A model-based extrapolation enabled labelling of emicizumab in haemophilia A paediatric patients <1 year old despite lack of clinical data

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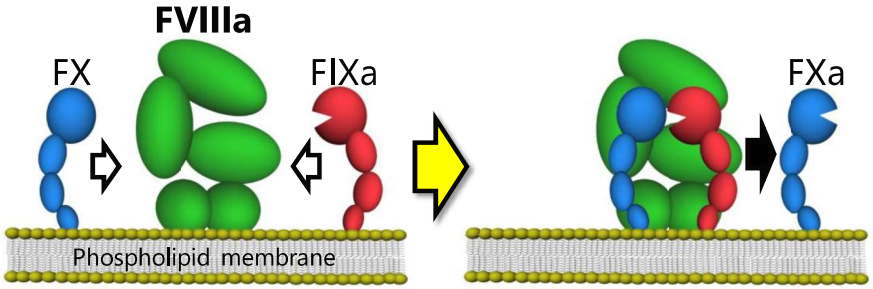
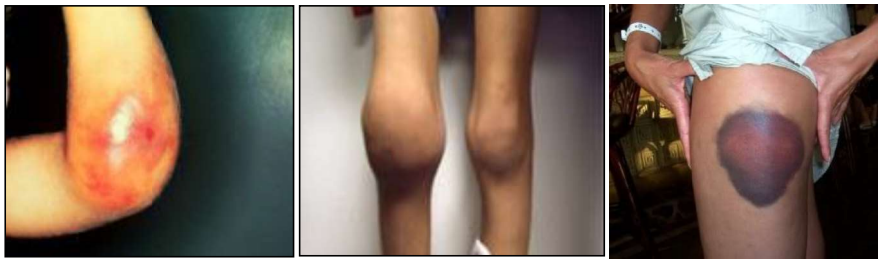
Emicizumab: Humanized bispecific antibody for hemophilia A treatment

Hemophilia A

- Inherited bleeding disorder due to deficiency or absence of coagulation factor VIII (FVIII)
- ~ 40,000 patients in the US and Western Europe
- Current therapies required frequent IV infusions
  - Inconvenience & lack of practicality especially in young infants
- Lack of prophylaxis can lead to severe damages





1. Kitazawa, et al. Nat Med.2012;18(10):1570.; 2. Sampei, et al. PLoS One. 2013;8(2):e57479.; 3. Muto, et al. J Thromb Haemost. 2014; 12(2): 206.

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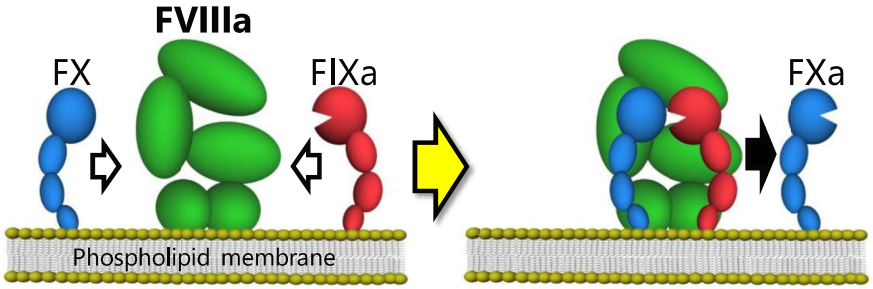
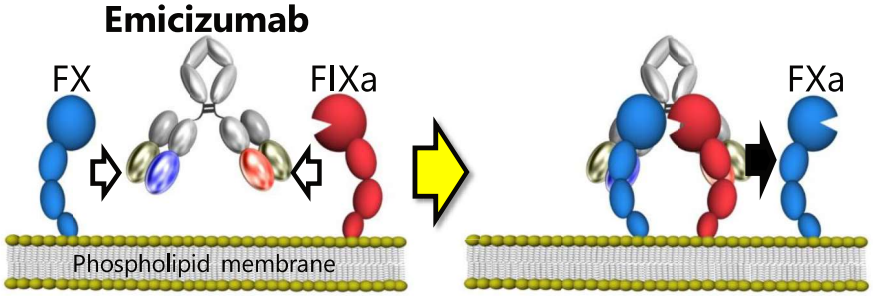


Emicizumab

- Restore function of missing FVIIIa[1-3]
- Subcutaneous formulation
- Favorable safety profile and clinically meaningful reductio in bleed rate [4]
  - 87% to 99 % bleeding rate reduction in Phase 3 studies



