Model Based Extrapolation of Efficacy to Support Baloxavir Marboxil for Uncomplicated Influenza in Children Aged < 1 Year

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33rd PAGE meeting - Thessaloniki - June 4th, 2025

Baloxavir Marboxil (Xofluza®) as new Standard of Care for Influenza Treatment

Influenza represents a significant disease and socioeconomic burden that is often underestimated [1–3]

Globally, annual epidemics result in:

- ***3 to 5** million cases of severe disease*
- ***290,000 to 650,000** deaths, including the deaths of **up to 100,000 children <5 yo**[4]*
- **374,000** hospitalisations are attributed to influenza **in children aged <1 year**

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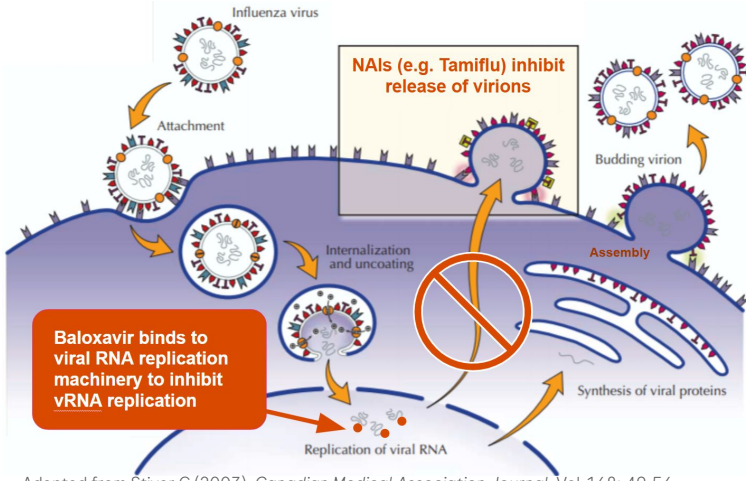
Baloxavir marboxil

- Pro-drug converted to the active form **Baloxavir**
- Cap-dependent endonuclease inhibitor
- **Baloxavir** mostly eliminated through hepatic metabolism by CYP3A and UGT1A3, and biliary excretion
- A single oral dose administration



Adapted from Stiver G (2003). *Canadian Medical Association Journal*, Vol.168: 49-56

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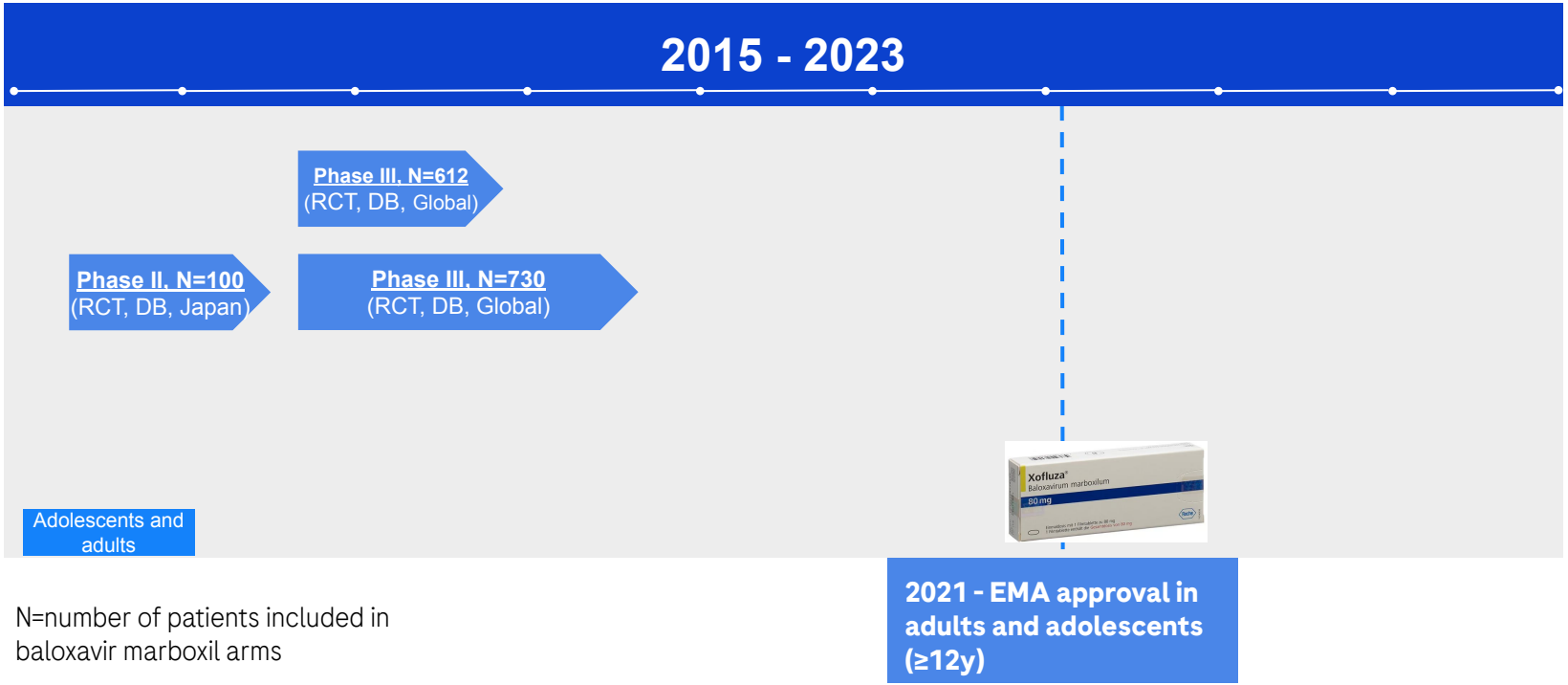
Clinical development plan & filing content



N=number of patients included in baloxavir marboxil arms

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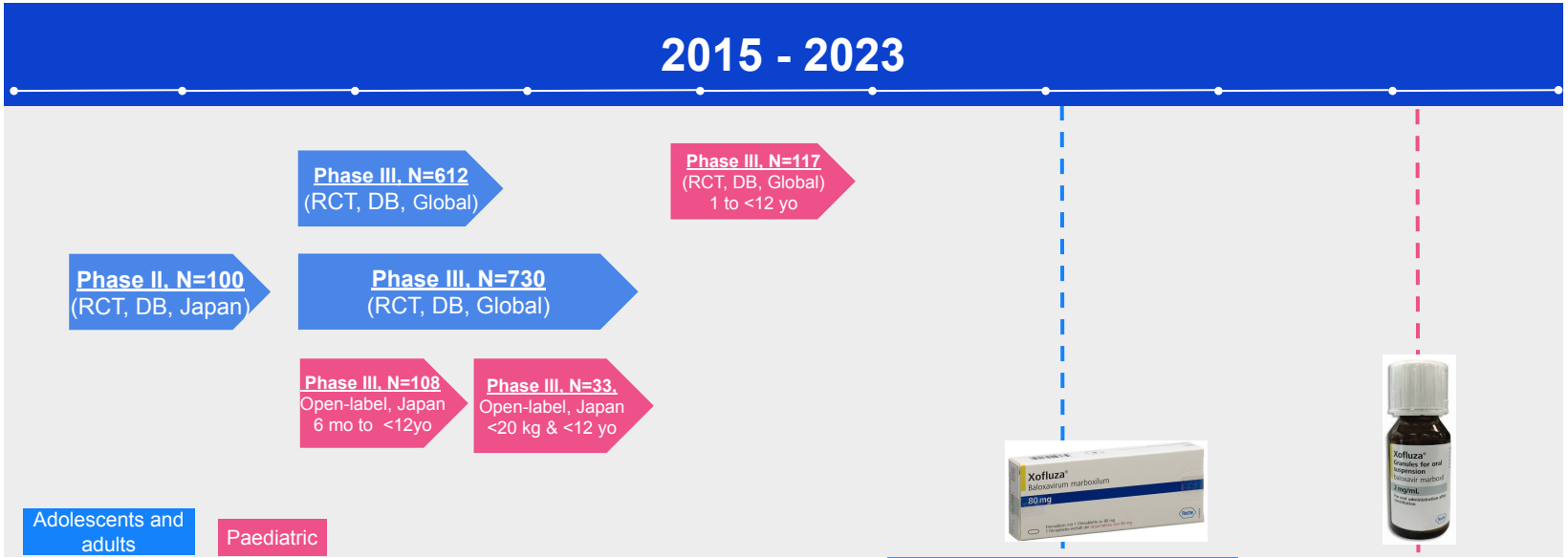

