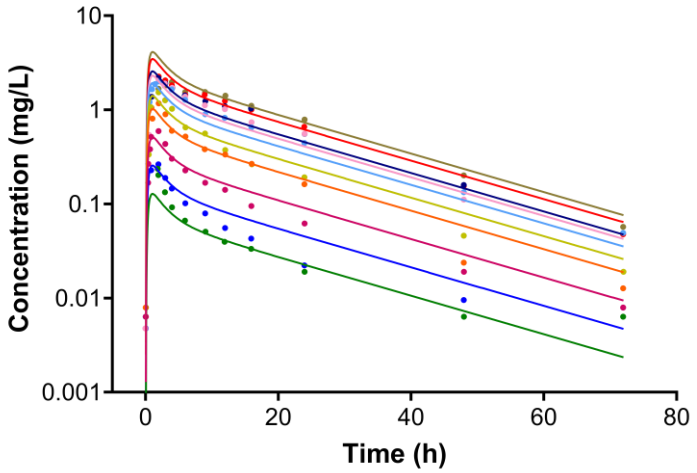
# Tips and tricks for BCS Class 2 compounds

| Problem | Solution |
|---|---|
| No IV data to confirm human volume of distribution | IV data from monkeys to inform volume of distribution; manual fit logP to $C_{max,ss}/C_{min,ss}$ |
| Food effect, formulation is an amorphous solid dispersion, poor solubility, sensitivity to changes in intestinal pH | Particle dissolution model |
| Evidence of gut metabolism by CYP3A4 from DDIs | Fix mucosal permeability (basolateral) to specific intestinal permeability from Caco-2 |
| Absorption and distribution show signs of being permeability rate limited; atypical curve shape | Cell permeability is included in the parameter identification while lipophilicity is fixed (tezacaftor) |

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# Model fit: Single dose

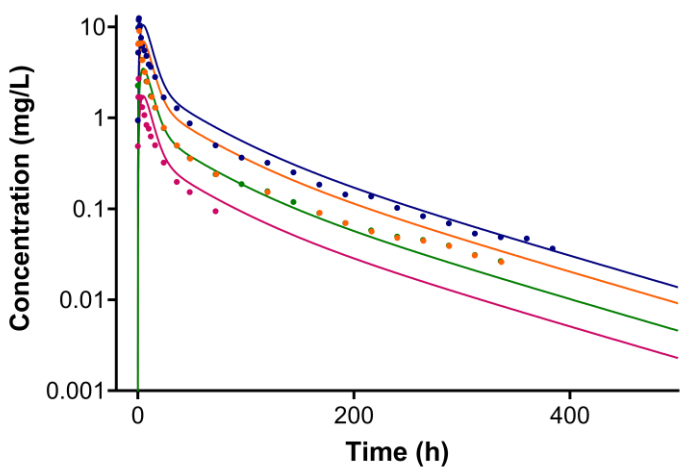
## Ivacaftor - Fasted




| | $AUC_{Inf}$ Simulated/observed | $C_{max}$ Simulated/observed |
|---|---|---|
| 25 mg | 1.04 | 0.59 |
| 50 mg | 1.45 | 1.0 |
| 100 mg | 1.21 | 0.84 |
| 200 mg | 1.06 | 0.85 |
| 275 mg | 0.93 | 0.83 |
| 375 mg | 0.79 | 1.1 |
| 450 mg | 0.90 | 1.17 |
| 500 mg | 0.72 | 1.51 |
| 675 mg | 0.81 | 1.79 |
| 800 mg | 1.24 | 1.78 |
| **GMFE** | **1.01** | **1.05** |