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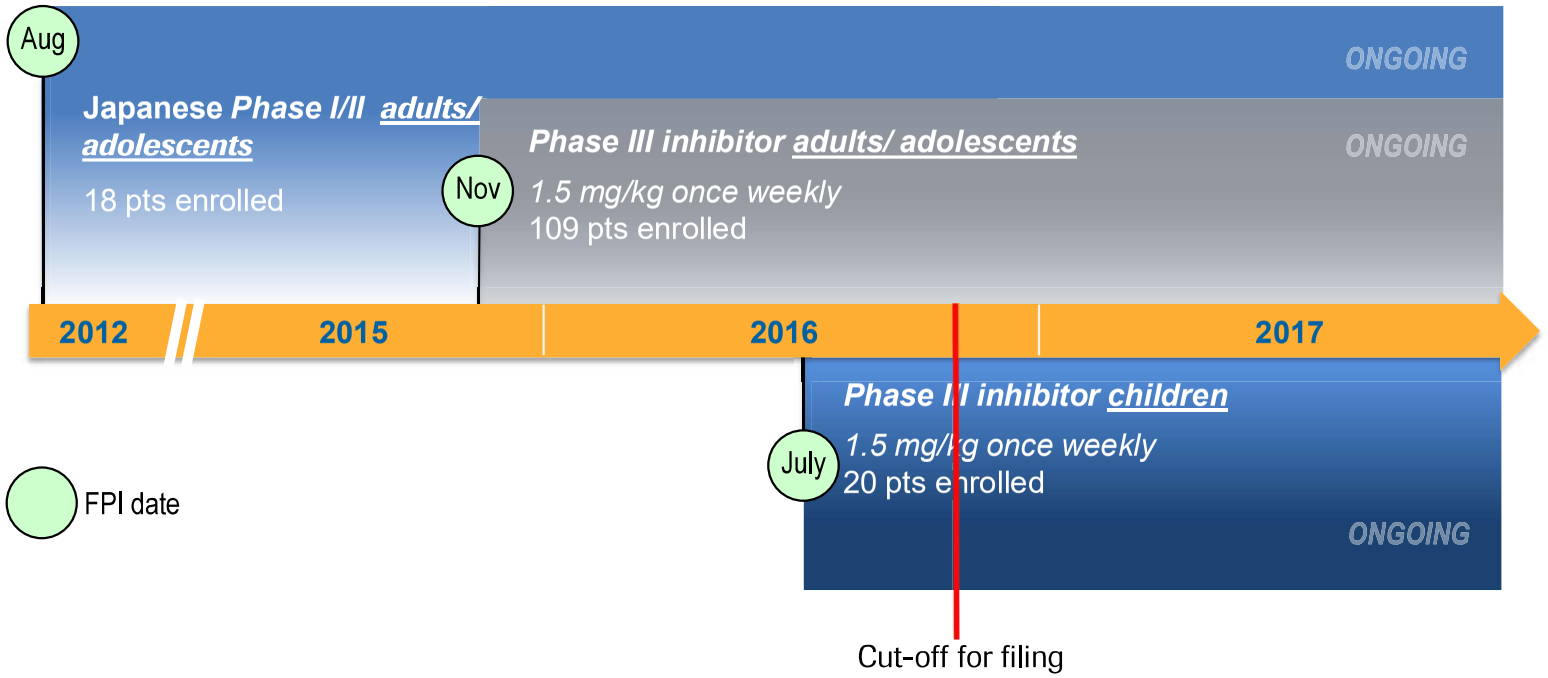
Clinical development plan & filing content

Inhibitor patients



Filing based on 147 enrolled patients aged 2 to 75 years old

Disease similarity and expected similar PKPD relationships in young infants

CHMP raised concern regarding to the lack of patient data <2 years old

- *"It is suggested that all methods: **weight based, with and without maturation functions** be used to investigate the most optimum fit to the PK data available and to simulate exposure in younger children."*

- *"The discussion should also be supported with **PK data for other similar drugs** (IgG antibodies; e.g. palivizumab), where paediatric data is available in the very young."*

- It was also suggested to use a **PBPK model with known properties of IgG disposition in small children**