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2021 - EMA approval in adults and adolescents (≥12y)

2023 - EMA approval in pediatrics 1-12 y

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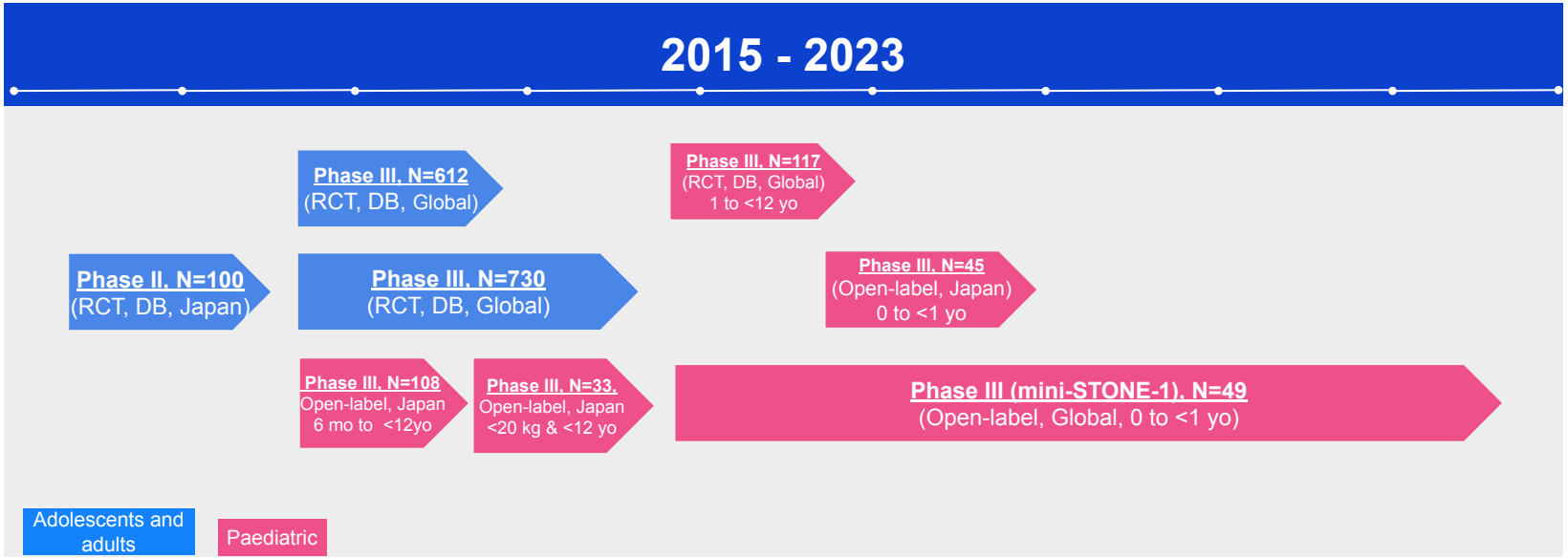

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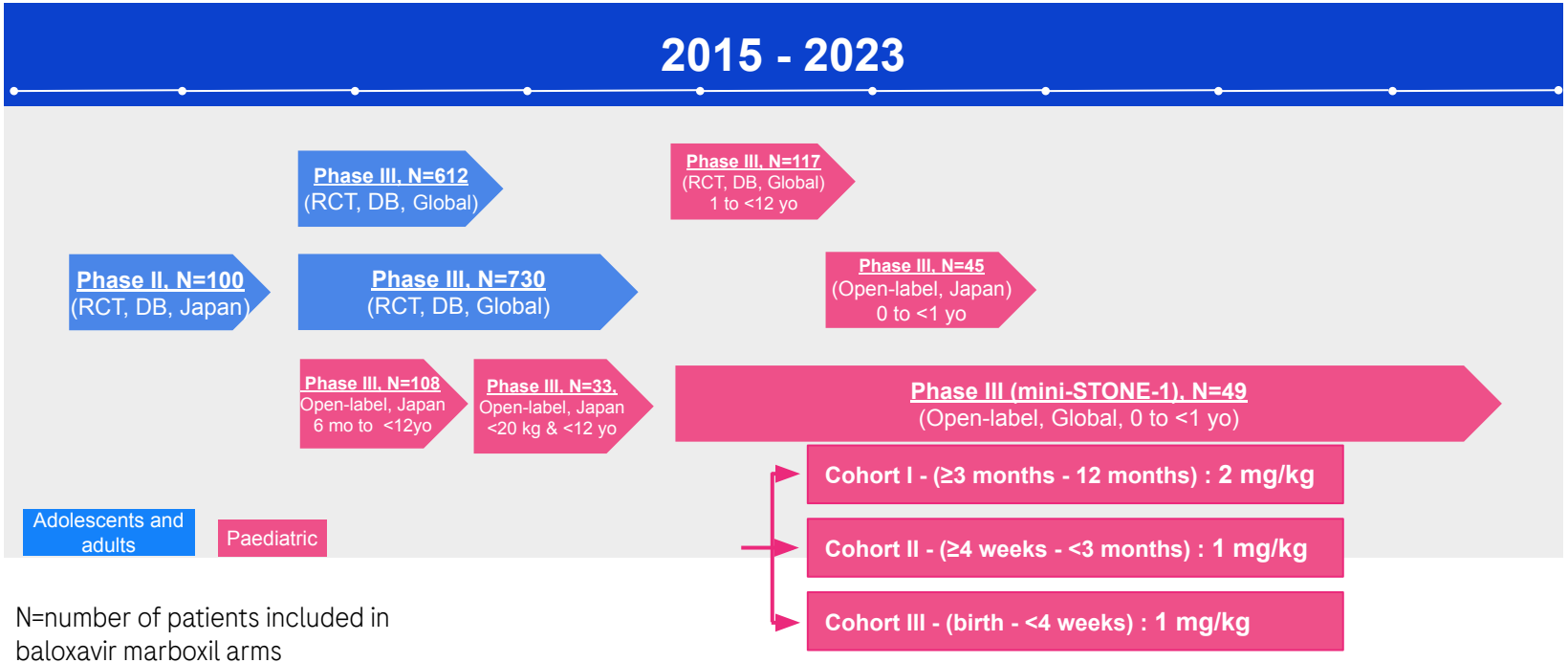

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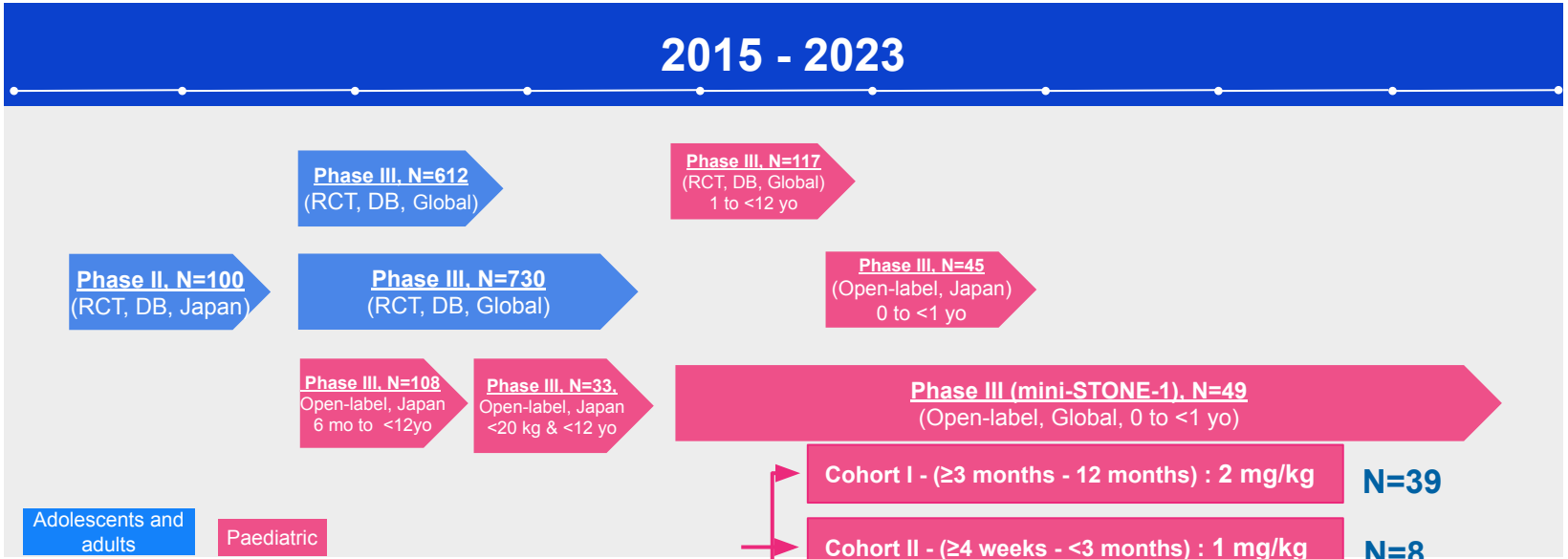

