Supporting a Pediatric Investigational Plan for Everolimus - Defining the extrapolation plan

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Summary

- An extrapolation analysis was added to the on-going PIP for everolimus to obtain a rational interpretation of the 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
- Tailored statistical and pharmacometric methods were successfully applied to account for the differences and obtain a valid assessment

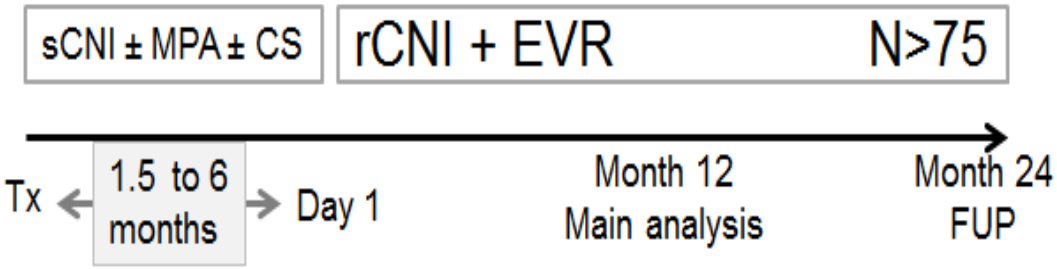
Background

- Indication
  - Prevention of acute rejections after kidney and liver transplantation
  - Endpoint: treated Biopsy Proven Acute Rejection (tBPAR)
  - Standard of care treatment: Quadritherapy including
    - Calcineurin inhibitors (CNI): tacrolimus (TAC) or cyclosporine (CsA)
    - Mycophenolate mofetil (MMF)
    - Corticosteroids (CS), possibly tapered
    - With/out induction therapy (e.g., basiliximab)
  - Interest in reducing CNI exposure, given high risk of developing renal injury
- Everolimus (EVR)
  - Mammalian target of rapamycin (mToR) inhibitor
  - Used with CNI at reduced exposure, CS, with/out induction therapy
  - Approved in adults in combination with
    - TAC in liver Tx in EU (2012) and US (2013)
    - CsA in kidney Tx in some EU countries (2003) + US (2010)