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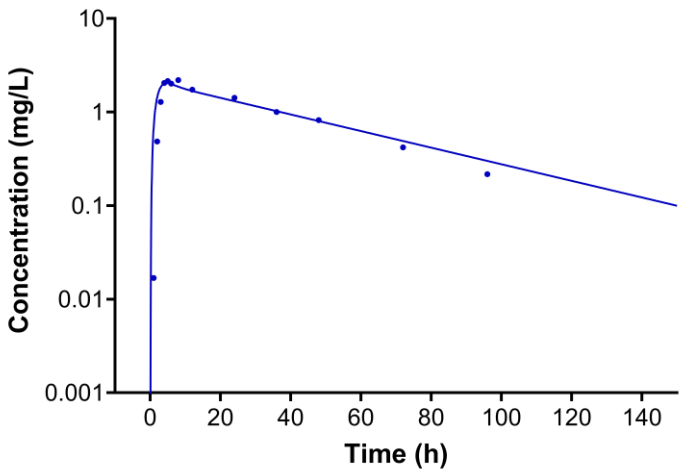
## Tezacaftor - Fasted




| | $AUC_{Inf}$ Simulated/observed | $C_{max}$ Simulated/observed |
|---|---|---|
| 50 mg | 1.40 | 0.54 |
| 100 mg | 1.05 | 0.60 |
| 200 mg | 1.73 | 0.67 |
| 300 mg | 1.37 | 0.77 |
| **GMFE** | **1.39** | **0.64** |

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## Elexacaftor - Fed

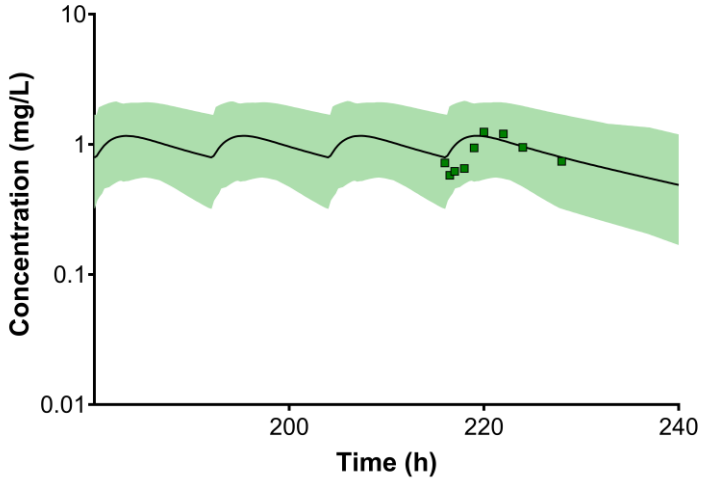



| | $AUC_{Inf}$ Simulated/observed | $C_{max}$ Simulated/observed |
|---|---|---|
| 120 mg | 1.07 | 0.81 |

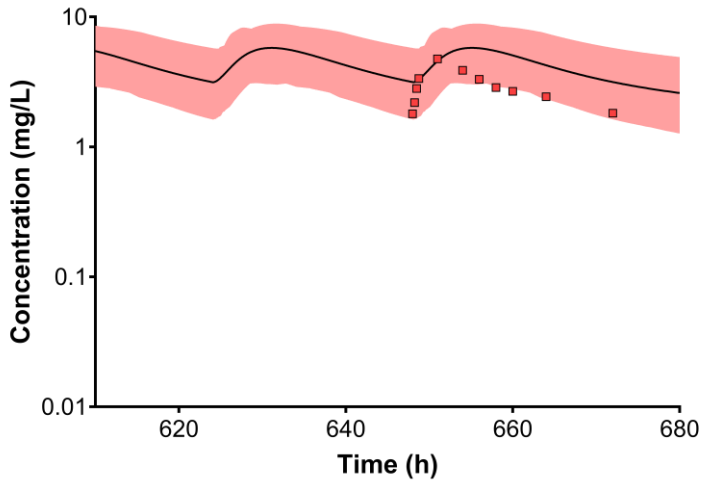
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# Model fit: Multiple dose population graphs