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June 2024 - Label extension request in EU for the <1 yo

Extrapolation framework following ICH E11A [2024] guideline

Adapted from ICH E11A Guideline on pediatric extrapolation
EMA/CHMP/ICH/205218/2022

Extrapolation framework following ICH E11A [2024] guideline

Disease & Drug Pharmacology

- Influenza disease considered "**sufficiently similar**" across age range
- Baloxavir targets the virus, not the host, hence drug pharmacology is expected to be age-independent

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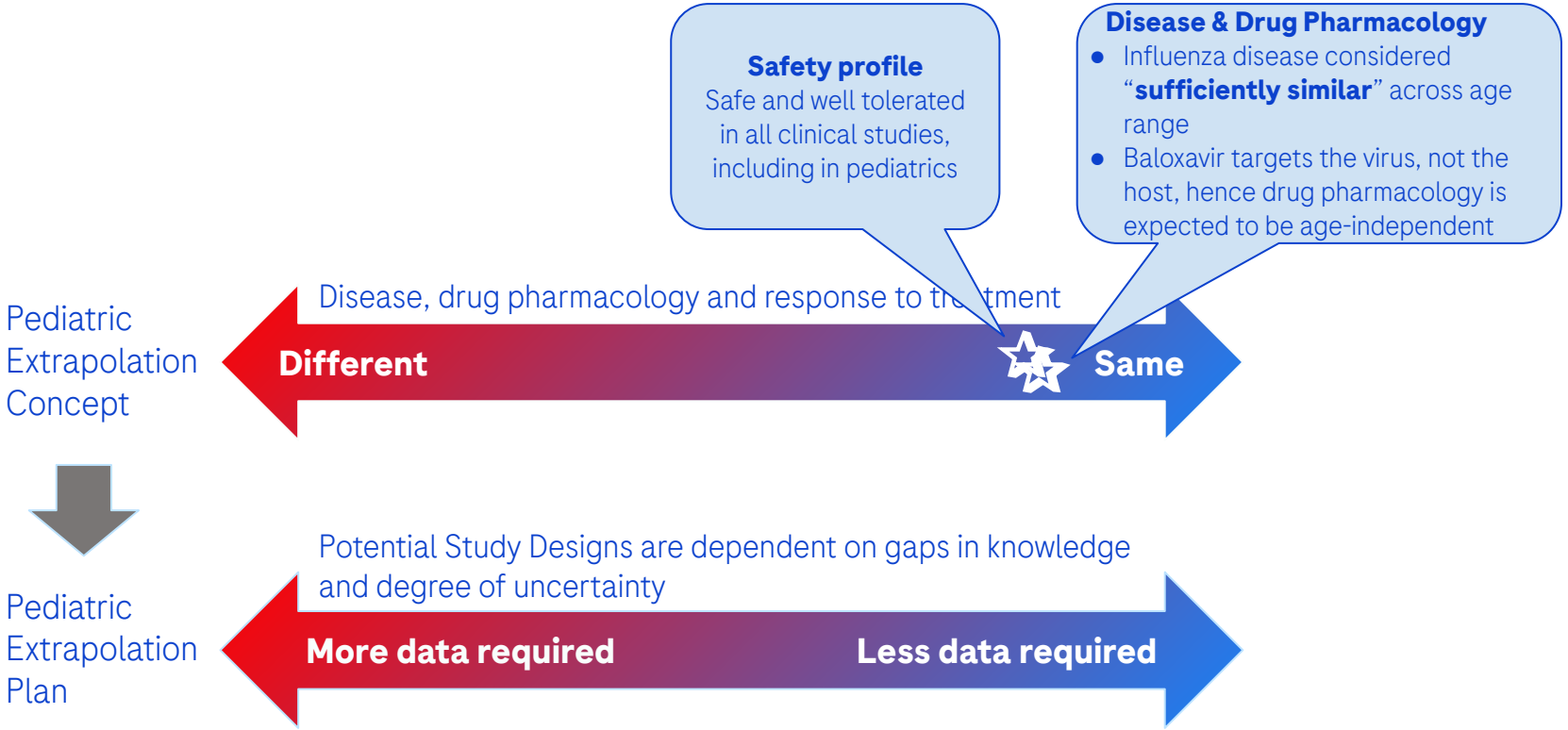

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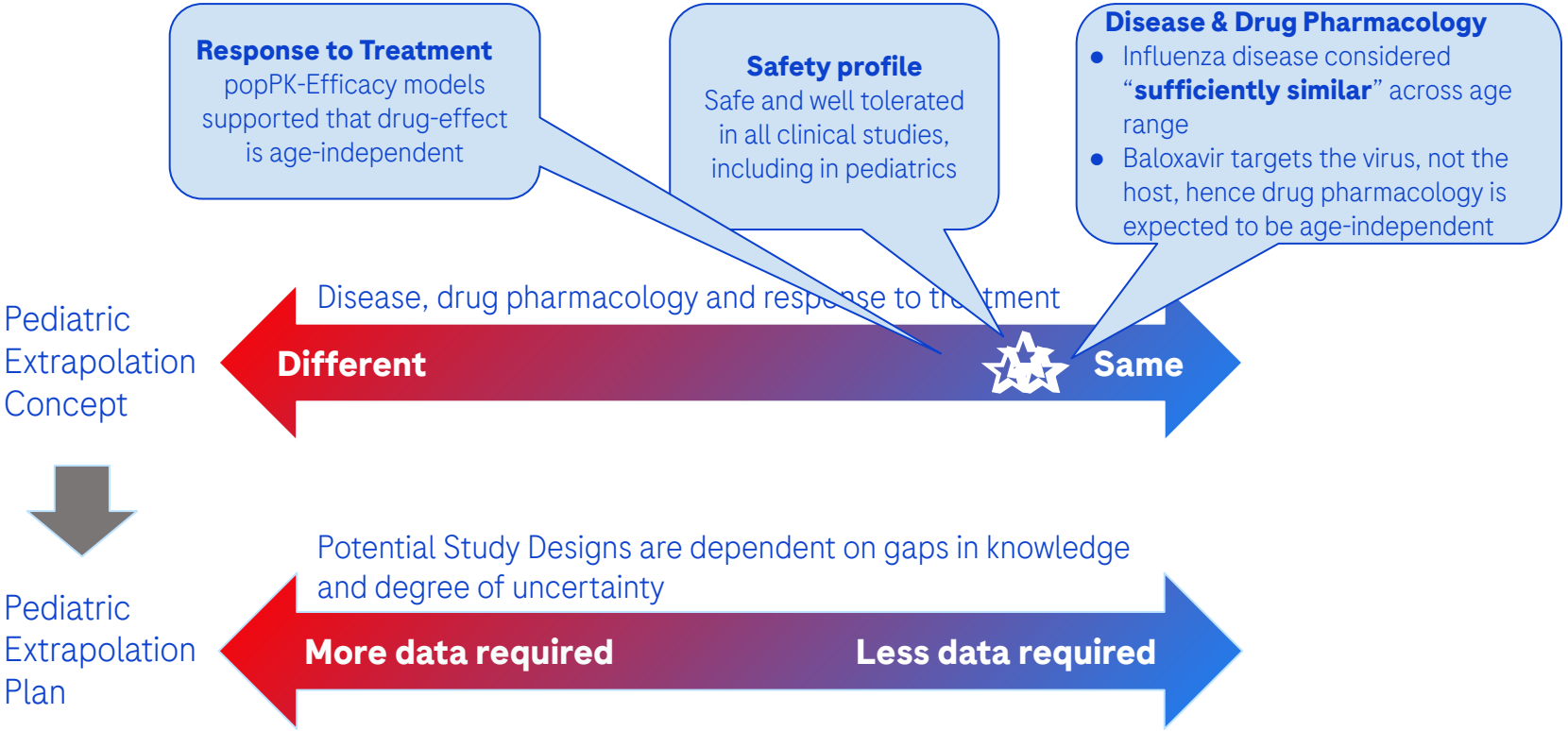