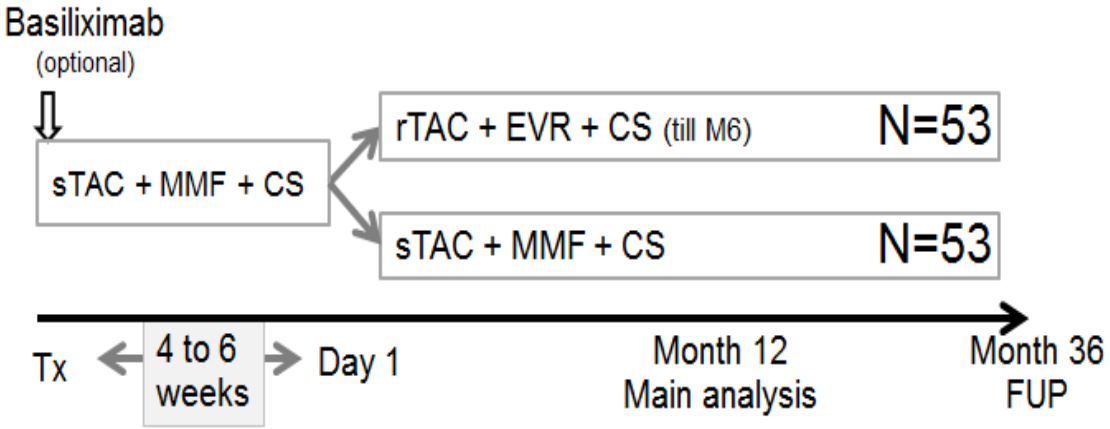
2009: Original PIP

Includes 2 paediatric studies

Liver Tx



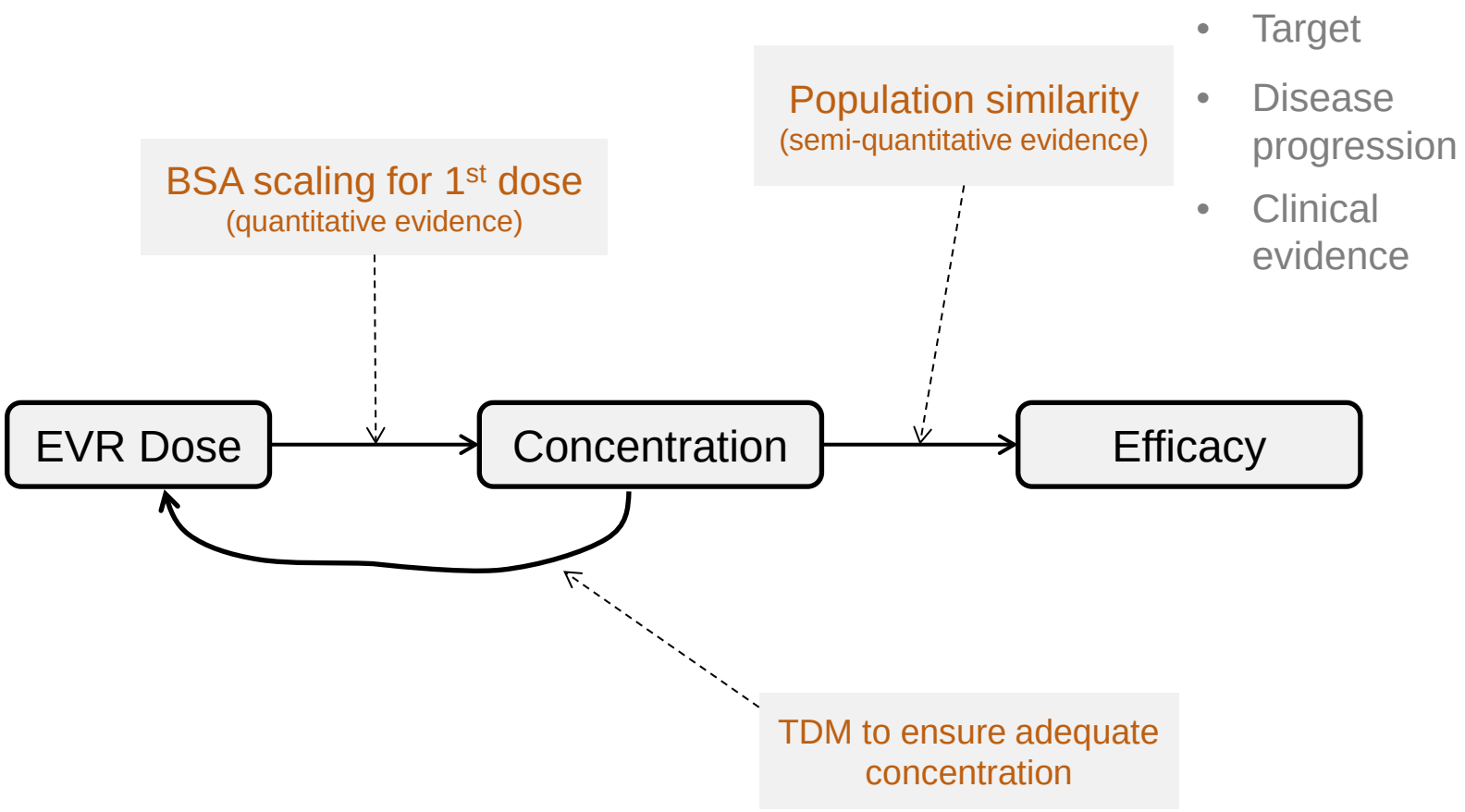
Kidney Tx



rCNI (rTAC) = CNI (TAC) at reduced exposure
sCNI (sTAC) = CNI (TAC) at standard exposure

2009: Original PIP

Extrapolation concept



- Target
- Disease progression
- Clinical evidence

BSA = Body surface area
TDM = Therapeutic Drug Monitoring

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2013: Request for modification

