Supporting a Pediatric Investigational Plan in liver transplantation – An example using a pharmacostatistical approach

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Summary

- The Paediatric Investigational Plan for everolimus included an extrapolation analysis to obtain a rational interpretation of limited paediatric data in the context of existing adult data
- The assessment of similar efficacy between paediatric and adult populations was an important step in this interpretation
- Given design differences between adult and paediatric studies, this assessment could not be obtained via a simple comparison of the study results
- A pharmacostatistical approach was applied to account for the differences and obtain a valid assessment which supported similar efficacy between the two populations

Background

Everolimus in solid organ transplantation

- Indication: Prevention of acute rejections after solid organ transplantation (Tx)
- Endpoint: Treated Biopsy Proven Acute Rejection (tBPAR)
- Standard of care: Multitherapy including Calcineurin inhibitors (CNI), e.g., Tacrolimus (TAC)
- Medical need at reducing CNIs (nephrotoxicity)
- Everolimus (EVR)
  - Mammalian target of rapamycin **(**mToR) inhibitor
  - Approved in adults in Tx in combination with CNI at reduced exposure

Background

Paediatric Investigational Plan (PIP) for Everolimus

- 2009: Determination of the PIP: Liver and Kidney* Tx
- 2010: Design of the paediatric liver Tx (PIP) study:
  - Single-arm, with 75 patients under EVR + rTAC
- 2013-2014: Request for modification of the PIP
  - Recruitment difficulties
  - Agreement that a Type-II variation can be submitted based on interim analysis data with (in Liver) reduced sample size of at least 20 patients
  - Inclusion of an extrapolation analysis as an additional measure

* Not covered here
TAC = Tacrolimus; EVR = Everolimus
rTAC = TAC at reduced exposure

Background

*General considerations about extrapolation**

* EMA's draft "Reflection paper on extrapolation of efficacy and safety in paediatric medicine development" (2016)

- Extrapolation concept: Use a model to predict "target data"
  - Target: Paediatric data, e.g. drug concentration or efficacy
  - Model quantified from systematic synthesis of all relevant data ('source') + assumptions
    - include (but is not restricted to) adult data
- Extrapolation plan:
  - if necessary to decrease uncertainty associated with prediction (precision and model assumption)
  - Design studies in the target population, and plan analyses
- Validation / confirmation:
  - by comparing observed vs predicted paediatric data

Everolimus PIP

Similar concentration-response: key assumption in extrapolation concept

- Assumption: Population similarity in concentration-response relationship

  Same EVR concentration in adults and children leads to same efficacy

- Assumption supported by semi-quantitative evidence
  - Target
  - Disease progression
  - Clinical evidence

- Under this assumption and given that concentration can be controlled in children by means of therapeutic drug monitoring (TDM), the model allows to determine a dosing regimen which delivers adequate efficacy in children

Everolimus PIP

Validation of the concept cannot be done by simple comparison of adults and paediatric data

- Uncertainty about extrapolation concept
  → Extrapolation plan: Use of paediatric data (PIP IA) study to validate the concept

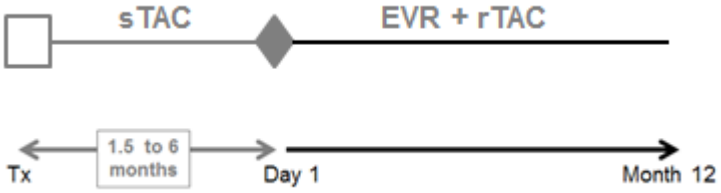
- In general, the paediatric trial is designed such that validation can be done by a simple comparison of efficacy results vs adult data

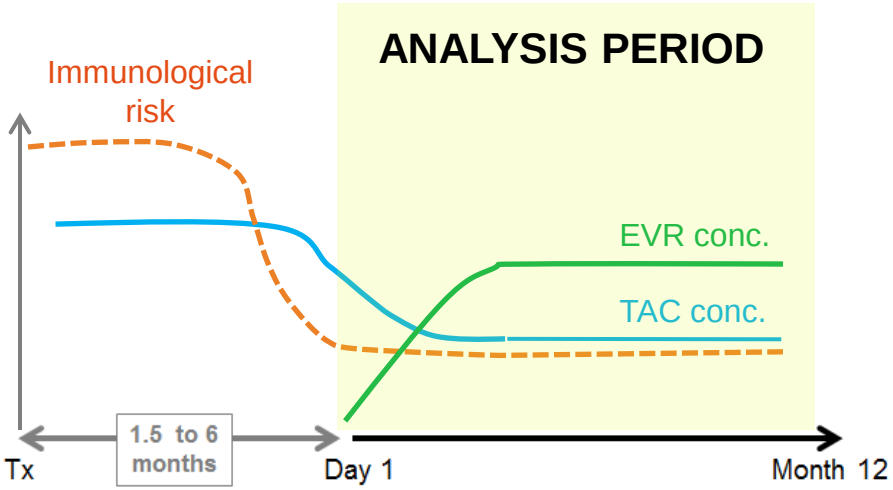
- In our EVR case,
  - Major design differences between adult and paediatric studies prevented the simple comparison to be relevant
  - We have used pharmacometric approaches tailored to the design differences to obtain a valid assessment of the concept

Extrapolation analysis plan

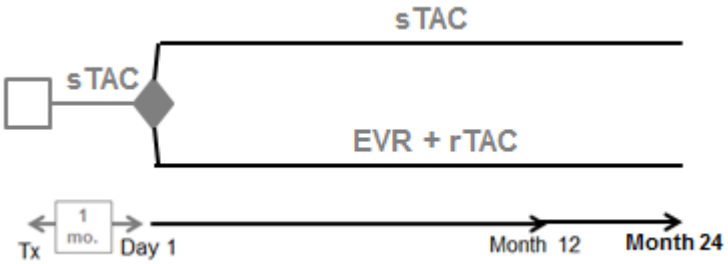
Major design differences between adult and paediatric studies prevented the simple comparison to be relevant

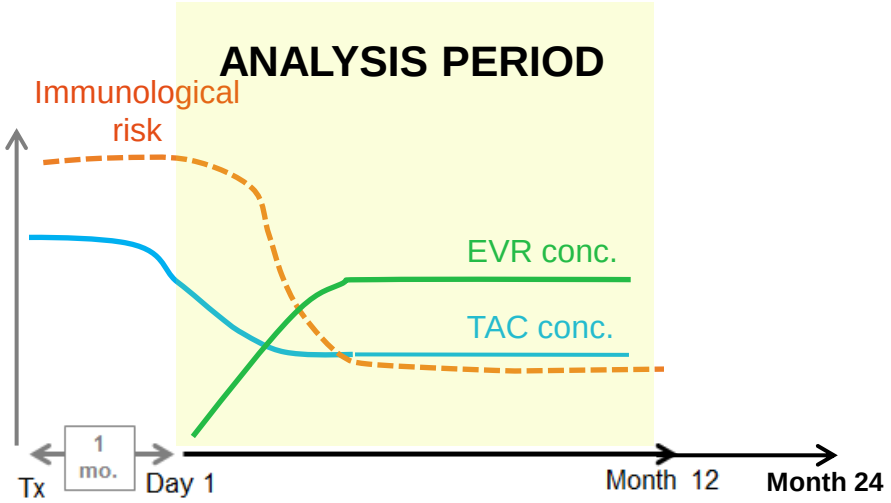
Paediatric





Adult





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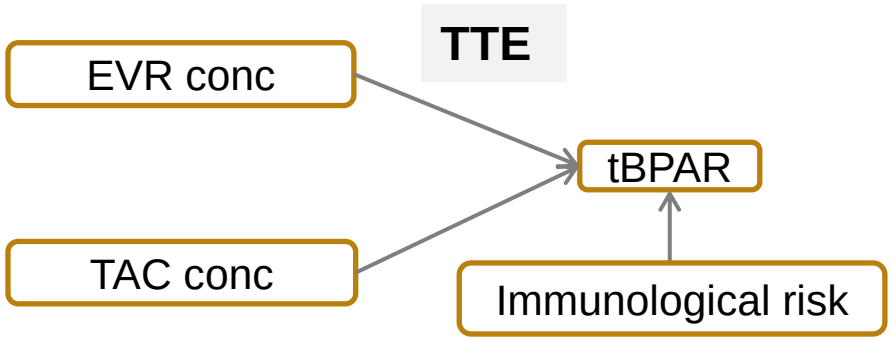
Extrapolation analysis plan