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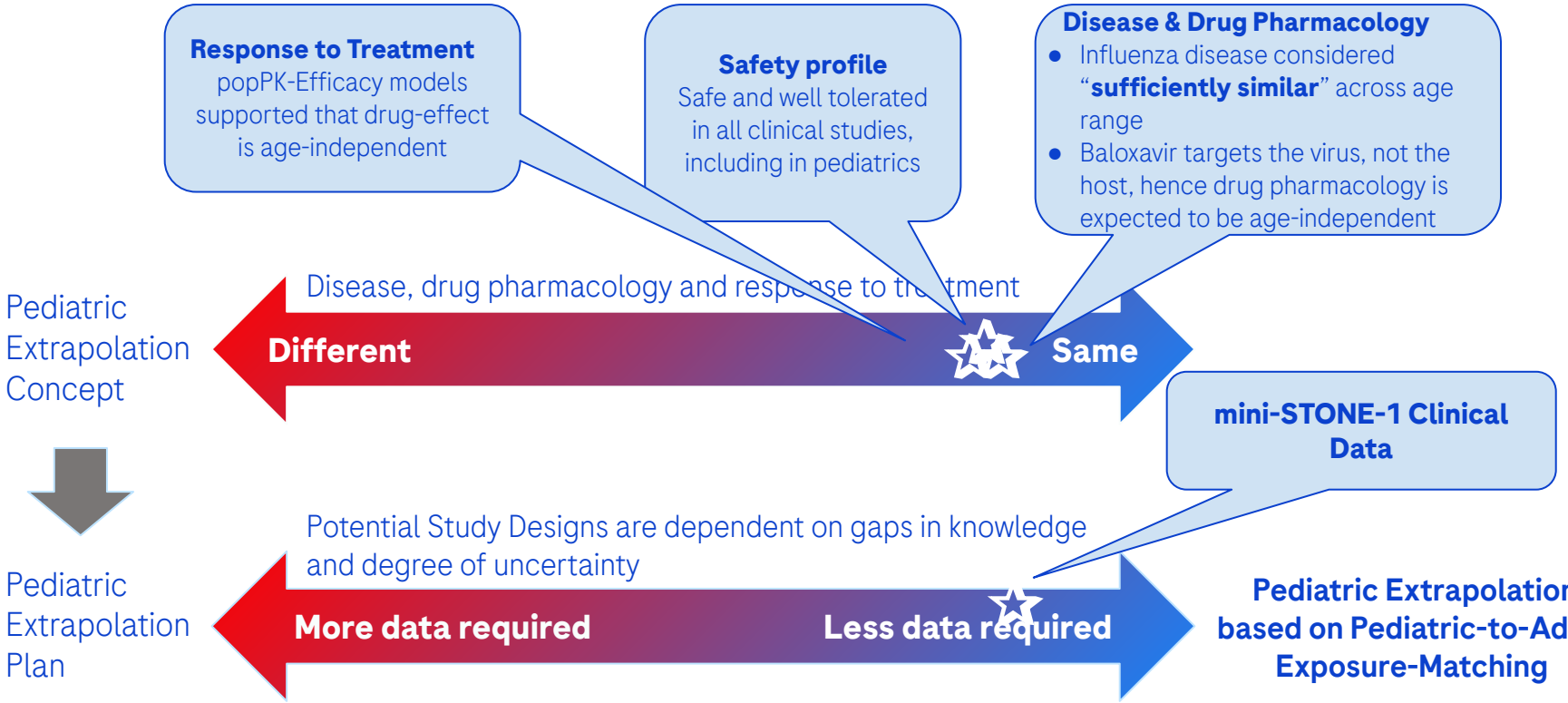

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Model-based pediatric extrapolation strategy

Pediatric-to-Adult Exposure-Matching ?

- Empirical PopPK model
- Population PBPK model
- Simulations using both models

Similar PK-Efficacy response irrespective of age ?

- PK-Efficacy model

Legacy PopPK model: Body weight and Race impacts on CL/F

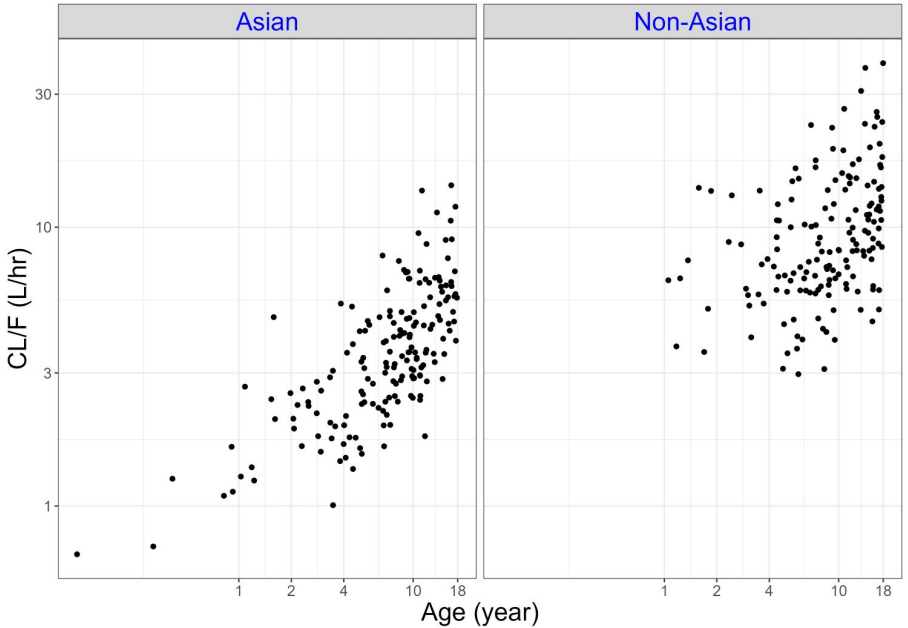
Developed at the time of the label request in >1 yo

1795 patients, including 245 pediatric patients

Age range from 1 month to 85 yo; only 6 patients (Asians) <1yo

Statistically significant effect	Covariate Description	% Change in parameter from Typical Value [min, max]
BW (kg) on CL/F, Q/F	[min, max] = [4, 217]	[-74%, +70%]
Race on CL/F	Asian / Non-Asian	-50.4% / 0

No age-effect on CL/F



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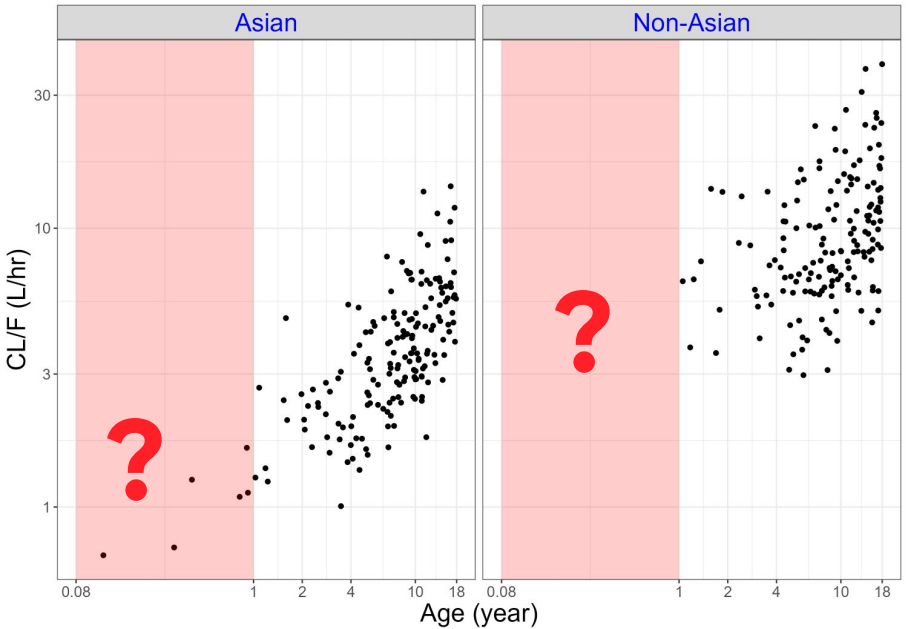
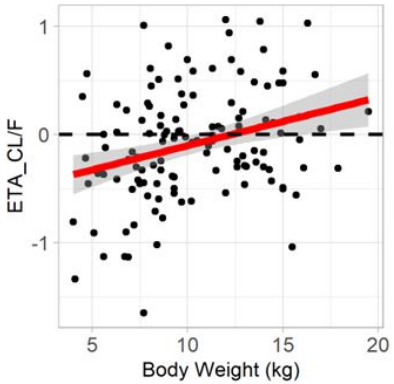
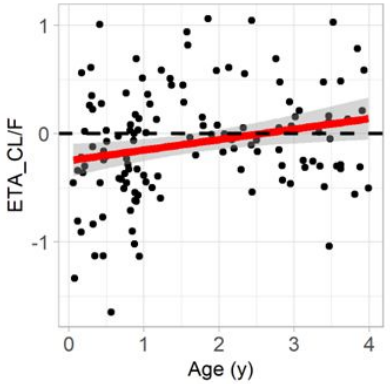