1. Leveraging the available emicizumab population PK model

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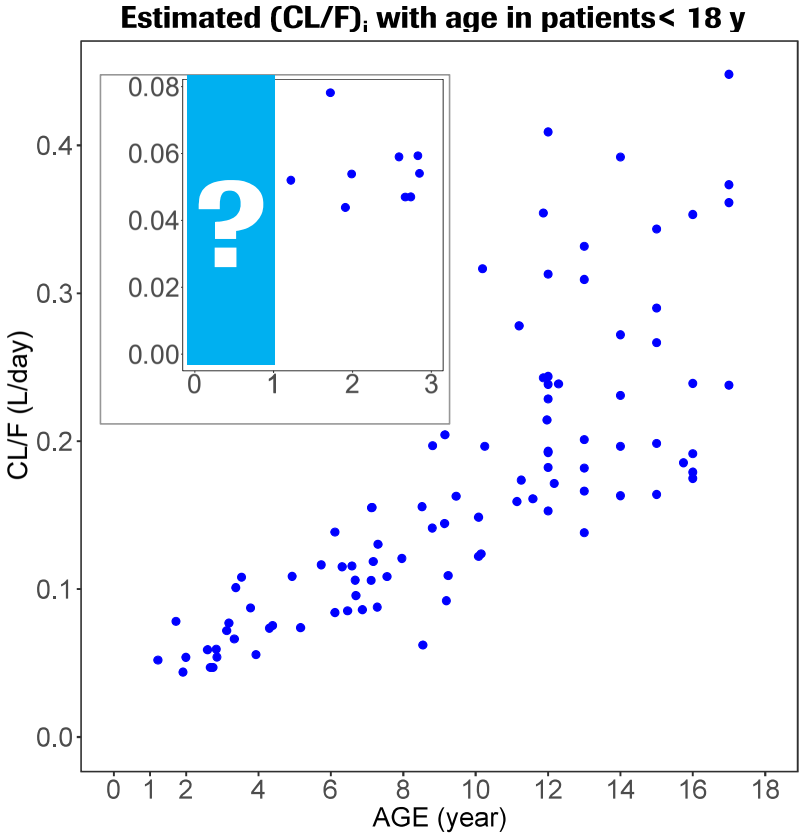
Body weight and albumin concentration as main covariates impacting CL/F

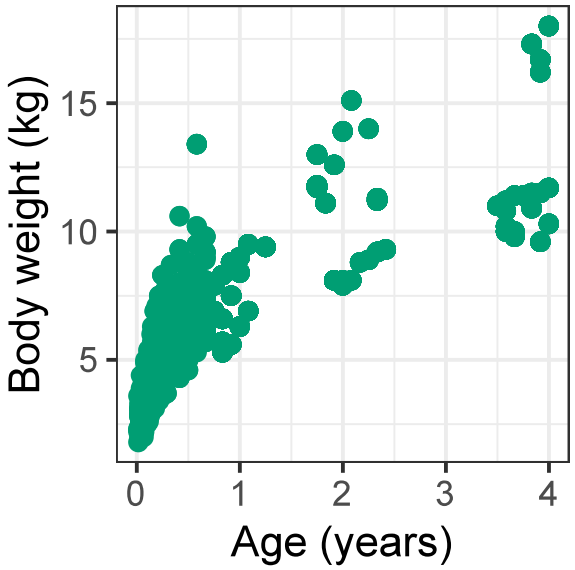
PopPK model updated including a larger paediatric database (N=63, 4 patients between 1 and 2 years)

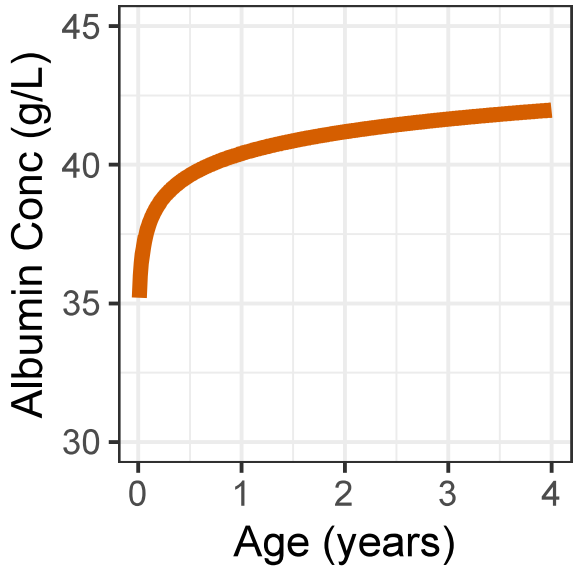
Statistically Significant Effect	Covariate Range [min, max]	% Change in CL/F from Typical Value [min, max]
BW (kg) on CL/F	[10, 131]	[− 82, + 83]
ALB (g/L) on CL/F	[34, 45[	[+ 22, 0[
	[45, 55]	[0, 0]



Predicted exposure at SS in patients <1 y

Approach #1: Extrapolation from the popPK model covariates (BW, ALB) and their correlation with age