Relevant adult efficacy obtained via model-based assessment

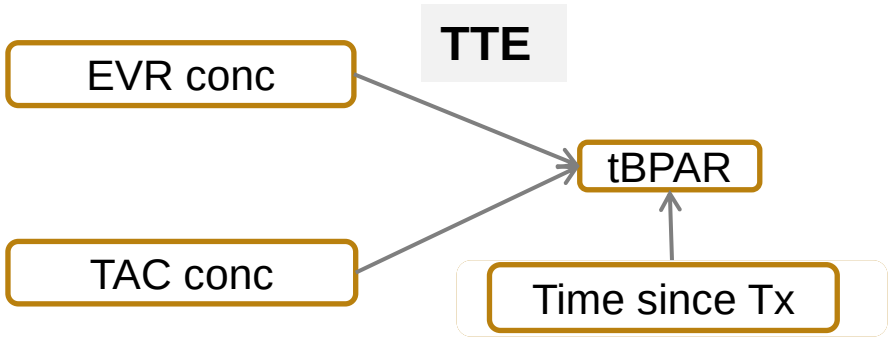
- Fair comparison of adults and children with same EVR concentration only possible if no confounders (immunological risk and possibly TAC)
- Adjusting for those confounders would allow to predict the counterfactual efficacy for adults with same EVR concentration as children of the paediatric study
  - Requires to distinguish the 'causal' relative contributions of those confounders
  - This was done using a time-to-event (hazard) model:



TTE = Time to event model.

Extrapolation analysis plan

Use time since transplantation as surrogate for immunological risk

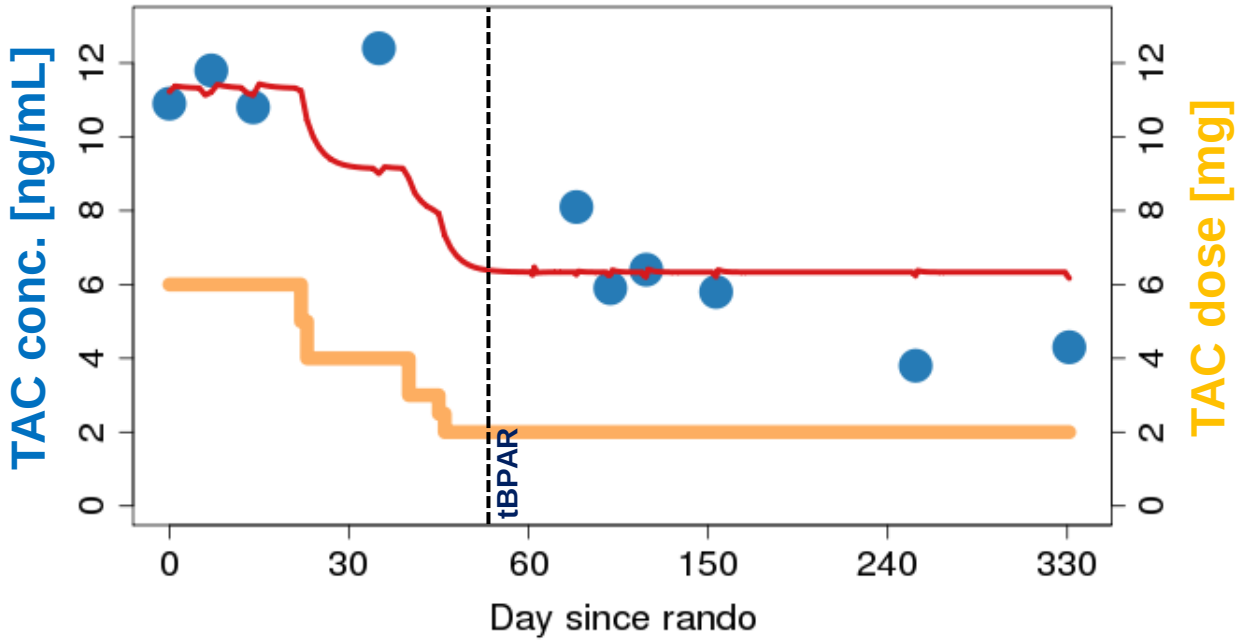


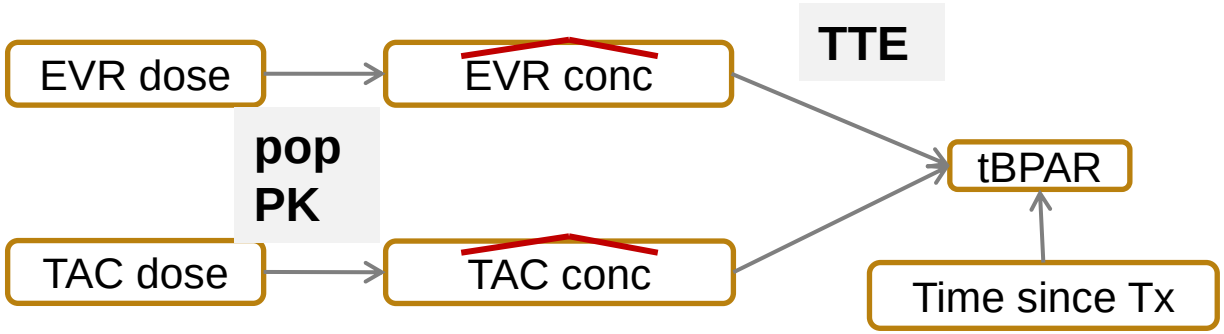
TTE = Time to event model.

Extrapolation analysis plan

Sparseness of PK samples and frequent dose changes require modeling the concentration time-course

Example of TAC dose and concentration for one study subject :





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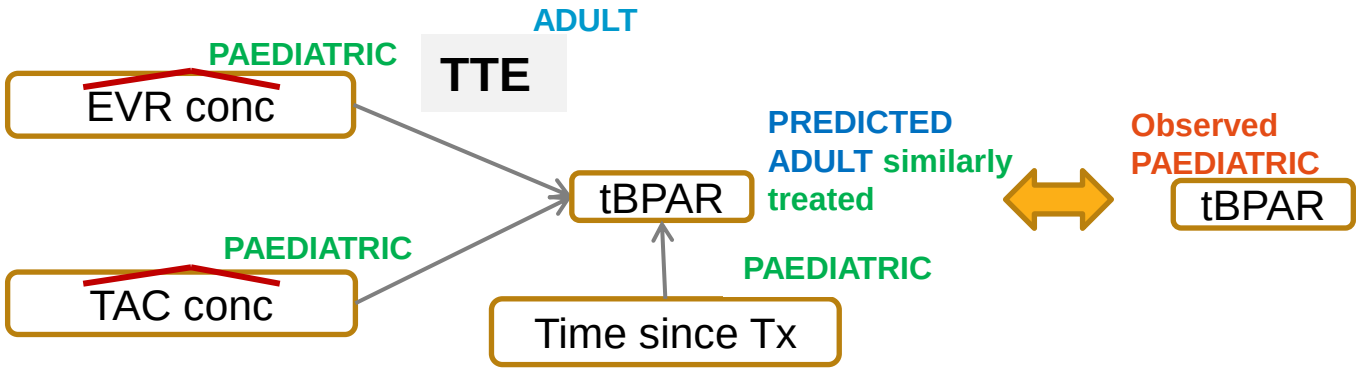
Extrapolation analysis plan