Update of the Legacy popPK model including data from 57 patients <1 yo

150 PK observations from 10 patients <3mo, 47 patients in [3 mo - 1y)

Parameters update only





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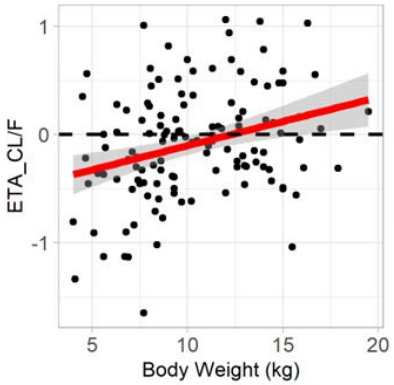
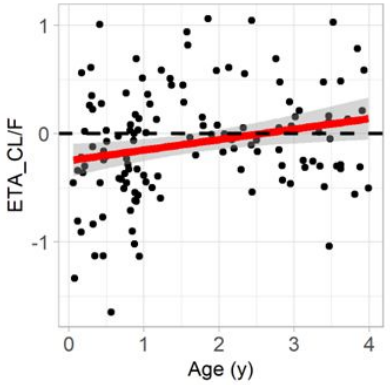
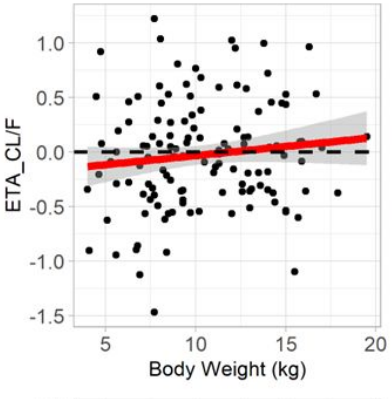
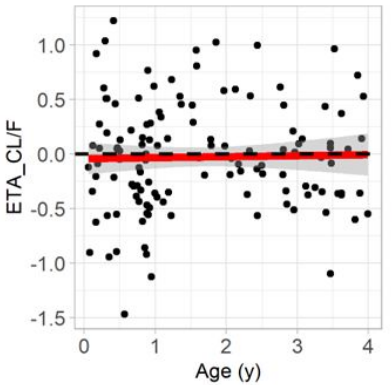




Parameters update + function of clearance maturation with age

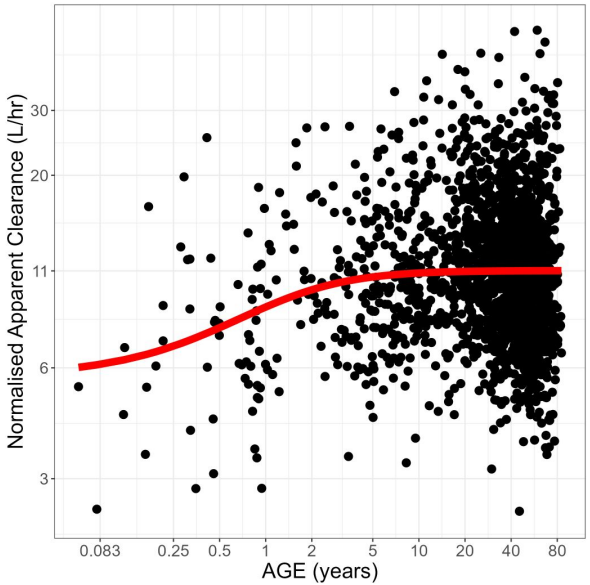


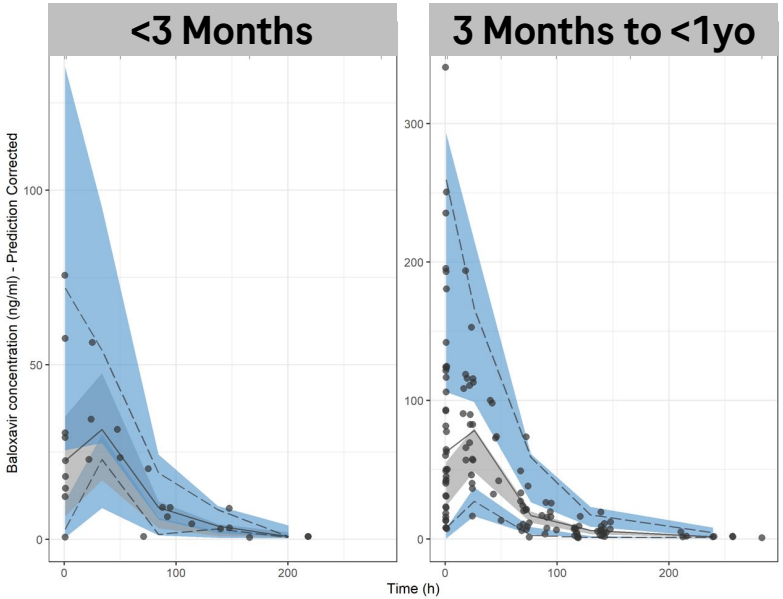


Update of the Legacy popPK model including data from 57 patients <1 yo - Cl maturation function*

$$CL/F = 11.02 \times \left(\frac{BWT}{70}\right)^{0.451} \times (1\text{-}0.502 \times \text{Asian}) \times \frac{(40+Age\times 52.18)^{\gamma}}{(40+Age\times 52.18)^{\gamma}+TM_{50}^{\gamma}}$$

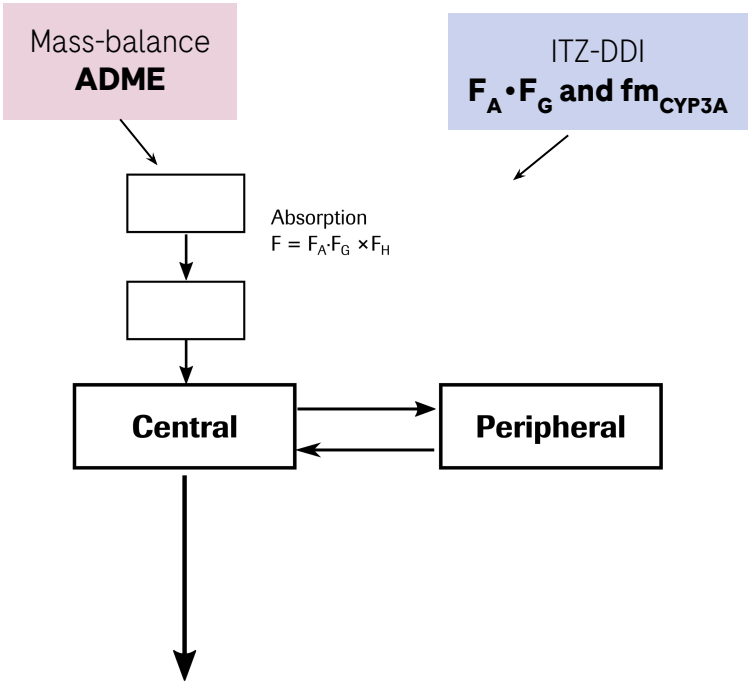
TM_{50} (maturation half-life) = 38.3 weeks (RSE=19%)





*Anderson & Holford Drug Metab Pharmacokinet. 2009;24(1):25-36

Population PBPK modelling of baloxavir in adult and pediatric subjects



Estimated $F_A \cdot F_G$ =83% and fm_{CYP3A} = 8%

$F_A \cdot F_G$: product of fraction of absorption and intestinal availability (P-gp/CYP3A)