External paediatric covariate database of 815 children from 0 to 12 y

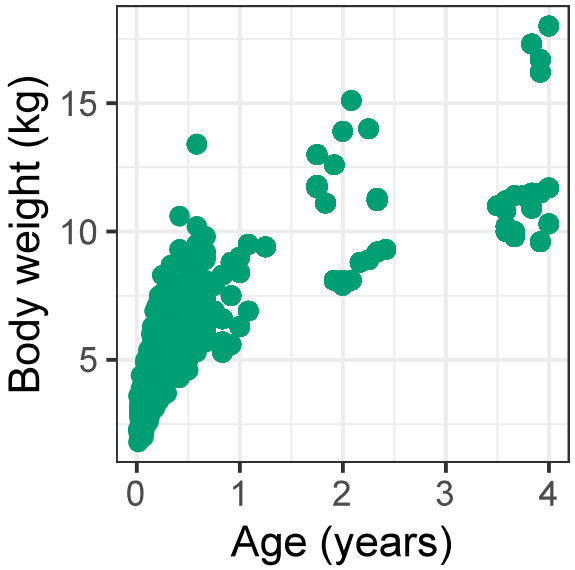
Jorga et al. Clin Pharmacol Ther. 2006

$$ALB_i = 1.1287 \times \ln(Age_i) + 33.746$$

Johnson et al. Clin Pharmacokinet. 2006

Predicted exposure at SS in patients <1 year old

Approach #2. Same as approach #1 + explicit CL maturation with age



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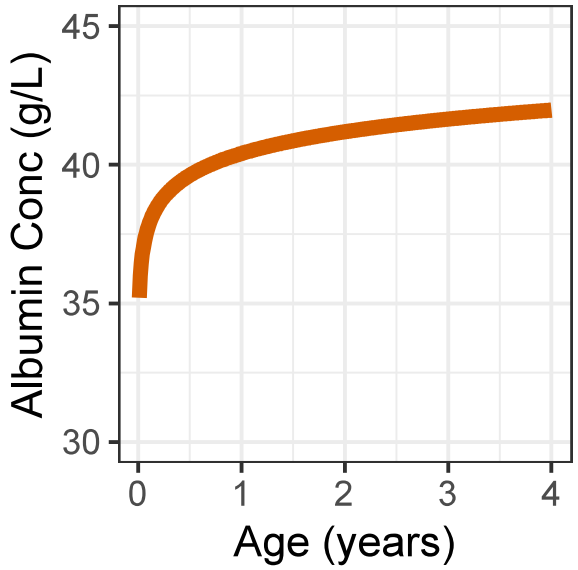

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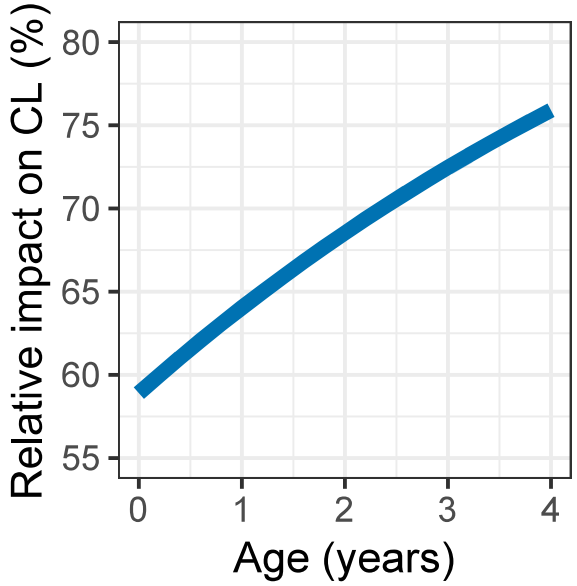
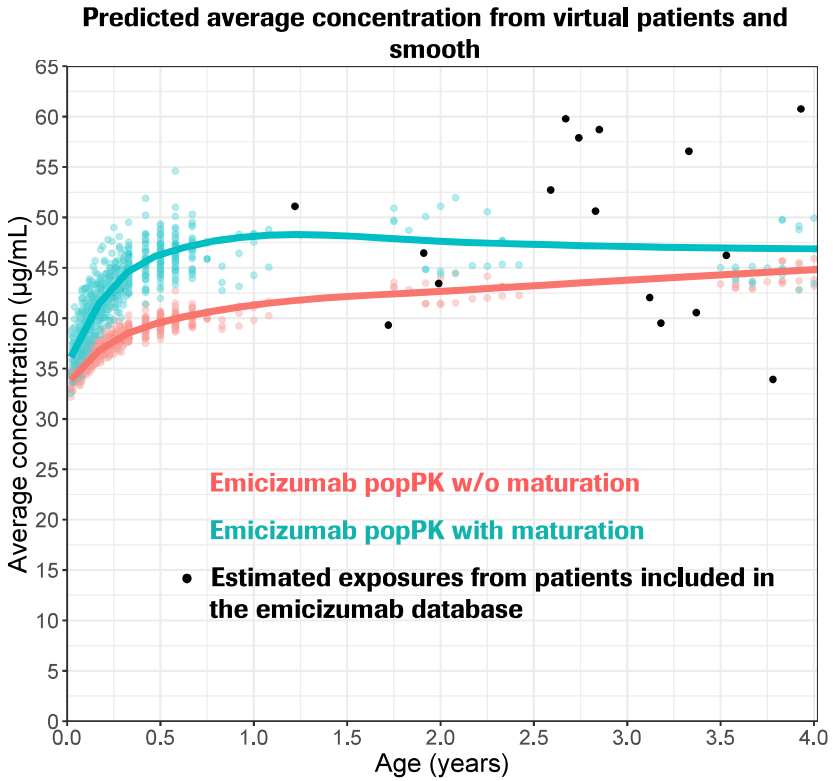