- Recruitment difficulties in the PIP studies
  - This jeopardized the possibility to timely bring an alternative choice to the paediatric medical community
- Sample size reduction proposed to PDCO
- Advice from SAWP sought as per PDCO's request
- Agreement in 2014:
  - Unchanged PIP studies in terms of design and treatment
  - Submit a Type-II variation based on
    - Interim analysis data at Year 1 for the PIP studies, with reduced sample size: N=15 by treatment arm in kidney; N>20 in liver
    - An extrapolation analysis (next slides)
  - Continue the PIP studies with the original sample size for the planned duration, including the follow up period

SAWP = Scientific Advice Working Party

Extrapolation plan

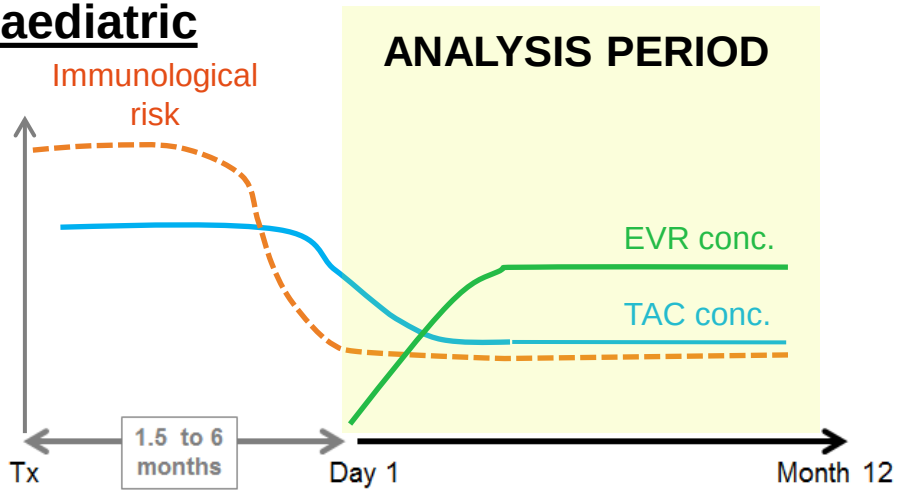
Need analysis methods tailored to design differences

- Extrapolation is used to obtain a rational interpretation of the limited paediatric evidence in the context of existing adult data
- An objective is to assess the extrapolation concept, e.g., ‘similar efficacy’ between children and adults with same treatment
- In general, this assessment can be done by a simple comparison of the efficacy of the adult and paediatric studies
- In our EVR case,
  - Major design differences between adult and paediatric (PIP) studies prevented the simple comparison to be relevant
  - We have used statistical models tailored to the design differences in order to obtain a valid assessment of the extrapolation concept

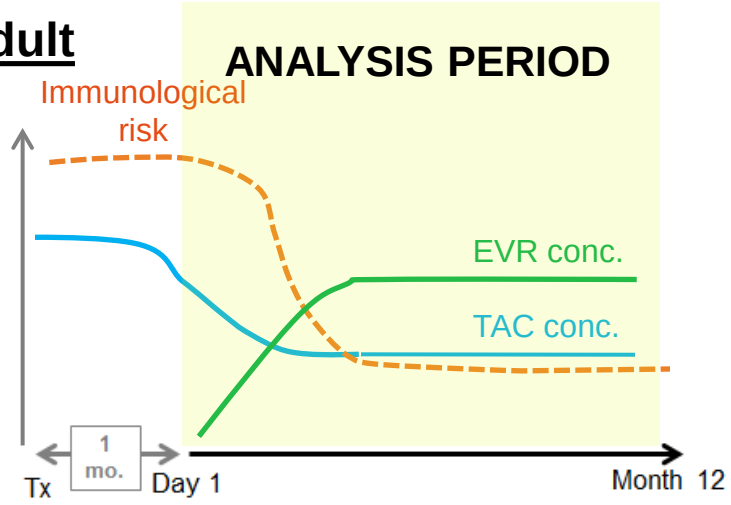
Extrapolation plan in liver Tx

PKPD approach adequate when necessary to adjust for time and exposure differences

Paediatric



Adult



- Goal: compare predicted efficacy between children and **adults similarly exposed at the same time**
- Require modeling of efficacy contribution of time-varying factors
- Done using a PKPD approach