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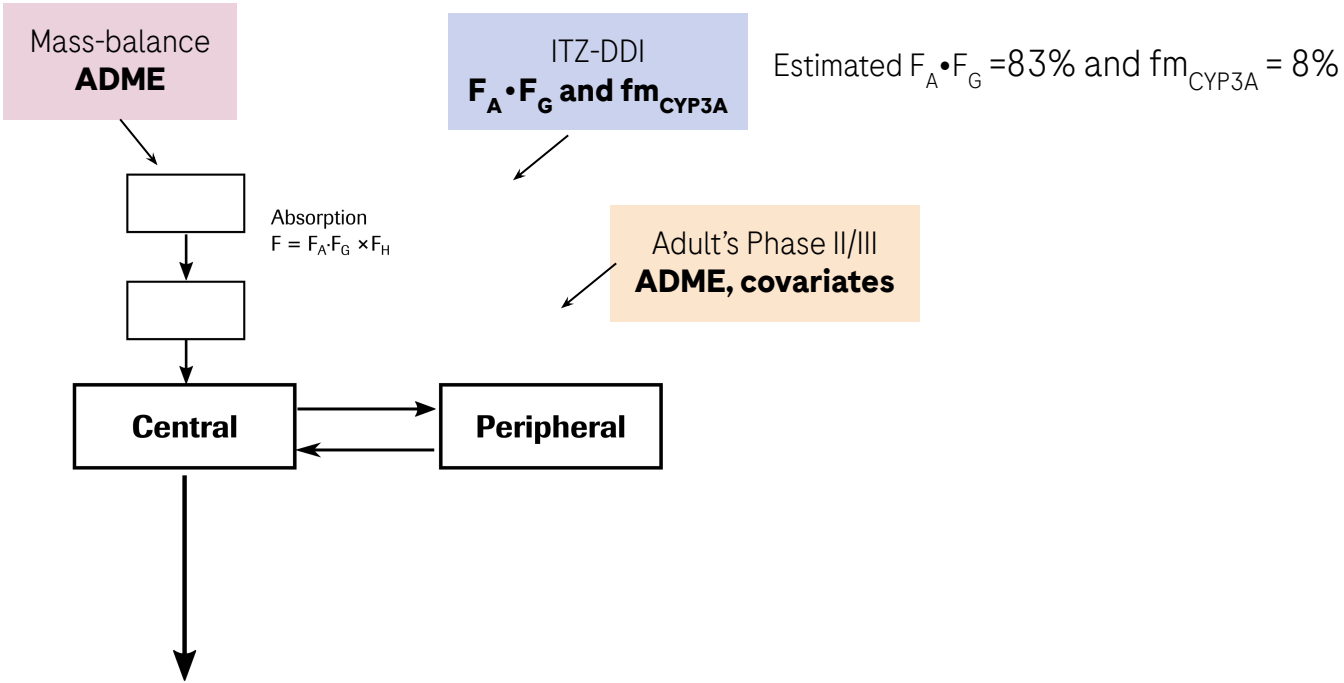

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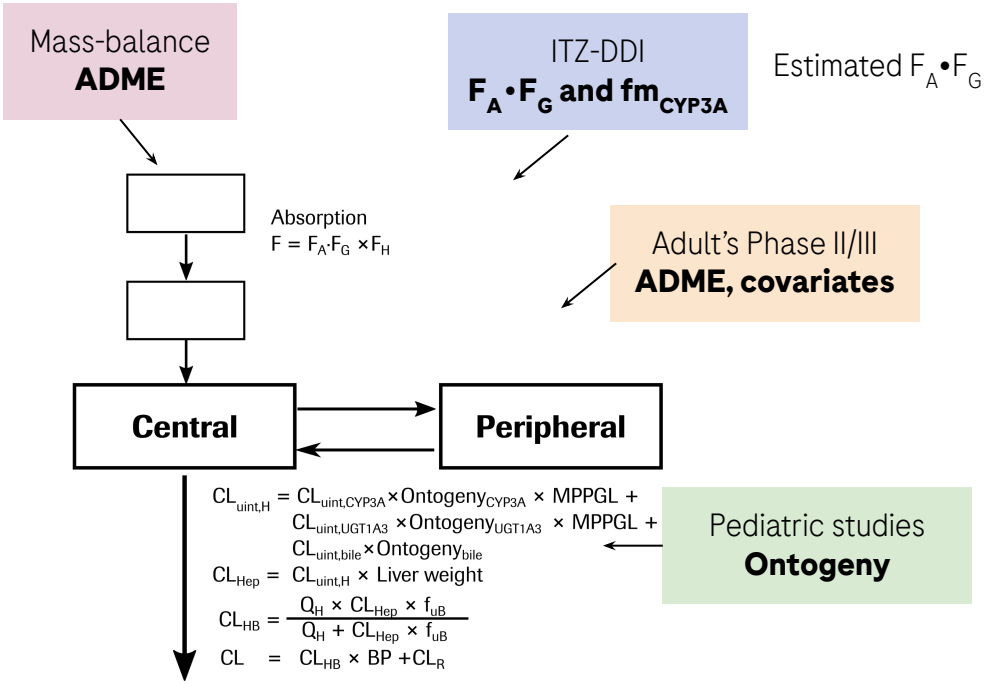
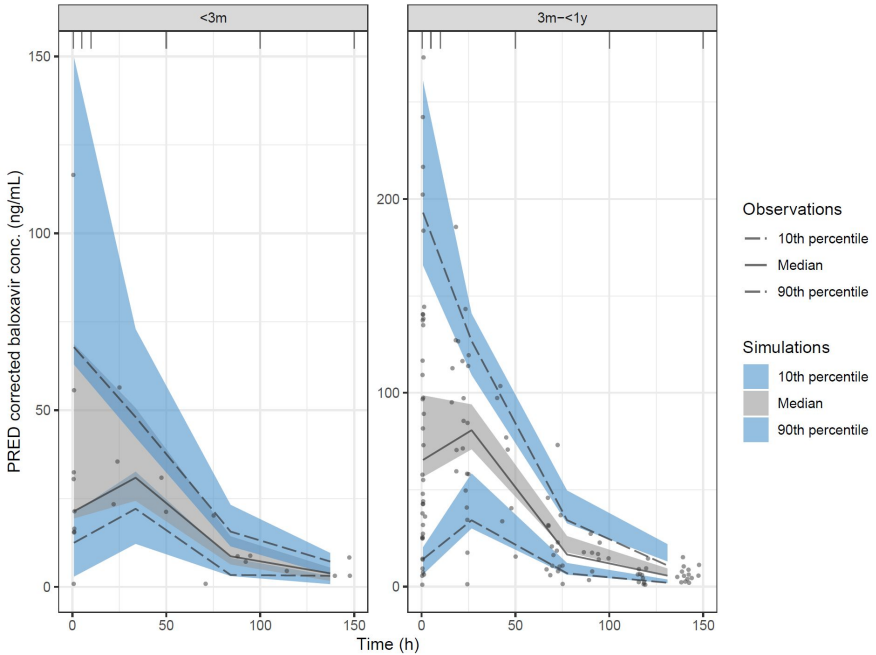


- Scaled the adult parameters to children with age-dependent anatomical and physiological data
- Fixed ontogeny models (literature) for UGT1A3[1], CYP3A[2] and biliary excretion[3]
- Estimated fm_{UGT1A3}/f_{bile}

1. Badee, J., et al., J Clin Pharmacol, 2019. 59 Suppl 1: p. S42-S55.
2. Upreti, V.V. and J.L. Wahlstrom, J Clin Pharmacol, 2016. 56(3): p. 266-83.
3. Johnson, T.N., M. Jamei, and K. Rowland-Yeo, Drug Metab Dispos, 2016. 44(7): p. 1090-8.