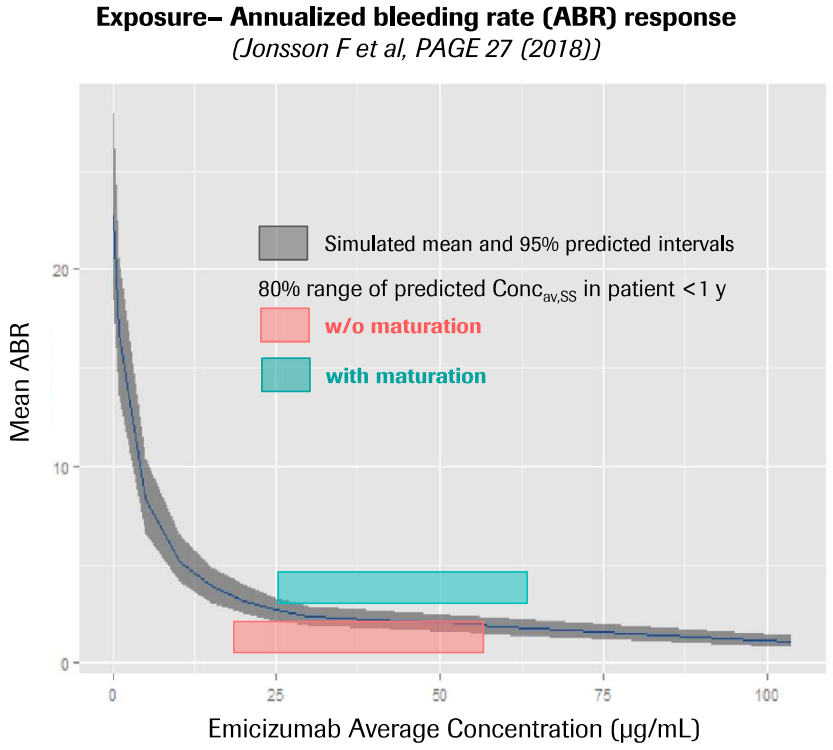
$$100 * \left(1 - \beta \times e^{-\frac{Age_i}{\theta} \times \ln(2)}\right)$$

β=0.411; θ = 62.3 *months*

Robbie et al. Antimicrob Agents Chemother. 2012 - describes the popPK in adults and children of ***Palivizumab****, a humanized monoclonal antibody*

In patients < 2 years old, medically meaningful efficacy is predicted, with or without maturation function





- Lower exposures predicted without maturation in patients < 2 years old
- Plateau of the exposure-efficacy relationship, even for neonate patients

2. Leveraging knowledge on other PK characteristics of mAbs in paediatrics

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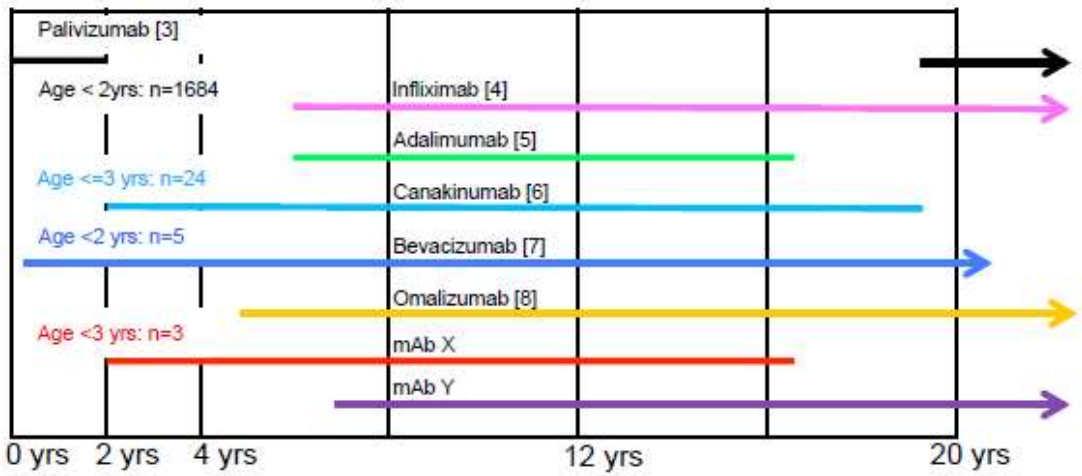
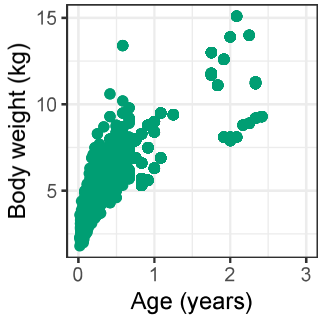
Palivizumab[1]: only robust popPK model published for mAbs PK in infants < 2 years old