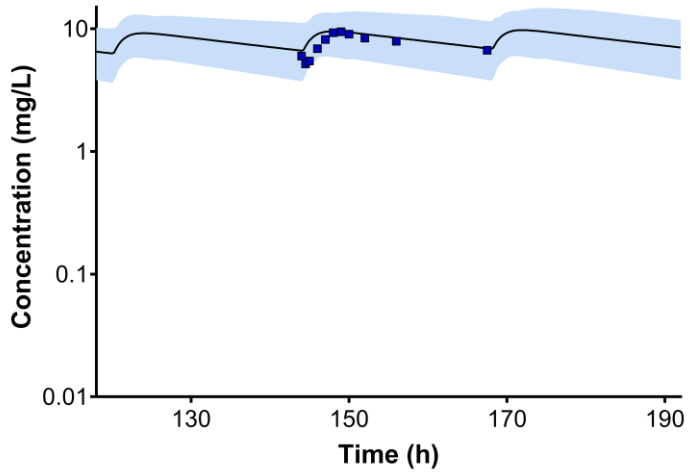
## Ivacaftor - Fed




## Tezacaftor - Fed




## Elexacaftor - Fed

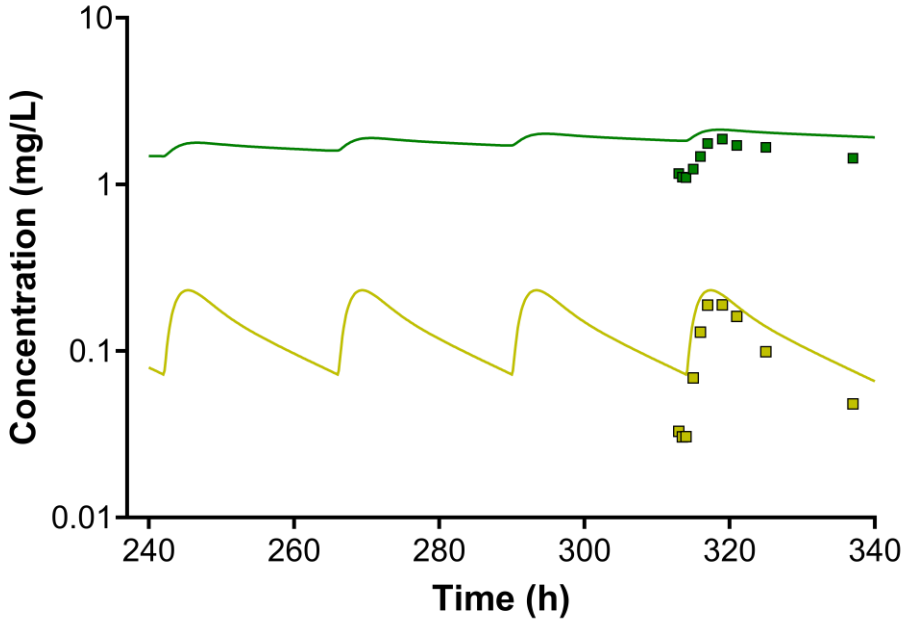



| | | AUC (mg*h/L) | | $C_{max}$ (mg/L) | |
|---|---|---|---|---|---|
| | | **Simulated** | **Predicted** | **Simulated** | **Predicted** |
| Ivacaftor | Mean | 12.0 | 11.0 | 1.6 | 1.3 |
| 150 mg BID | CV (%) | 48.0 | 39.2 | 31.1 | 32.3 |
| | Simulated/observed | 1.09 | - | 1.23 | - |
| Tezacaftor | Mean | 107.9 | 92.4 | 5.8 | 6.7 |
| 100 mg QD | CV (%) | 36.1 | 25.8 | 30.5 | 20.8 |
| | Simulated/observed | 1.17 | - | 0.87 | - |
| Elexacaftor | Mean | 198.3 | 186.0 | 9.5 | 10.0 |
| 200 mg QD | CV (%) | 28.1 | 23.9 | 26.2 | 20.6 |
| | Simulated/observed | 1.07 | - | 0.95 | - |