3 analysis steps

- Step 1: Estimate the time-to-event model on adults only
- Step 2: Predict efficacy for adults similarly treated* as children of the paediatric study (predictive distribution)
  - Same tacrolimus and everolimus concentrations at the same time
- Step 3: Validation: Compare this predictive distribution to the observed paediatric efficacy



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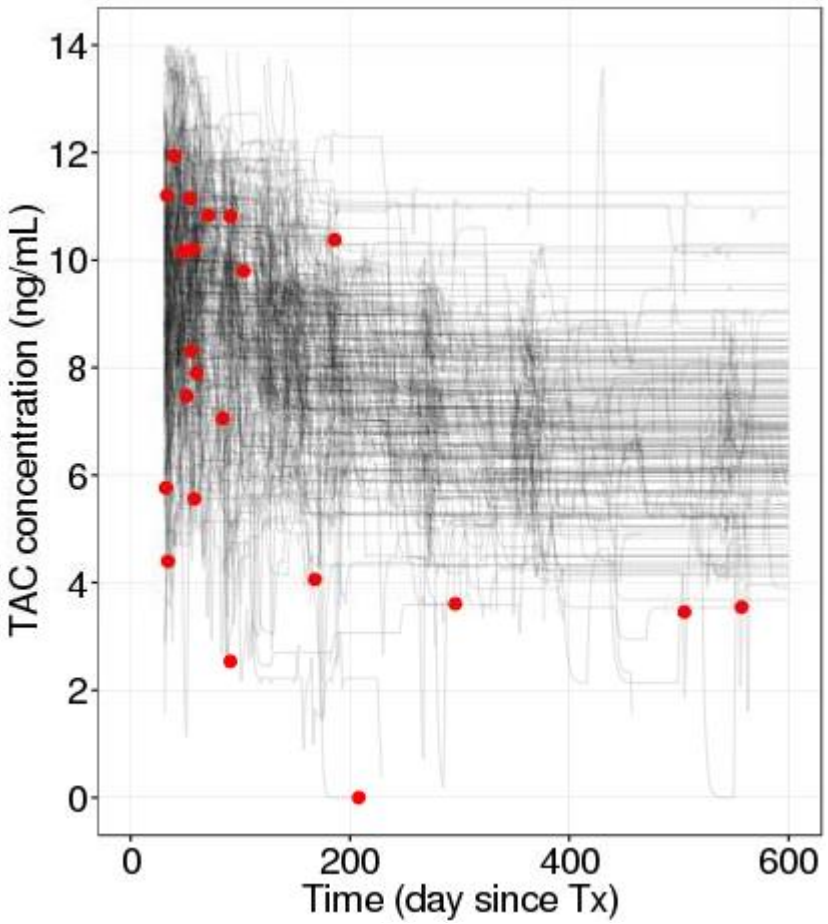
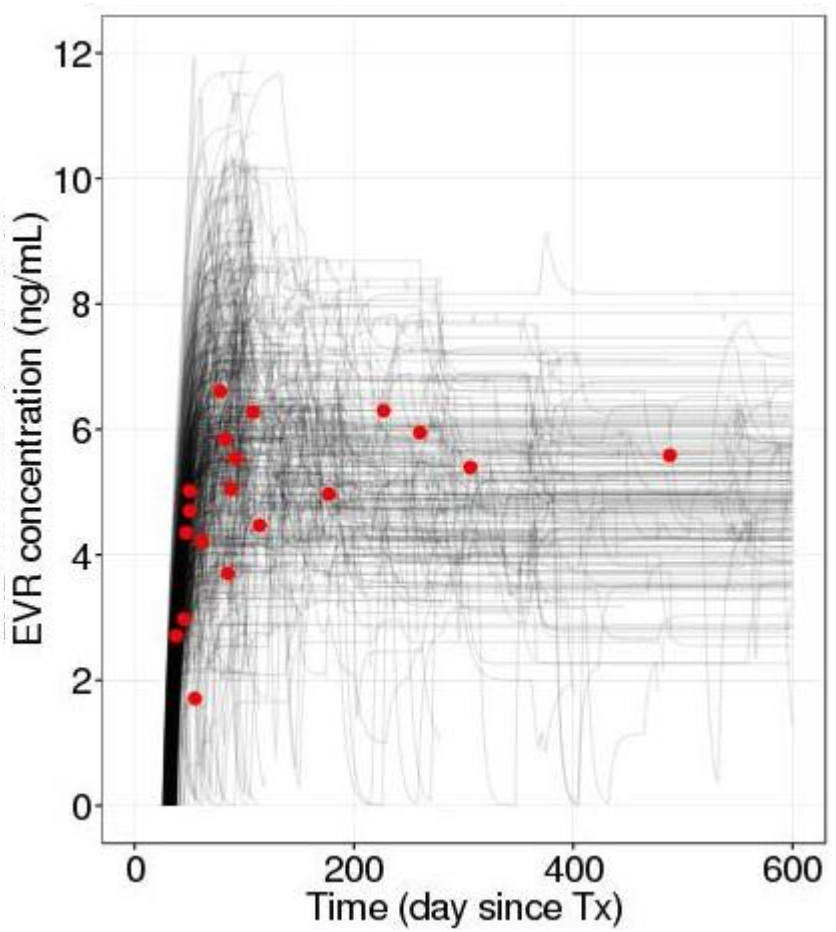
Step 1: Estimate concentration-tBPAR model in adults

Graphical exploration identifies TAC, but no EVR, conc. effect and confirmed the expected higher early immunological risk





N pats (EVR + rTAC): 237 N (%) tBPAR: 15 (6%)

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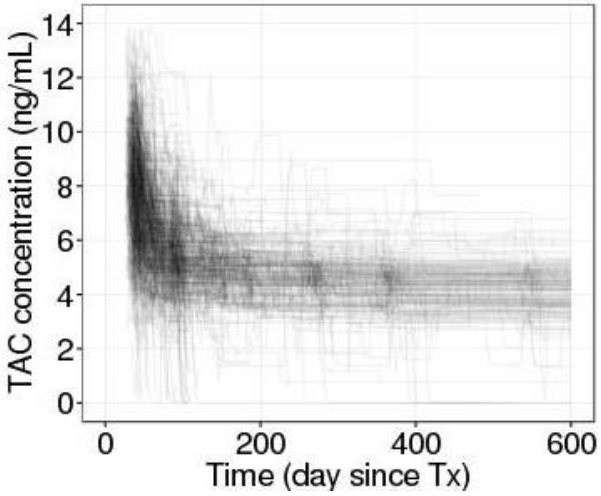
Step 1: Estimate concentration-tBPAR model in adults

Model prediction consistent with proportion of tBPAR events

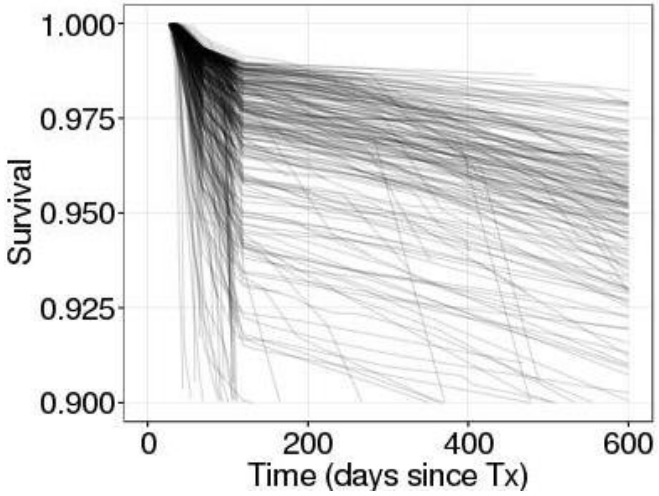
Final adult model (EVR + rTAC): $\boldsymbol{h_i(t) = \widehat{h_0(t)} e^{\hat{\alpha} * max\left(\widehat{TAC_i}(t), \hat{\gamma}\right)}}$