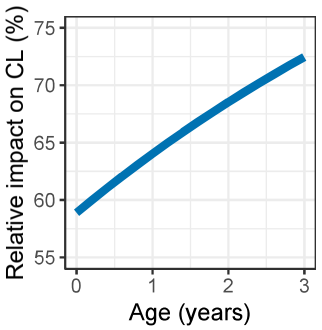
Age range of published popPK models in infants and children

Fuhrmann et al. PAGE 26 (2017)



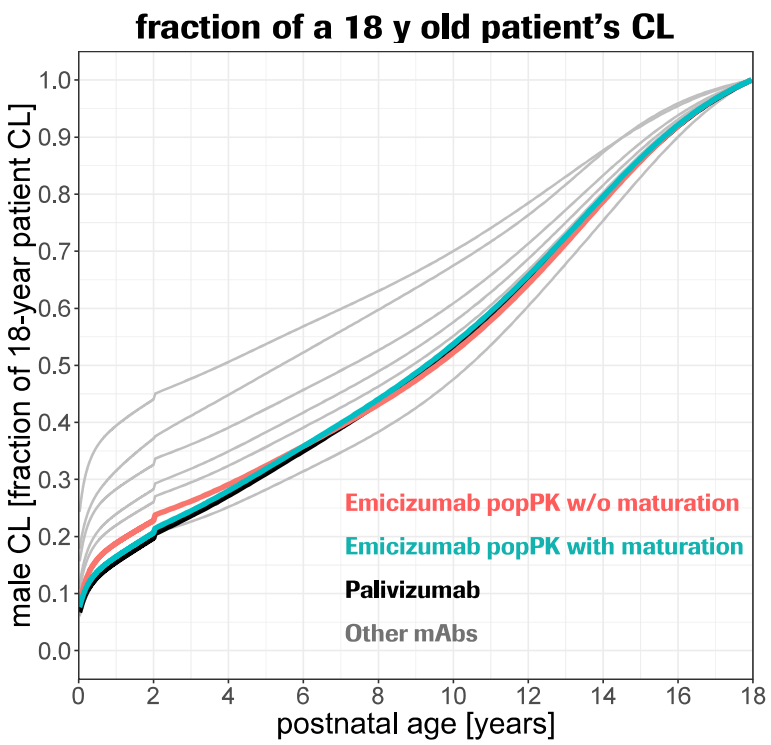
- **Explicit age-based maturation function: only in Palivizumab popPK model**