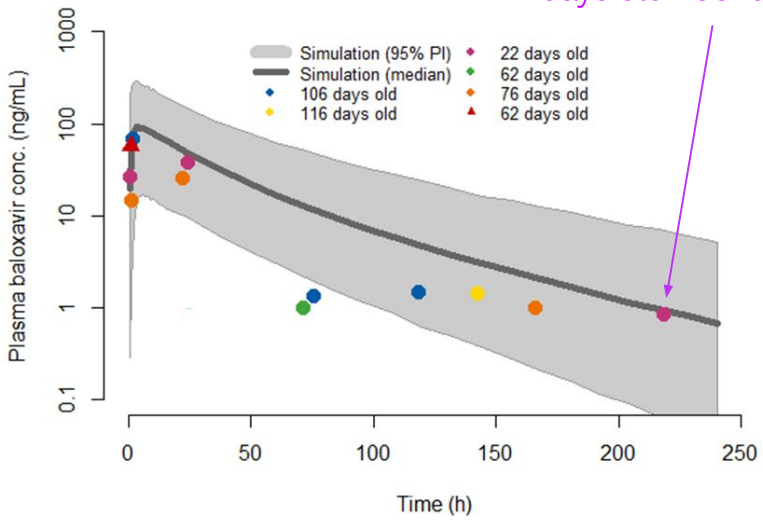
VPC and external data validation supported robustness of the population PBPK model for neonates and infants

Prediction Corrected -VPC



External data validation (n=6; 22 days to 3.8 months old)

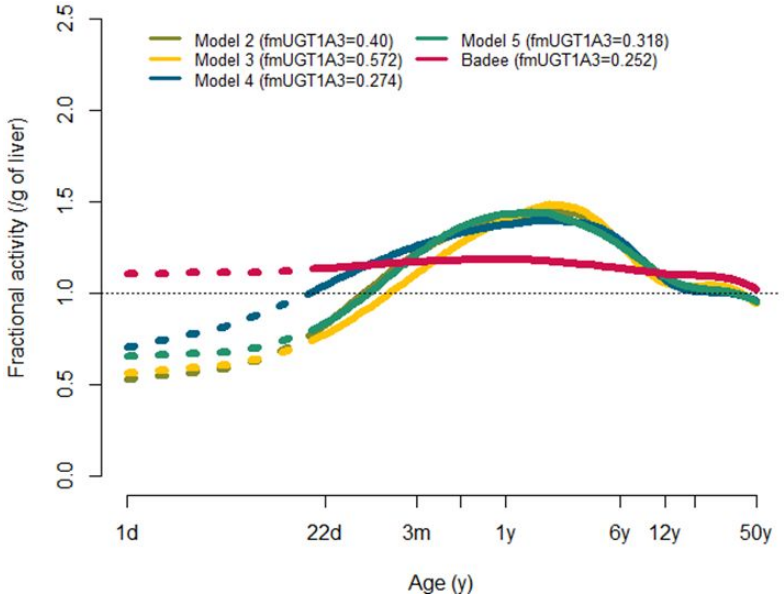
22 days old neonate



Uncertainty in the ontogeny of UGT1A3 and fm_{UGT1A3} was considered

- Estimate fm_{UGT1A3} and UGT1A3 ontogeny while fixing the ontogeny of CYP3A[2] and biliary excretion[3] (Models 2 to 5)

=> Simulations using three UGT1A3 ontogeny models: **Badée[1]**, **Model 3 (low CL) or Model 4 (high CL)**



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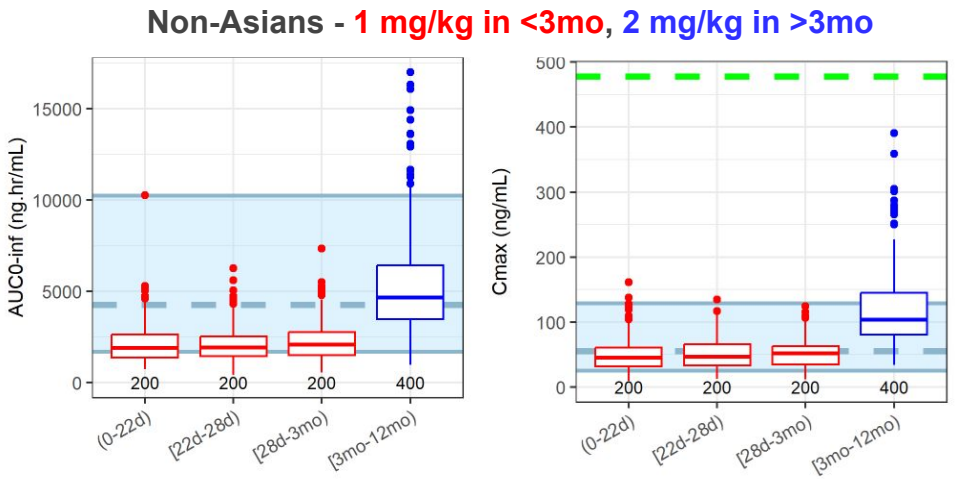
Pediatric to adult exposure matching

Pediatrics <3 mo at 1 mg/kg show sub-optimal pediatric-to-adult exposure-matching

Empirical popPK model



- Blue zone: Target exposure range in adults (5^{th} and 95^{th} percentiles of simulated adults at the recommended dose);

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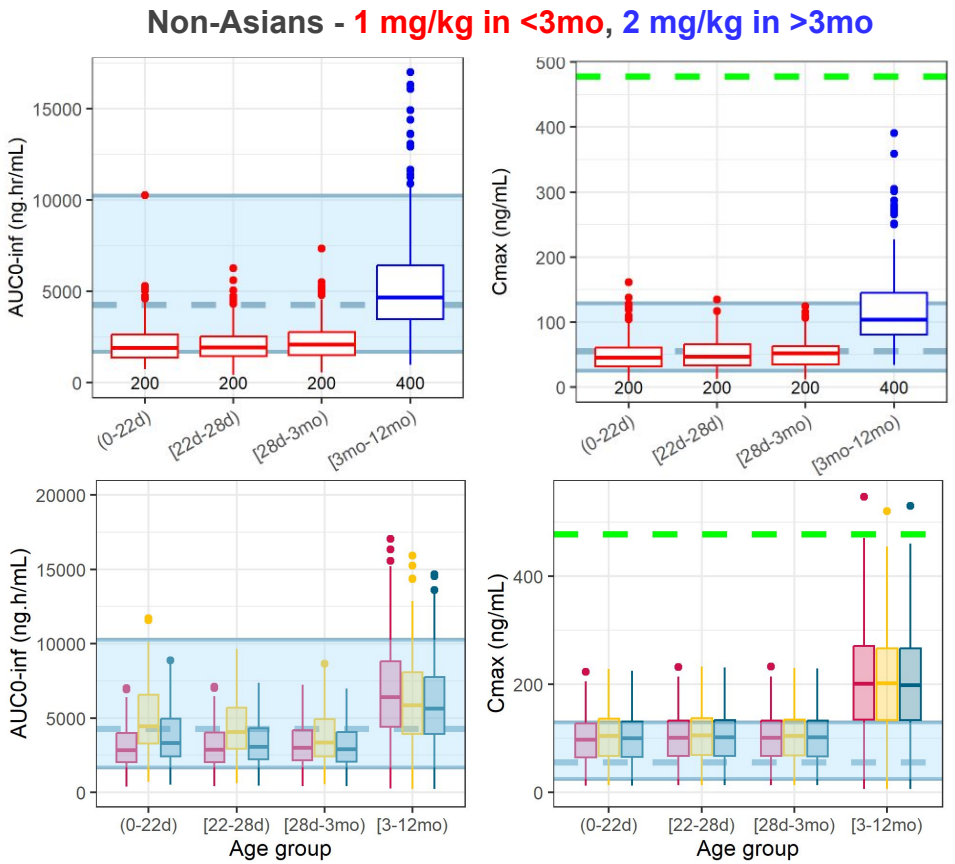

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- UGT1A3-**Badee**, **Model 3**, and **Model 4** used

Pediatric to adult exposure matching achieved at a dose of 2 mg/kg in all pediatrics <1 yo

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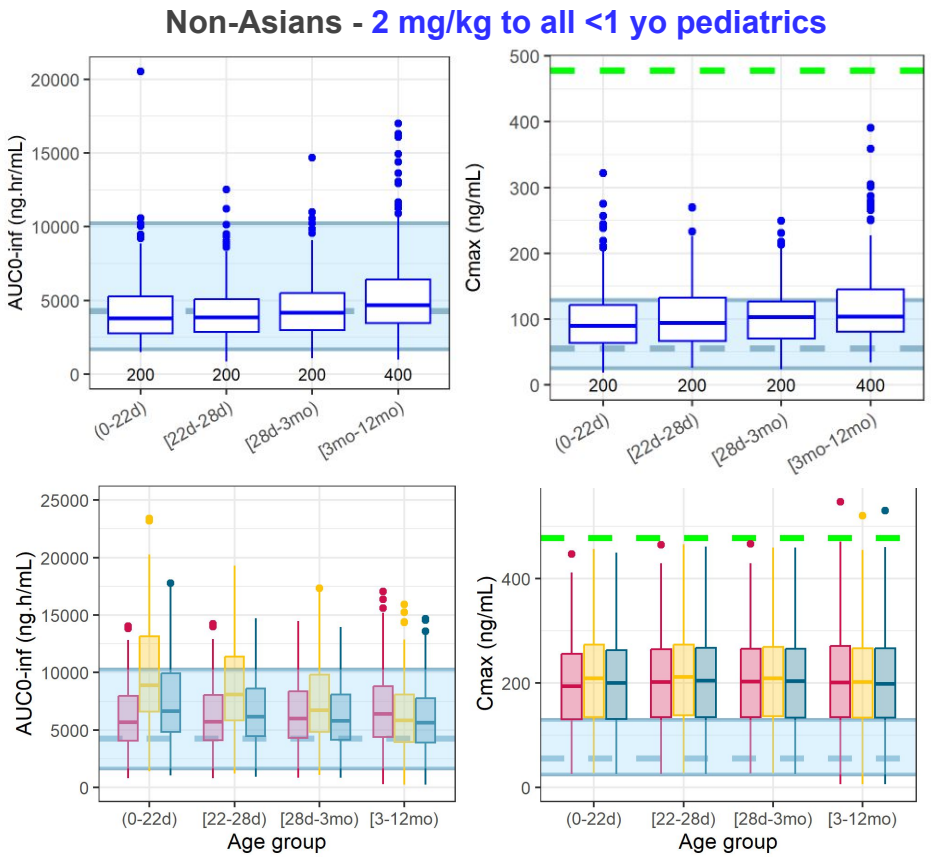

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A PK-Time To Alleviation of Symptoms (TTAS) model had been developed at the time of the label extension in >1 yo

Efficacy endpoint

Time to meet TTAS criteria and to remain so for at least 21.5 hours.