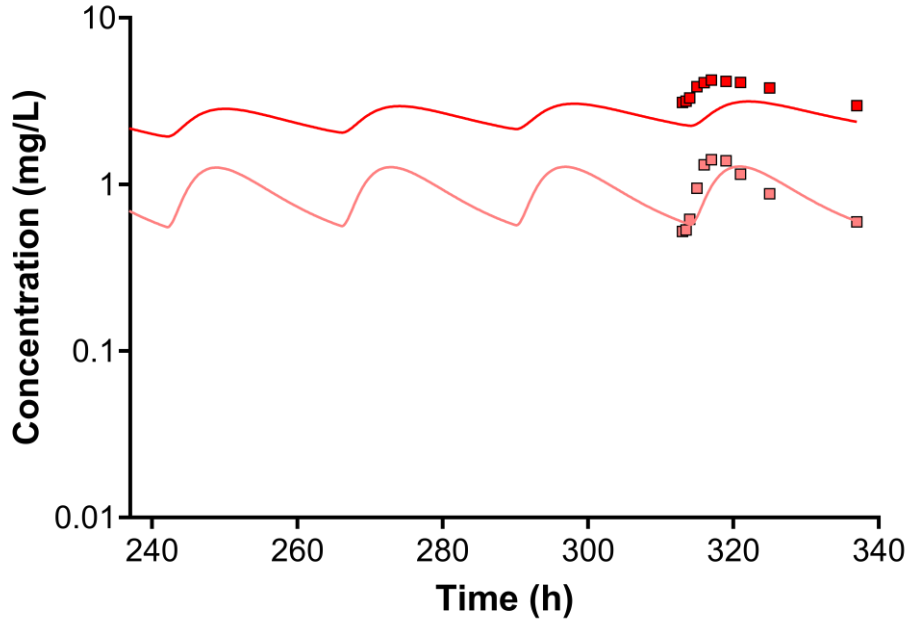
*Observed data:*
*FDA Clinical Pharmacology review Symdeko®*
*FDA Clinical Pharmacology review Trikafta®*

# Validating sensitivities to clearance pathways

DDI: Ivacaftor itraconazole




DDI: Tezacaftor itraconazole




| Enzyme | Victim | Perpetrator | AUCR | | $C_{max}$R | |
|---|---|---|---|---|---|---|
| | | | Simulated | Observed | Simulated | Observed |
| CYP3A4 | Ivacaftor | Itraconazole | 14.5 | 15.6 | 9.3 | 8.6 |
| CYP3A4 | Tezacaftor | Itraconazole | 2.99 | 4.01 | 2.5 | 3.0 |
| CYP3A4 | Elexacaftor | Itraconazole | 2.14 | 2.83 | 1.01 | 1.05 |

*Observed data:*
*Garg et al. Clin Transl Sci. 12, 2019*
*FDA Clinical Pharmacology review Trikafta®*

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# Pediatric scaling

| Scaling point | Model implementation |
|---|---|
| Gastrointestinal pH | Adult pH values applied across pediatric ages |
| Plasma protein binding | Age-dependent albumin ontogeny applied (PK-Sim Ontogeny Database) |
| Biliary excretion | Adult P-gp activity applied |
| Pediatric formulation | Granule bioavailability applied: unchanged for ivacaftor and tezacaftor, 20% lower for elexacaftor |
| Food effect | Pediatric simulations performed under fasted conditions as meal intake in sick children is often insufficient to drive a substantial food effect |

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# Pediatric scaling: Metabolism

## Before any pediatric data

Which ontogeny function should you use?

## Once sparse pediatric data are available

How to evaluate and refine the model with sparse pediatric data?

- CYP3A4 is the source of the greatest uncertainty
- Sparse pediatric data, does that give you enough to select the optimal ontogeny function?
- How to handle this?

*“Sensitivity and uncertainty analyses”*

# Pediatric populations

## 2 to <6 years, 14 to <25 kg

| | **Ivacaftor** (75 mg BID) $AUC_{0-12h}$ Simulated/observed | | **Tezacaftor** (50 mg QD) $AUC_{0-24h}$ Simulated/observed | | **Elexacaftor** (100 mg QD) $AUC_{0-24h}$ Simulated/observed | |
|---|---|---|---|---|---|---|
| | Flat | Johnson *et al.* | Flat | Johnson *et al.* | Flat | Johnson *et al.* |
| Emoto *et al.* | 0.85 | 1.01 | 1.18 | 1.36 | 1.13 | 1.21 |
| Upreti *et al.* | 1.02 | 1.06 | 1.28 | 1.33 | 1.22 | 1.20 |
| Edginton *et al.* | 1.13 | 1.10 | 1.40 | 1.40 | 1.61 | 1.28 |
| Anderson *et al.* | 1.08 | 1.18 | 1.44 | 1.32 | 1.45 | 1.40 |
| Salem *et al.* | 1.57 | 1.61 | 1.52 | 1.59 | 1.89 | 1.71 |
| Björkman *et al.* | 1.78 | 1.96 | 1.31 | 1.74 | 1.94 | 2.24 |
| **GMFE** | **1.24** | **1.32** | **1.36** | **1.46** | **1.54** | **1.51** |