ADULT

Predicted concentration



Predicted survival (under adult model)



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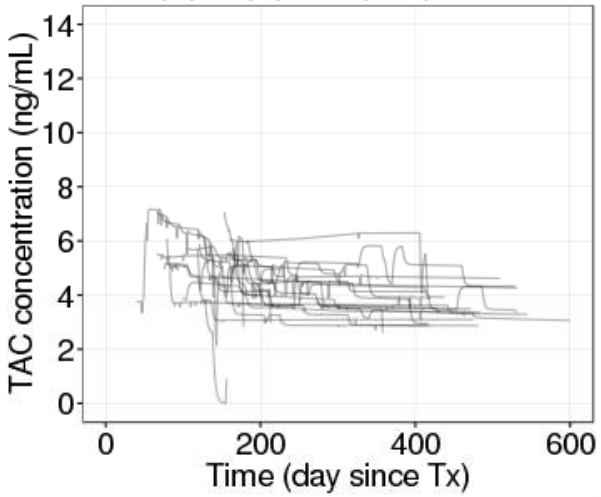
Step 2 - Prediction from adult model

Better survival for hypothetical adults with same exposure as children at the same time, given the delayed start of paediatric analysis period

PAEDIATRIC (N=22)

ADULT

Predicted concentration



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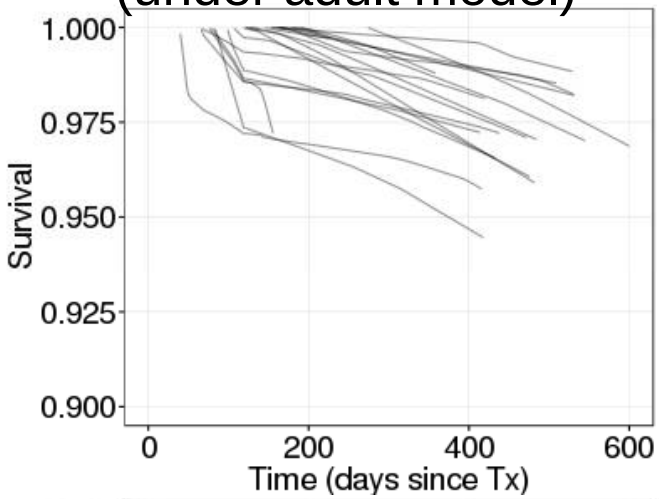
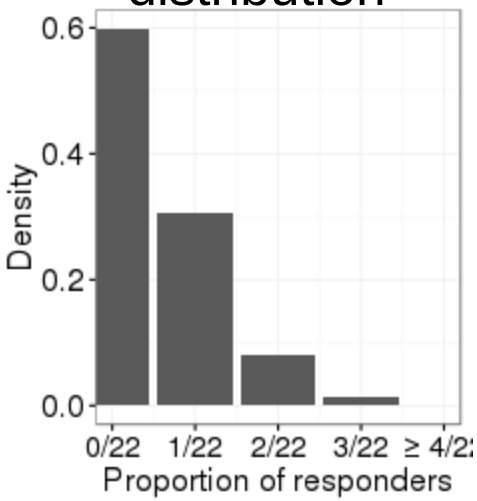
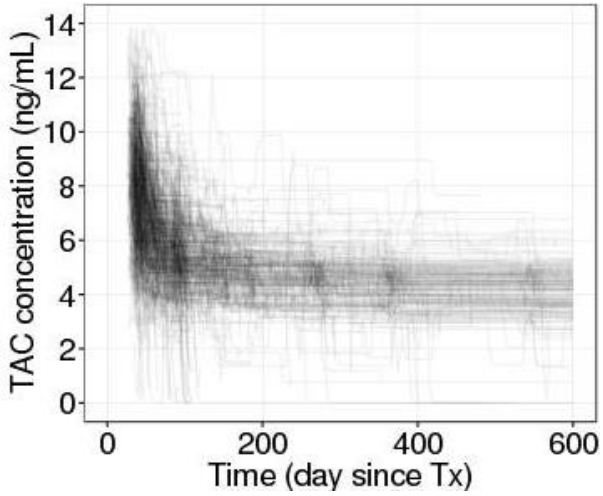
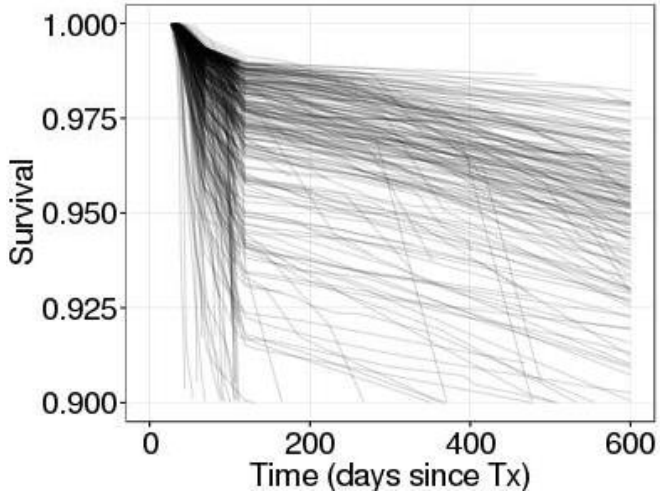


Predictive distribution







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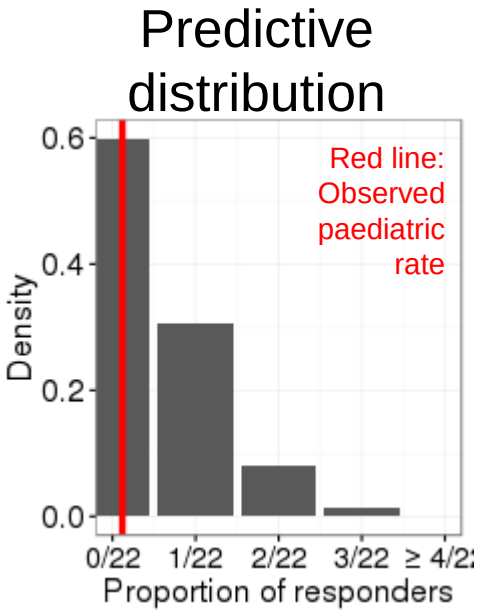
Step 3: Validation and interpretation

From comparison of the predictive distribution to the observed paediatric efficacy

- No event observed in 22 patients of the paediatric study
- This observed efficacy is at the mode of the predictive distribution
- **This support validation of the extrapolation concept**