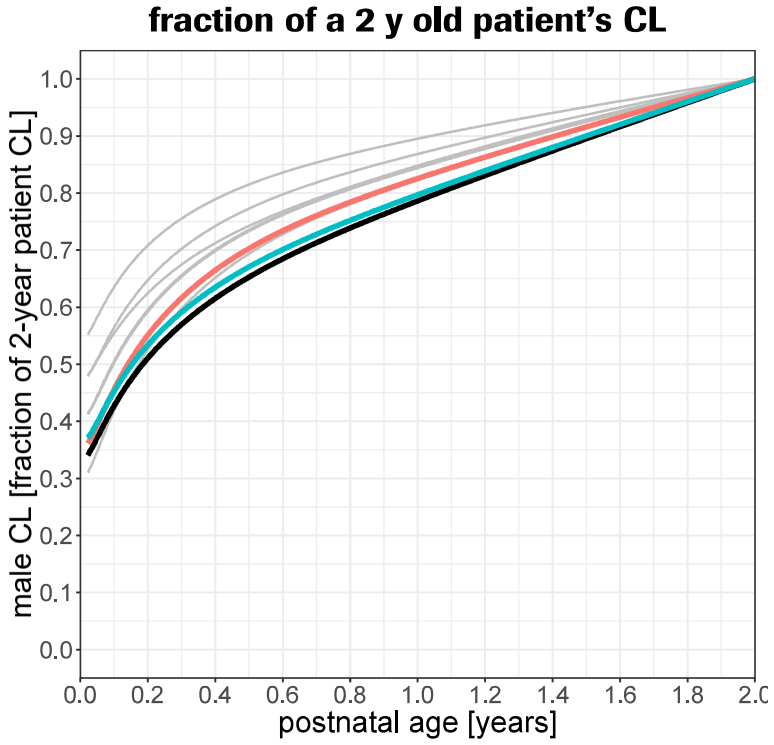




1. Robbie et al. 2012.

Emicizumab has CL values similar to Palivizumab in paediatric population





⇒ **Emicizumab / Palivizumab: similar relationships of CL with age**

⇒ **Increase confidence on extrapolated emicizumab exposure for patients <1 year old**

3. Leveraging available PBPK knowledge for emicizumab

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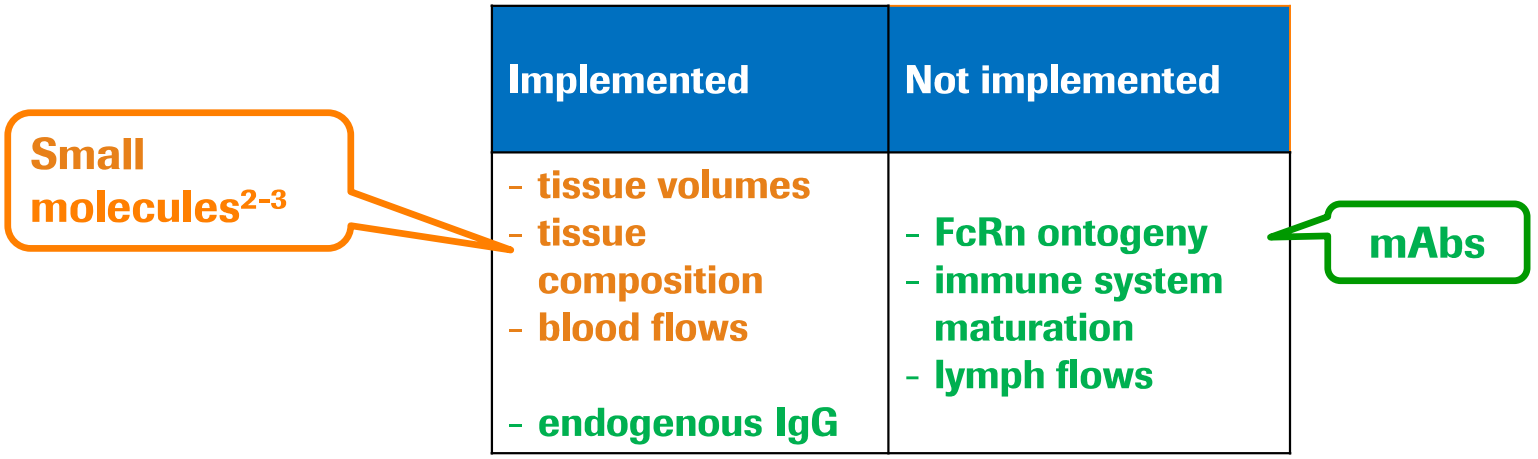
Age-effect on mAbs PK not well characterized in current paediatric PBPK models

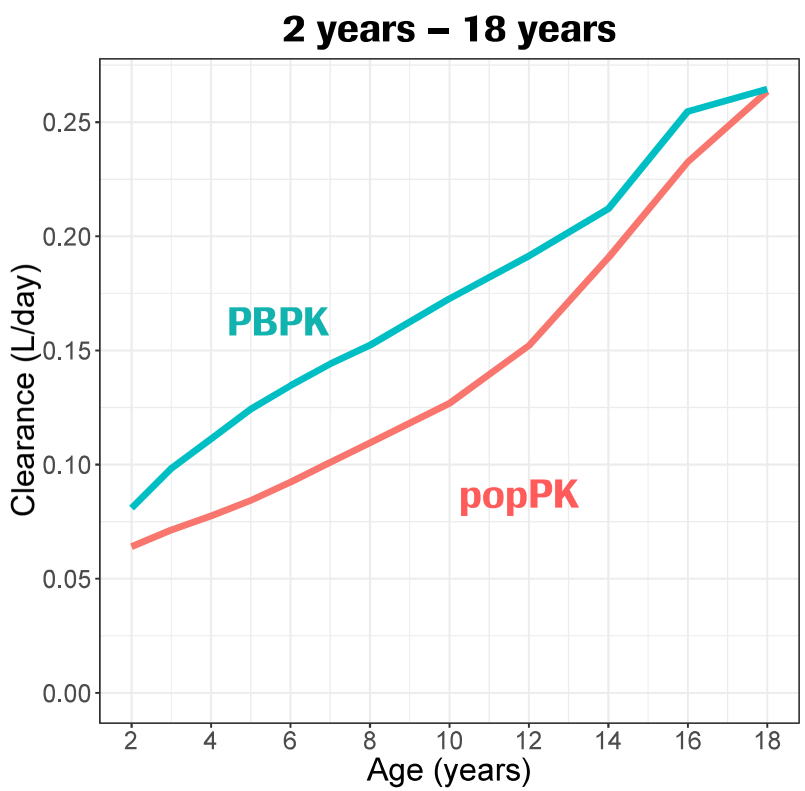
- **PBPK modeling**: Methodology with the potential to include molecular ontogeny and other age-dependency of anatomy and physiology
- **SimCYP®**
  - FcRn-linked disposition of mAbs: at the time, most advanced implementation[1]
  - Paediatric module for small molecules available