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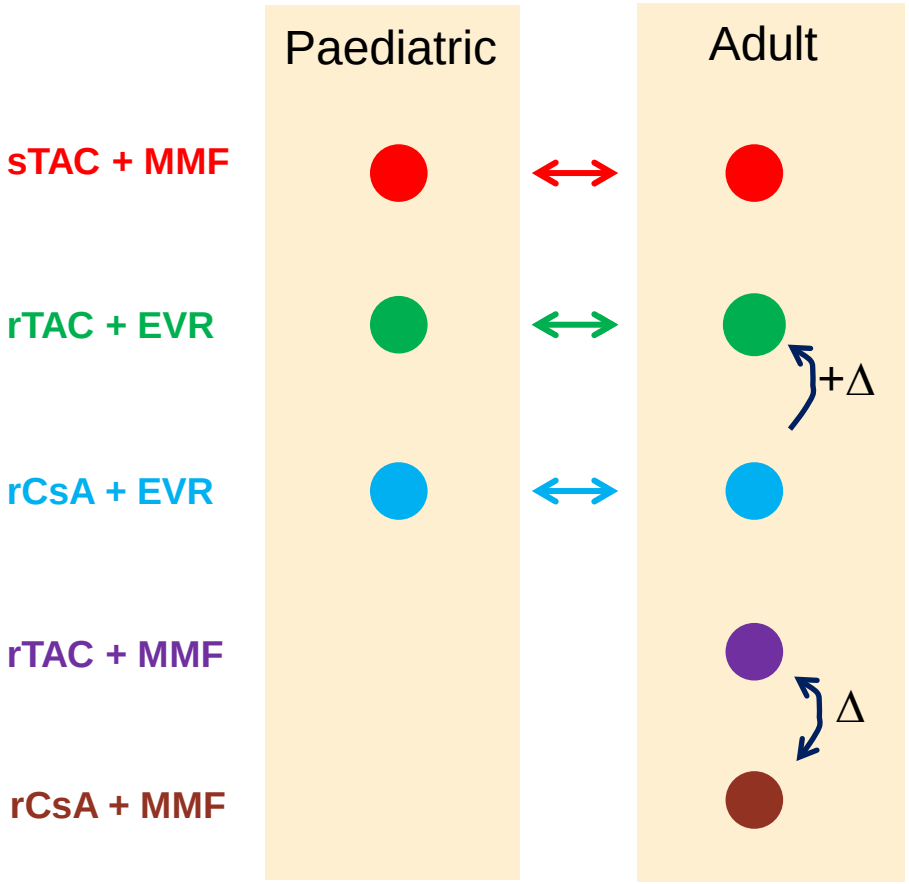
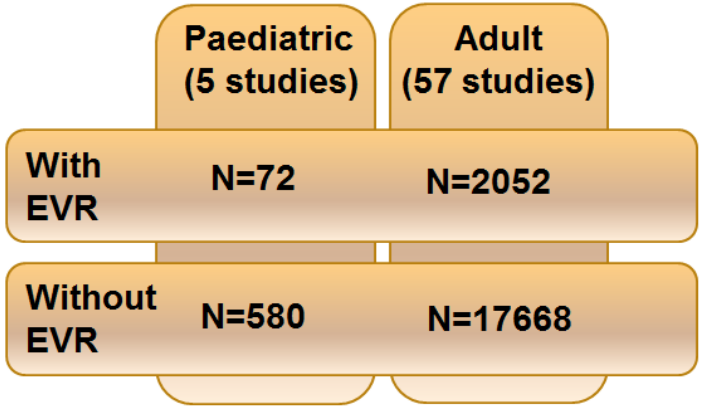
Extrapolation plan in kidney Tx (1/2)

Network meta-analysis adequate when necessary to adjust for components of combination therapies



- Goal: compare predicted efficacy between children and **similarly treated adults**
- Require modeling of efficacy contribution of individual components of quadritherapy regimens
- Done using network meta-analysis
- Data source:



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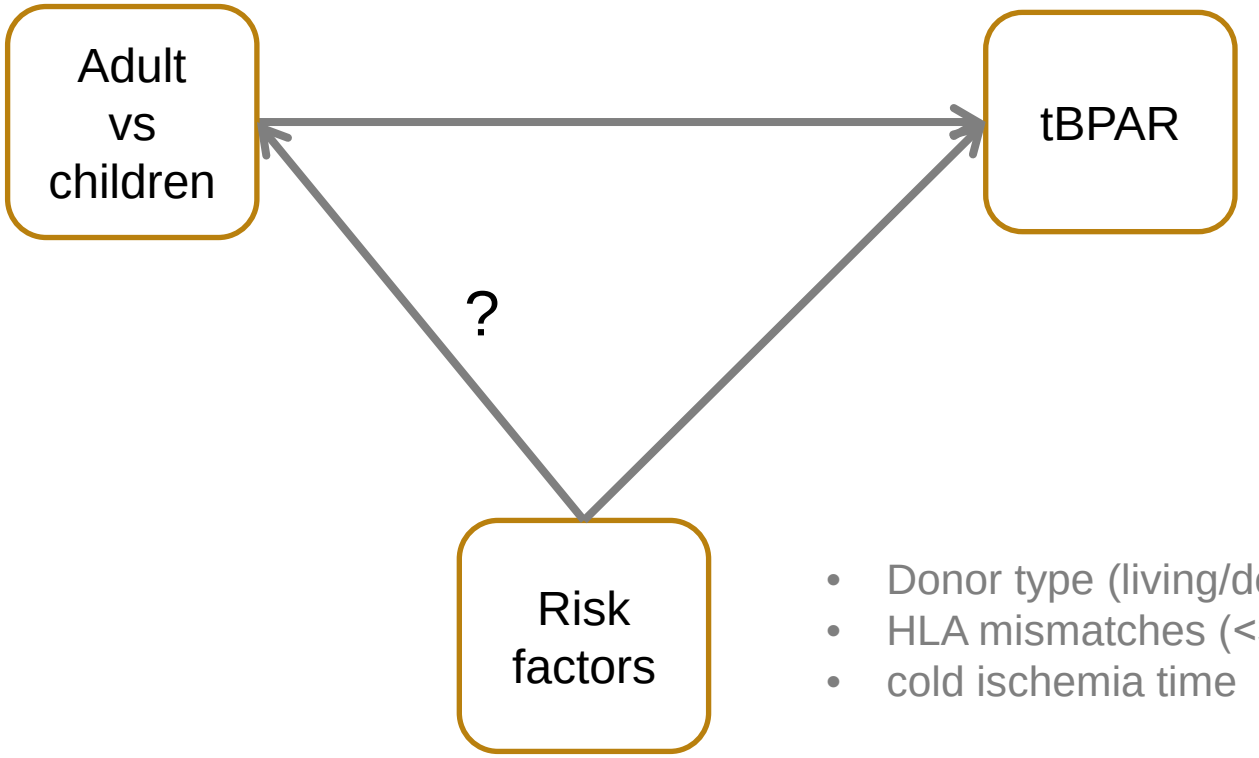
Extrapolation plan in kidney Tx (2/2)