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Conclusion

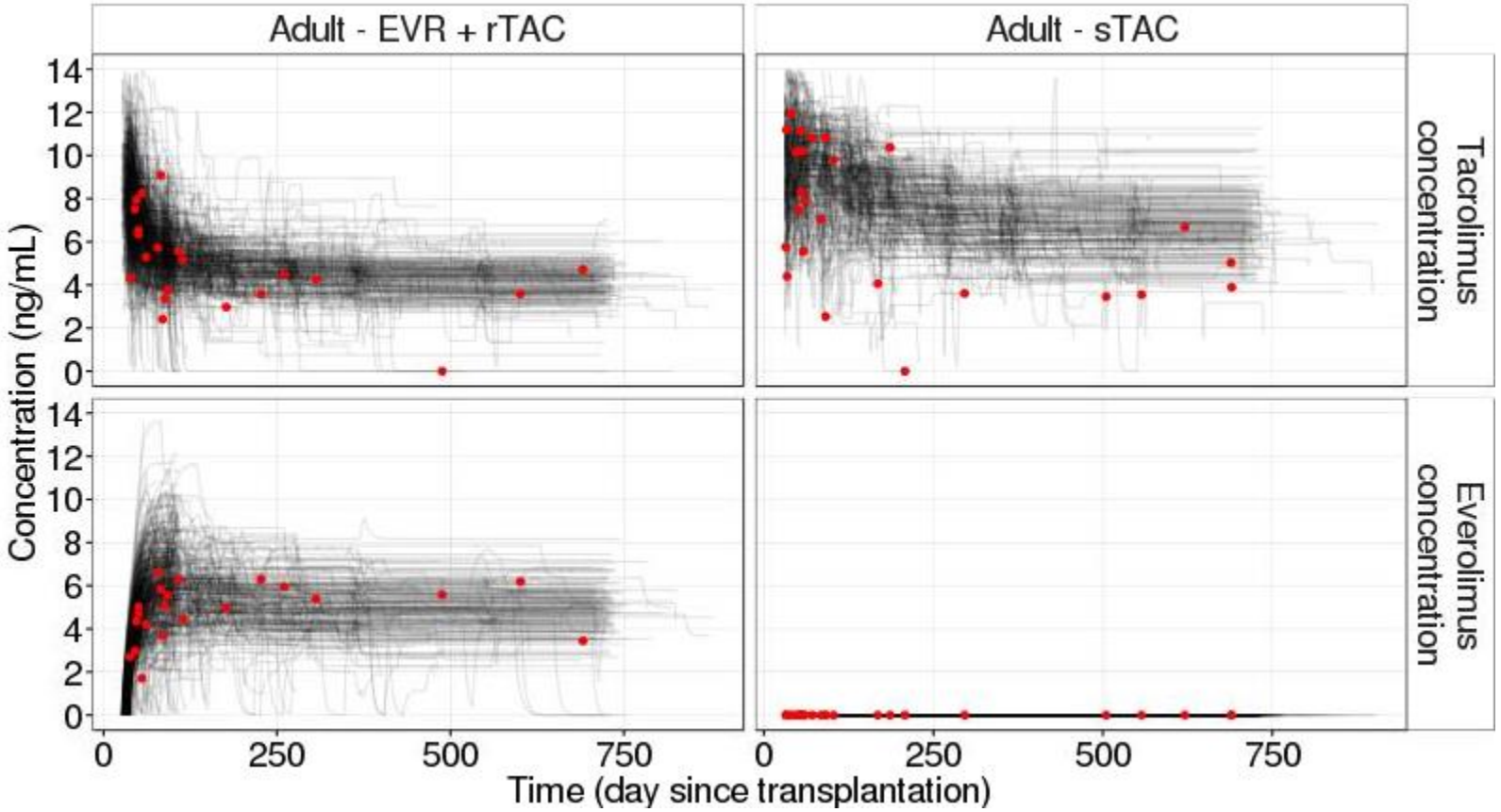
- The PIP for everolimus included an extrapolation analysis to obtain a rational interpretation of limited paediatric data in the context of existing adult data
  - The assessment of similar efficacy was an important step in this interpretation
- Given design differences btw adult and paediatric studies, pharmacostatistical methods, combining dose and concentration and handling time-varying covariates, had to be used to obtain a valid assessment
- The analyses showed a paediatric rejection similar to this predicted from the adult patient similarly exposed at the same time
  - This supported validation of the extrapolation concept
- The interim analysis data and the extrapolation analysis results were submitted, and paediatric information was included in the label

- Thank you

BACK-UP

Step 1: Estimate concentration-tBPAR model in adults

Graphical exploration identifies a TAC conc. effect and confirmed the expected higher early immunological risk



N pats =	**461**	**239**
N (%) tBPAR =	**21 (4.5%)**	**25 (10.5%)**

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Step 1: Estimate concentration-tBPAR model in adults

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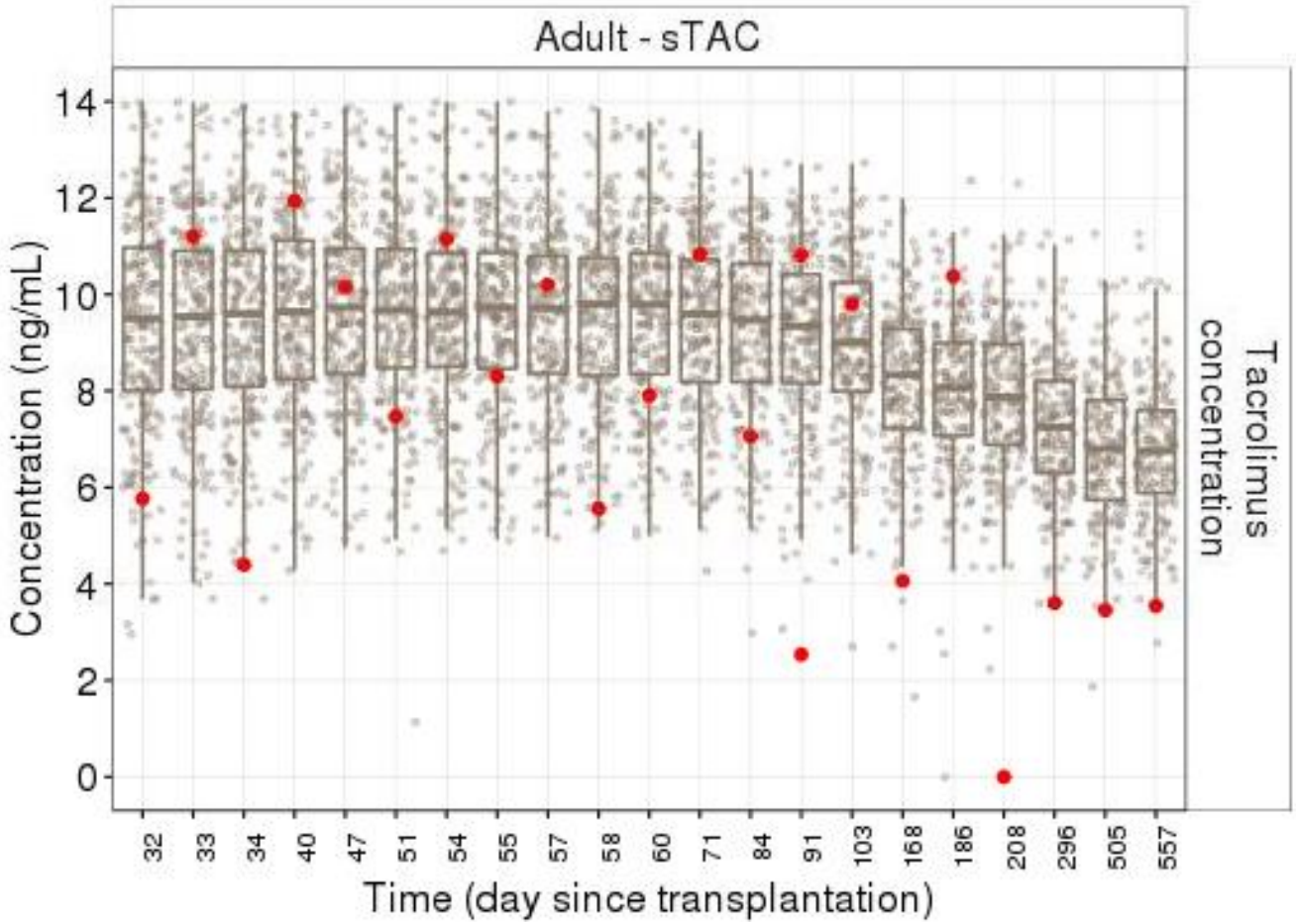