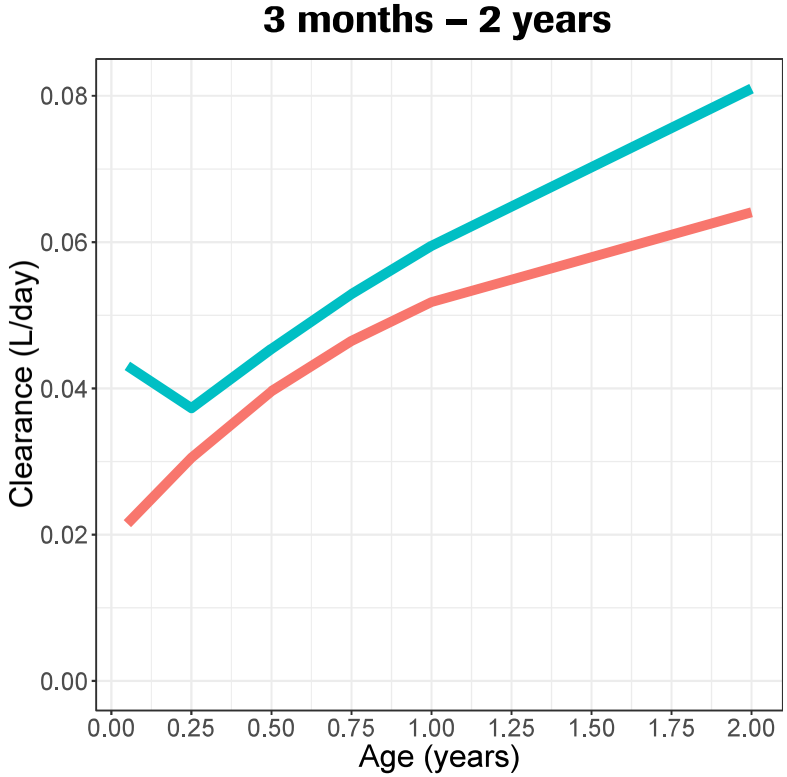
  ⇒ Extrapolation approach combining paediatric and mAbs modules *(Roche initiative – not validated)*



1. Dostalek et al. 2013; 2. Johnson et al. 2006; 3. Zhou et al. 2017;

Larger CL_{PBPK} compared to CL_{POPPK} in an age range where popPK approach adequately describes data





⇒ **Doubt regarding PBPK performances to predict paediatric mAbs PK at its current state.**

Conclusions

- PopPK models, with or without maturation, were leveraged to underline the confidence that the proposed dosing of emicizumab is appropriate also for infants lower than 1 year old

- While the main argumentation was based on a popPK approach, impact of physiological factors on PK were also investigated using PBPK approach

- However, for therapeutic proteins, PBPK has not yet reached the same level of maturity as for small molecules, although increasing attention is given

- Positive feedbacks from EMA

Positive feedbacks from EMA

- Emicizumab (Hemlibra) has been approved by EMA among others at a maintenance dose of 1.5 mg/kg/week with the following indication:

  *"Hemlibra is indicated for routine prophylaxis of bleeding episodes in patients with haemophilia A with factor VIII inhibitors. Hemlibra can be used **in all age groups**."*

- EMA acknowledges that the modeling activities were decisive in the emicizumab approval for patients aged less than 1 year, an age group for which no clinical data exist.

- Emicizumab M&S activities for paediatric extrapolation highlighted in an EMA presentation at ACOP 9

  "High regulatory Impact M&S – The EMA experience and outlook"

  (Efthymios Manolis, ACOP 9, San Diego, 2018)

Thank you

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Doing now what patients need next