Acceptance range: 0.67-1.5

*Observed data: EMA Product Information Kaftrio®*

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# Pediatric populations

## 2 to <6 years, 10 to <14 kg

| | **Ivacaftor** (60 mg qAM, 59.5 mg qPM) | | **Tezacaftor** (40 mg QD) | | **Elexacaftor** (80 mg QD) | |
|---|---|---|---|---|---|---|
| | $AUC_{0-12h}$ Simulated/observed | | $AUC_{0-24h}$ Simulated/observed | | $AUC_{0-24h}$ Simulated/observed | |
| | Flat | Johnson *et al.* | Flat | Johnson *et al.* | Flat | Johnson *et al.* |
| Emoto *et al.* | 0.85 | 1.01 | 1.18 | 1.36 | 1.13 | 1.21 |
| Upreti *et al.* | 1.02 | 1.06 | 1.28 | 1.33 | 1.22 | 1.20 |
| Edginton *et al.* | 1.13 | 1.10 | 1.40 | 1.40 | 1.61 | 1.28 |
| Anderson *et al.* | 1.08 | 1.18 | 1.44 | 1.32 | 1.45 | 1.40 |
| Salem *et al.* | 1.57 | 1.61 | 1.52 | 1.59 | 1.89 | 1.71 |
| Björkman *et al.* | 1.78 | 1.96 | 1.31 | 1.74 | 1.94 | 2.24 |
| **GMFE** | **1.24** | **1.32** | **1.36** | **1.46** | **1.54** | **1.51** |

Acceptance range: 0.67-1.5

*Observed data: EMA Product Information Kaftrio®*

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# Pediatric populations

## Ivacaftor (2 to <6 years, 7 to <14 kg): 50 mg BID

| | Flat | | Johnson *et al.* | |
|---|---|---|---|---|
| | $AUC_{0\text{-}12h}$ Simulated/observed | $C_{min}$ Simulated/observed | $AUC_{0\text{-}12h}$ Simulated/observed | $C_{min}$ Simulated/observed |
| Emoto *et al.* | 0.76 | 0.38 | 0.83 | 0.41 |
| Upreti *et al.* | 0.97 | 0.57 | 1.05 | 0.62 |
| Edginton *et al.* | 1.07 | 0.69 | 1.06 | 0.66 |
| Anderson *et al.* | 0.99 | 0.57 | 1.06 | 0.64 |
| Salem *et al.* | 1.41 | 1.03 | 1.45 | 1.07 |
| Björkman *et al.* | 1.57 | 1.24 | 1.75 | 1.41 |
| **GMFE** | **1.13** | **0.75** | **1.20** | **0.80** |

Acceptance range: 0.67-1.5

*Observed data: Davies et al. Lancet Respir Med. 4, 2016*

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# Pediatric populations

## Ivacaftor (1 to <2 years, 7 to <14 kg): 50 mg BID

| | Flat | | Johnson *et al.* | |
|---|---|---|---|---|
| | $AUC_{0\text{-}12h}$ Simulated/observed | $C_{min}$ Simulated/observed | $AUC_{0\text{-}12h}$ Simulated/observed | $C_{min}$ Simulated/observed |
| Emoto *et al.* | 1.09 | 0.70 | 1.14 | 0.70 |
| Upreti *et al.* | 1.24 | 0.84 | 1.29 | 0.91 |
| Edginton *et al.* | 1.54 | 1.20 | 1.62 | 1.23 |
| Anderson *et al.* | 1.70 | 1.48 | 1.89 | 1.57 |
| Salem *et al.* | 2.43 | 2.41 | 2.52 | 2.41 |
| Björkman *et al.* | 2.99 | 3.23 | 3.67 | 4.16 |
| **GMFE** | **1.83** | **1.64** | **2.02** | **1.83** |