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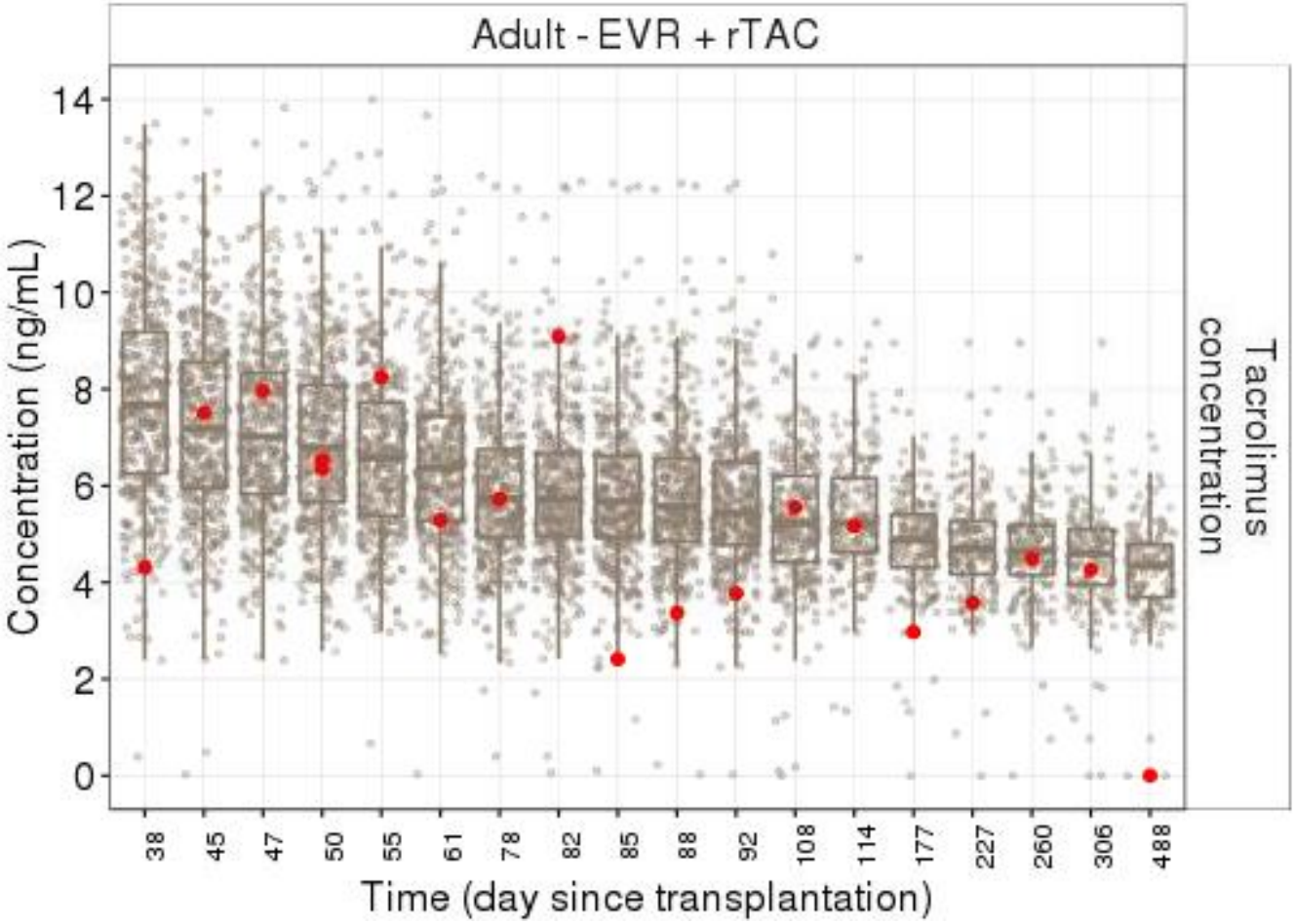

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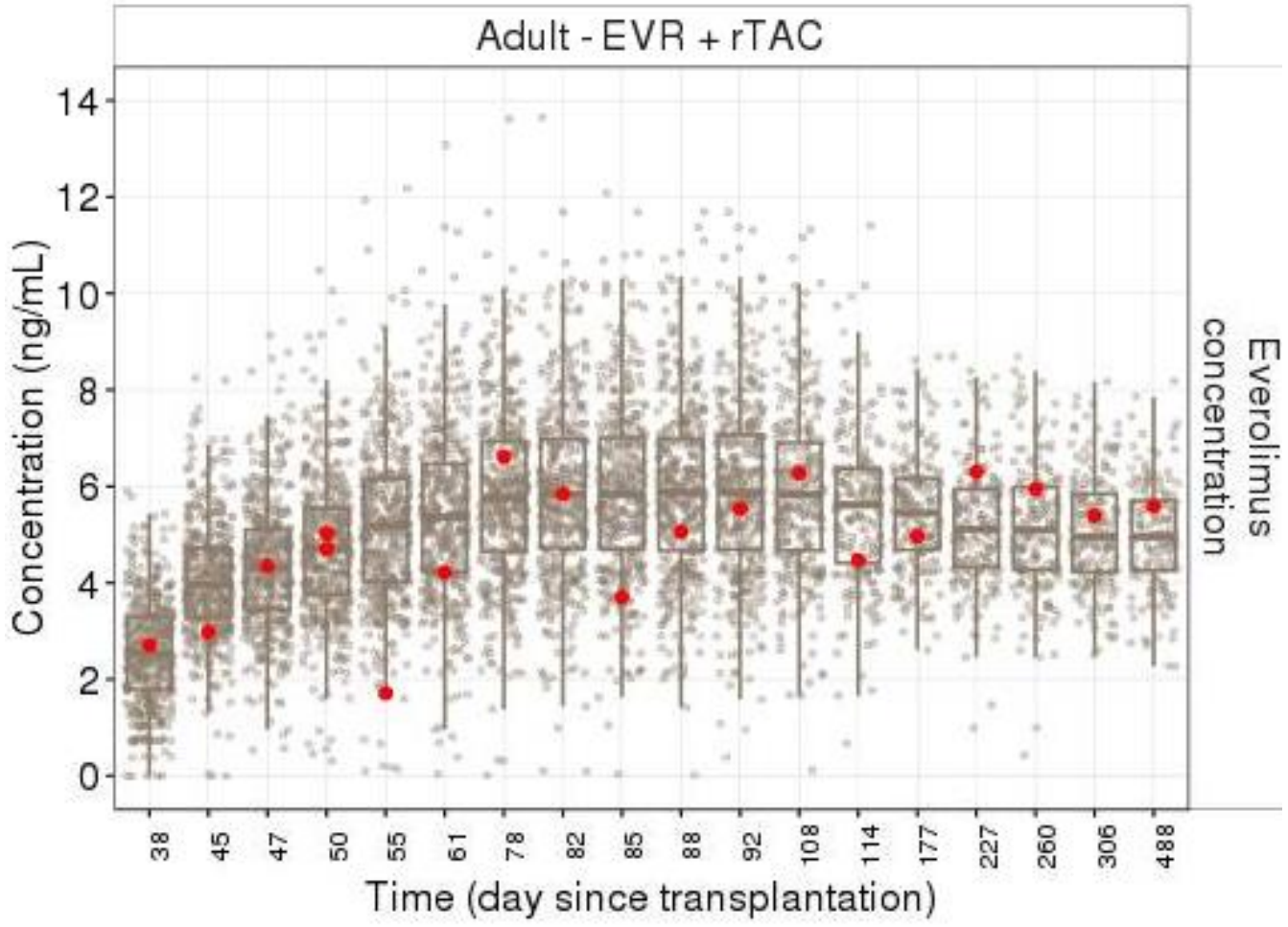