None or Minor for cough and nasal symptoms*

Return to afebrile state

Database of 2,216 patients from 1 to 86 yo.
Placebo: 901; Baloxavir Marboxil: 1315

See Retout S, Jolivet S, Cosson V, Delporte ML. PAGE 33 (2025) Abstr 11401 [Poster Session]

*(Canadian Acute Respiratory Illness and Flu Scale)

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Time to event analysis

Parametric proportional hazard model

Placebo model & influential covariates → Base PK-TTAS model & Covariates influencing baloxavir drug effect

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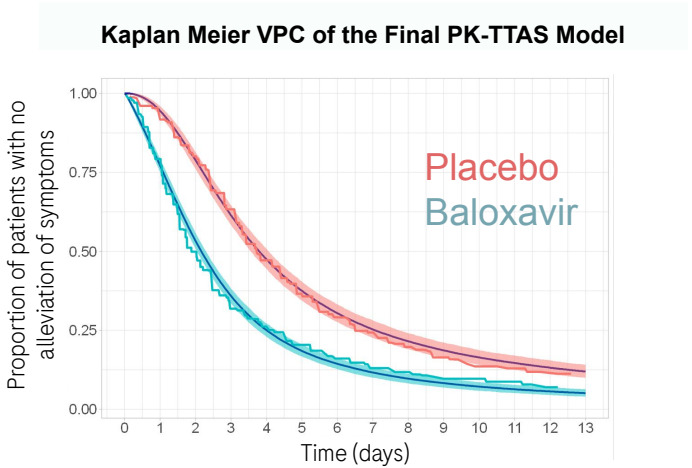
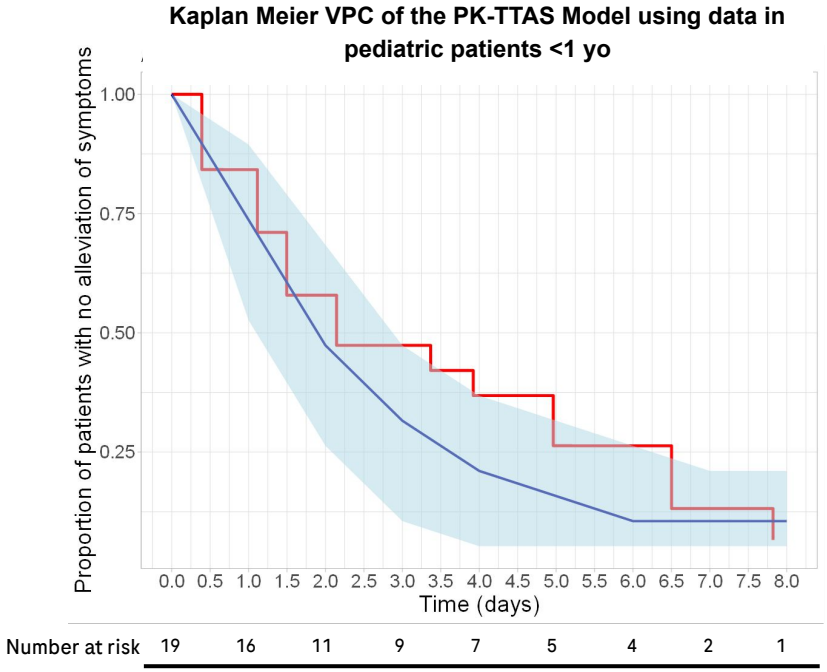


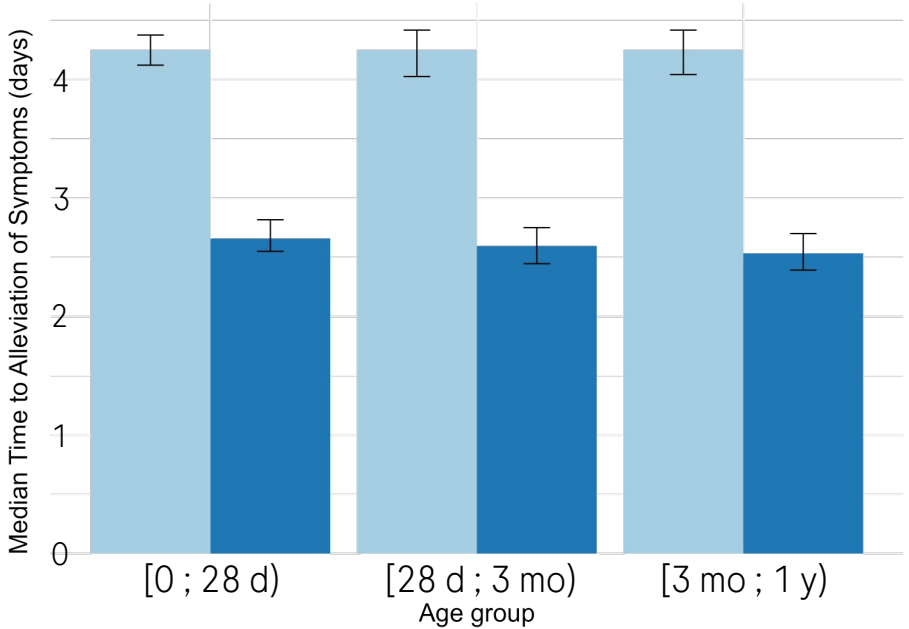
=> drug effect is race- and age-independent

See Retout S, Jolivet S, Cosson V, Delporte ML. PAGE 33 (2025) Abstr 11401 [Poster Session]

PK-TTAS predictions at the dose of 2 mg/kg in all patients <1 yo

Consistent reduction of ~1.7 days in non-Asians





Conclusions

- A model-based approach demonstrated that pediatric to adult exposure matching was achieved <1 yo
- An empirical popPK approach was complemented with a population PBPK modeling
- Whilst infants <3 months were dosed at 1 mg/kg in miniStone-1 study, model-based simulations (empirical and population PBPK) demonstrated that the best exposure-matching is achieved with a 2 mg/kg dose
- Collectively, data indicate a positive benefit-risk with the 2 mg/kg dose in <1 yo
    - PK-based extrapolation supported by simulations with popPK-TTAS and popPK-VK models,
    - No anticipated safety risk in <1 yo based on exposure-matching across ages

=> Baloxavir marboxil label requested at the dose of 2 mg/kg in pediatrics from 3 weeks to 1 year.

Rapporteur assessment

“ 5.3.6. Conclusions on clinical pharmacology

- Comparability of key PK-parameters of baloxavir in children in the age range 3 weeks to 1 year to children above 1 year and adults were **investigated using Pop-PK modelling**.
- It has been demonstrated that **the proposed dosing regimen of 2 mg/kg baloxavir marboxil is adequate in children from 3 weeks to 1 year,** providing in general similar exposure as children above 1 year [...].
- **Positive exposure-response was established for efficacy in two population PK/PD models [...] [PK-TTAS and PK-VK models]**.
- **No relationship between baloxavir exposure and adverse events (AEs) were identified** [...].

In conclusion, on basis of the provided clinical pharmacology data the approval of the current variation is supported.”

April 2025

Positive CHMP Opinion for the extension of the Baloxavir marboxil (Xofluza) indication in EU for the treatment of uncomplicated influenza in patients aged 3 weeks to <1 yo at the dose of 2 mg/kg.

Doing now what patients need next