Acceptance range: 0.67-1.5

*Observed data: Davies et al. Lancet Respir Med. 4, 2016*

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# Pediatric populations

## Ivacaftor (6 to <12 months, 7 to <14 kg): 50 mg BID

| | Flat | | Johnson *et al.* | |
|---|---|---|---|---|
| | $AUC_{0\text{-}12h}$ Simulated/observed | $C_{min}$ Simulated/observed | $AUC_{0\text{-}12h}$ Simulated/observed | $C_{min}$ Simulated/observed |
| Emoto *et al.* | 1.57 | 0.98 | 1.49 | 0.84 |
| Upreti *et al.* | 1.58 | 0.98 | 1.87 | 1.16 |
| Edginton *et al.* | 2.31 | 1.76 | 2.51 | 0.73 |
| Anderson *et al.* | 2.98 | 2.55 | 3.50 | 1.22 |
| Salem *et al.* | 4.44 | 4.31 | 4.90 | 4.90 |
| Björkman *et al.* | 5.00 | 5.29 | 5.38 | 5.49 |
| **GMFE** | **2.98** | **2.65** | **3.26** | **2.39** |

Acceptance range: 0.5-2.0

*Observed data: Davies et al. Lancet Respir Med. 4, 2016*

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# Pediatric populations

## Ivacaftor (6 to <12 months, 5 to <7 kg): 25 mg BID

| | Flat | | Johnson *et al.* | |
|---|---|---|---|---|
| | $AUC_{0\text{-}12h}$ Simulated/observed | $C_{min}$ Simulated/observed | $AUC_{0\text{-}12h}$ Simulated/observed | $C_{min}$ Simulated/observed |
| Emoto *et al.* | 1.30 | 0.47 | 1.56 | 0.62 |
| Upreti *et al.* | 1.39 | 0.56 | 1.67 | 0.68 |
| Edginton *et al.* | 1.80 | 0.85 | 2.17 | 1.09 |
| Anderson *et al.* | 3.09 | 2.09 | 2.98 | 1.82 |
| Salem *et al.* | 4.02 | 3.03 | 4.30 | 3.24 |
| Björkman *et al.* | 5.39 | 4.53 | 5.69 | 4.76 |
| **GMFE** | **2.83** | **1.92** | **3.06** | **2.03** |