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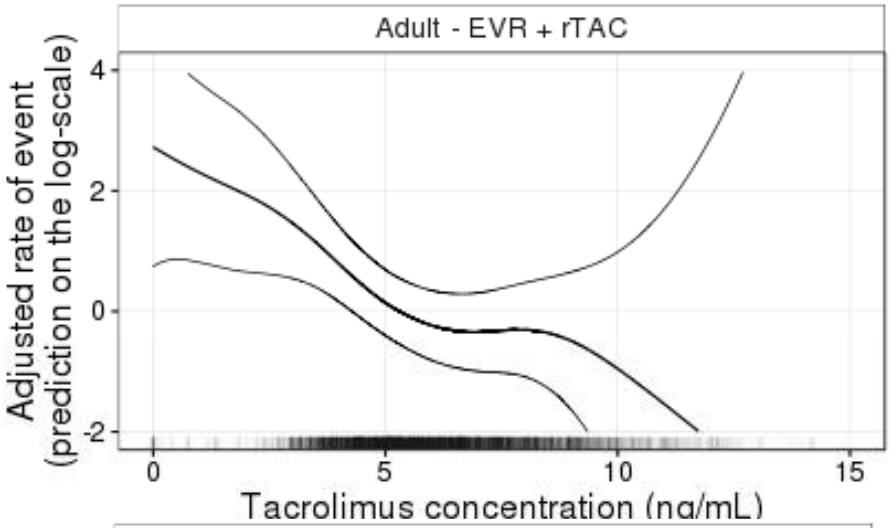
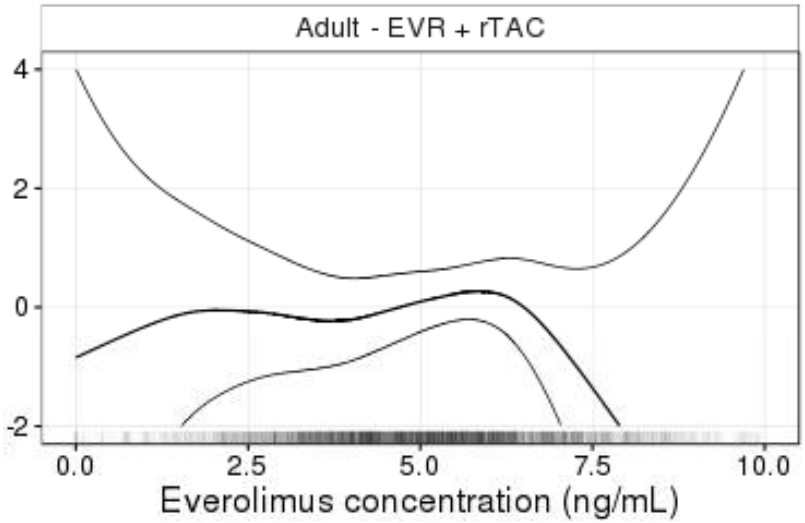
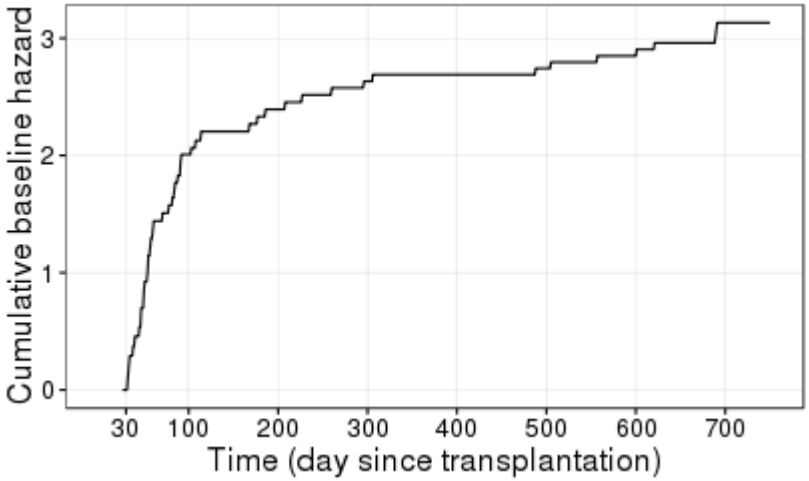
Investigation of adult model







Final adult model
(EVR + rTAC)

$$h_i(t) = \widehat{h_0(t)} e^{\hat{\alpha} * max\left(\widehat{TAC_i}(t), \hat{\gamma}\right)}$$

Grambsch (2005) Diagnostic plots to reveal functional form for covariates in multiplicative intensity models

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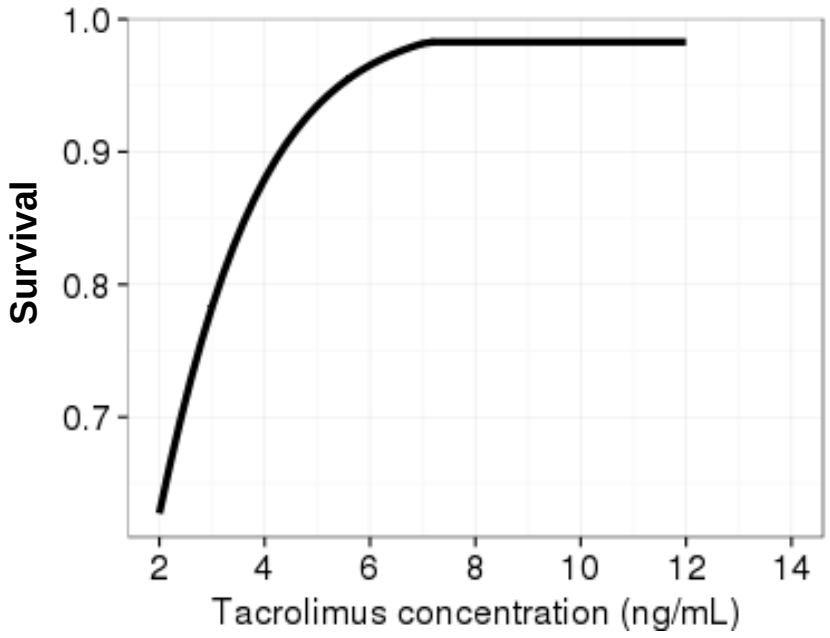
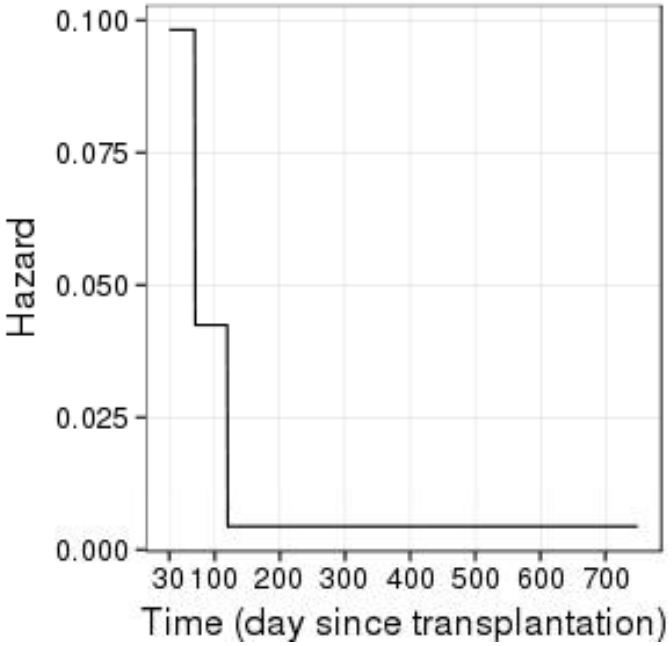
Final Adult model

Final adult model $h_i(t) = \widehat{h_0(t)} e^{\hat{\alpha} * \max\left(\widehat{TAC_i}(t), 7.1\right) + \hat{\beta} * 1_{EVR_i}}$

Probability being tBPAR–free (between Days 30 and 750) given constant TAC concentration