Acceptance range: 0.5-2.0

*Observed data: Davies et al. Lancet Respir Med. 4, 2016*

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# Pediatric populations

## Ivacaftor (4 to <6 months, 5 to <7 kg): 25 mg BID

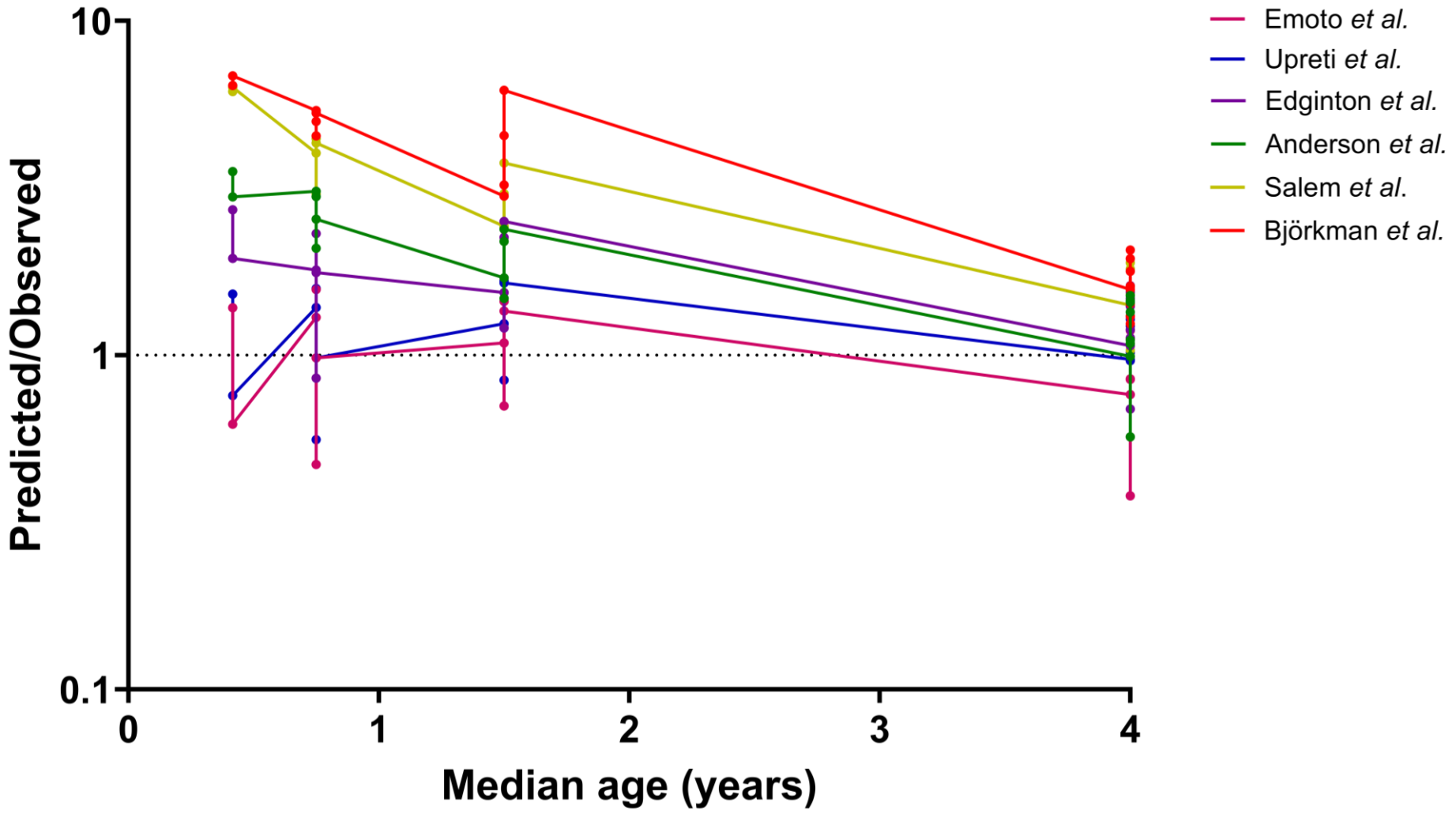
| | Flat | | Johnson *et al.* | |
|---|---|---|---|---|
| | $AUC_{0\text{-}12h}$ Simulated/observed | $C_{min}$ Simulated/observed | $AUC_{0\text{-}12h}$ Simulated/observed | $C_{min}$ Simulated/observed |
| Emoto *et al.* | 1.38 | 0.62 | 1.62 | 0.73 |
| Upreti *et al.* | 1.52 | 0.77 | 1.83 | 0.95 |
| Edginton *et al.* | 2.72 | 1.95 | 3.18 | 2.41 |
| Anderson *et al.* | 3.54 | 2.97 | 3.94 | 5.97 |
| Salem *et al.* | 6.14 | 6.32 | 7.31 | 7.84 |
| Björkman *et al.* | 6.40 | 6.84 | 6.83 | 7.14 |
| **GMFE** | **3.62** | **3.24** | **4.12** | **4.17** |

Acceptance range: 0.5-2.0

*Observed data: Davies et al. Am J Respir Crit Care Med. 203, 2021*

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# Pediatric populations



# Conclusions

- A clear workflow for first-in-pediatric dose selection for CYP3A4-sensitive compounds was provided
  - Standard is compatible with global regulatory acceptability
- Emoto hepatic ontogeny combined with flat intestinal CYP3A4 activity was the best-performing ontogeny combination for these cases and others; additional validation still required
  - Upreti and flat are recommended, conservatively
- Next steps in research: evaluate the generalizability of this approach using tacrolimus

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# Take home message

- Verify the metabolic pathways before scaling to children
  - Use DDI data to confirm that the adult model captures changes in CYP3A4 activity
- Different ontogeny functions can lead to substantially different PK (and dose) predictions in children 6 months to 4 years old
- Use pediatric PK data to evaluate and refine the model
  - Sparse pediatric PK data available from your clinical trial can help evaluate the model and ultimately inform pediatric dose selection
  - In many cases the pediatric ontogeny function used for metabolism is the most uncertain parameter to refine

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# Acknowledgements


- Dr. Paola Mian (UMCG)
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- Prof. Dr. Gerard Koppelman (UMCG)

# Thank you!




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