Baseline hazard $\widehat{h_0(t)}$ (immunological risk)



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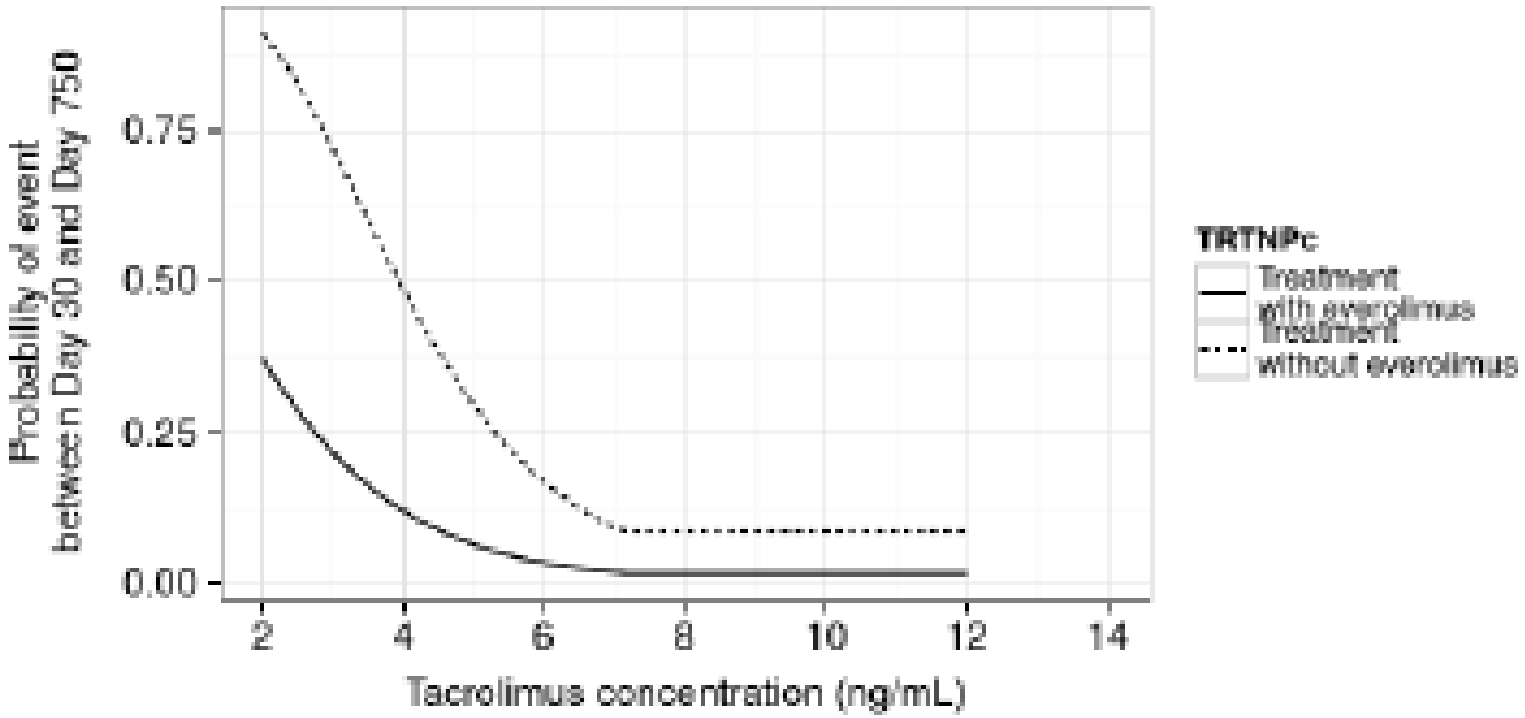
Final adult model

$$h_i(t) = h_0(t)e^{\alpha * \max(TAC_i(t),7.1) + \beta * 1_{EVR_i}}$$



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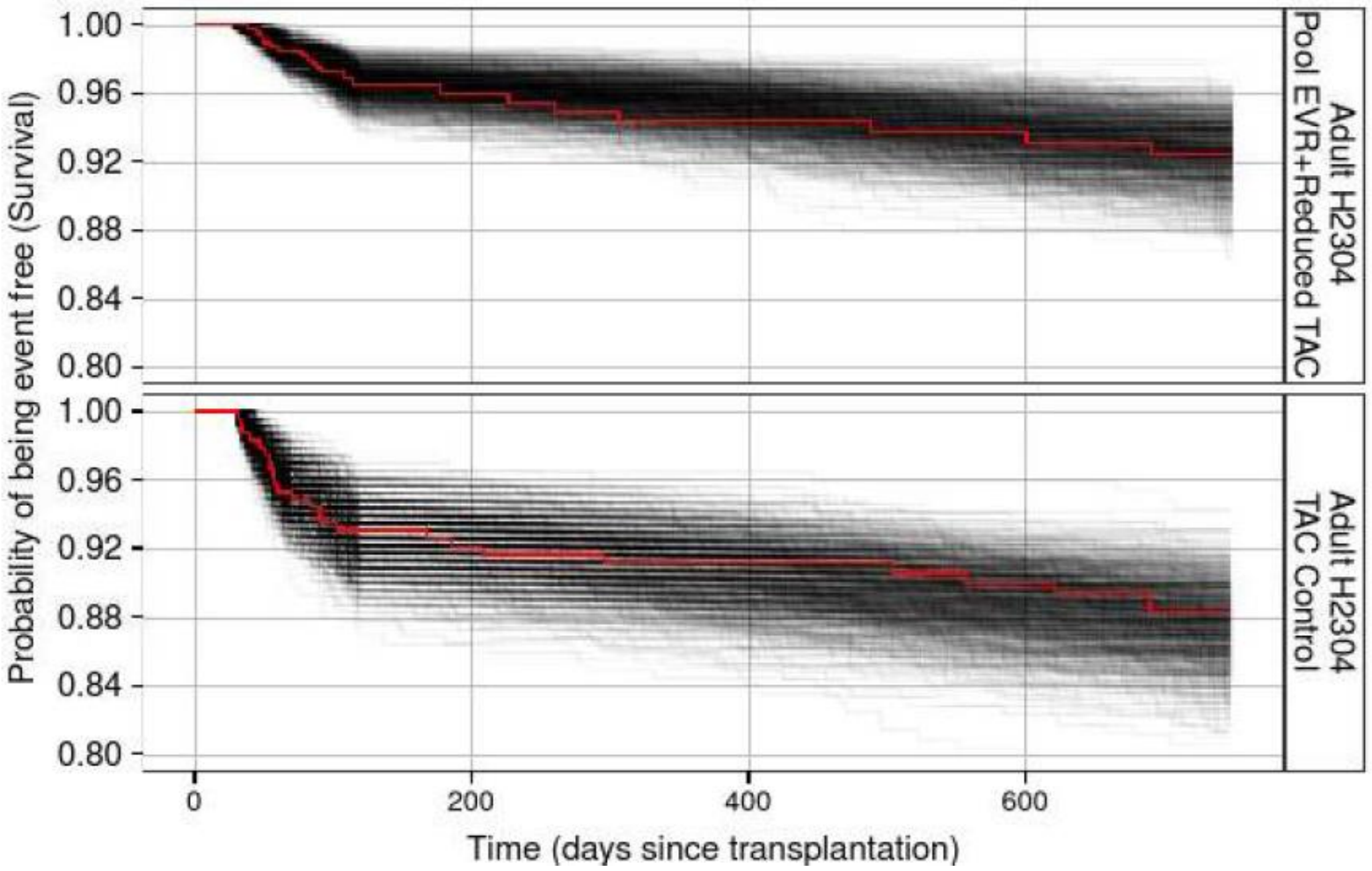
Validation of final adult model

Figure 5-20 **Visual Predictive Check for Model MLp3, by treatment group**



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