Account for possible unbalance in risk factors

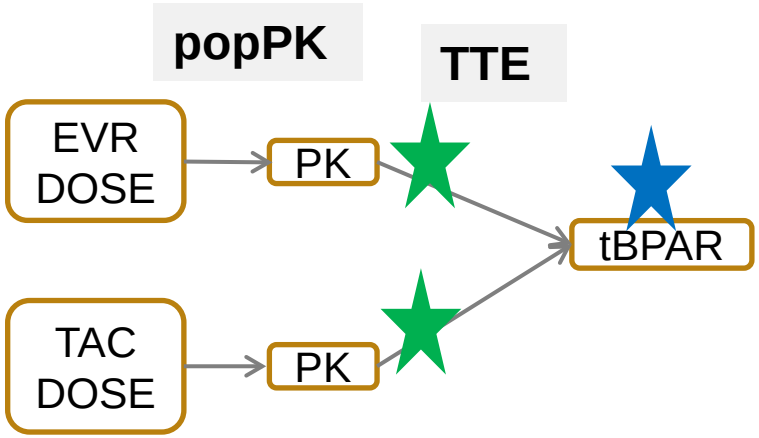


- Donor type (living/deceased)
- HLA mismatches (<3, ≥3)
- cold ischemia time

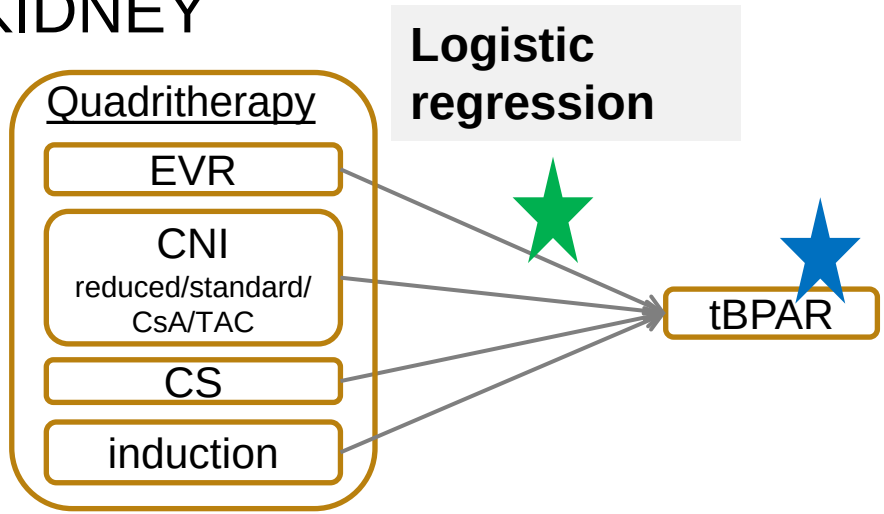
Extrapolation plan

Different, indication-specific methods to address similar objectives

LIVER



KIDNEY



TTE = Time to event model. PopPK = population PK model

- Assessment of population differences
  - Population difference estimation
  - Comparison between observed efficacy in the paediatric study vs predicted efficacy of adults similarly treated/exposed as children (predictive distribution)
- Other analyses:
  - Assessment of population differences on eGFR
  - Safety meta-analysis on a pool of EVR paediatric and adult data

GFR = Glomerular Filtration rate

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Extrapolation plan

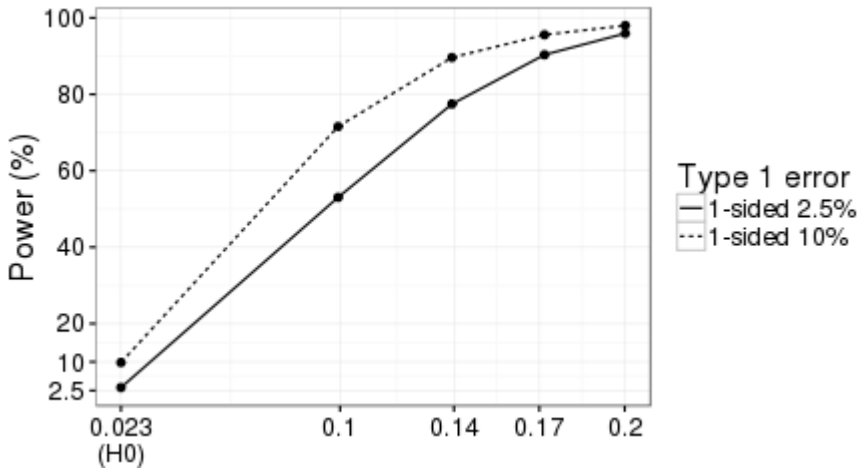
The extrapolation analysis had the power to detect clinically relevant differences in tBPAR rate between children and adults

- A meaningful analysis should provide population difference estimates in tBPAR rate which are sufficiently precise in order to validate the similarity assumption

- No clear criterion defined that must be fulfilled to validate the similarity assumption

- Instead, we have addressed this by showing that the analysis has the power to detect clinically relevant differences

Power to detect a true probability of children experiencing tBPAR - Liver Tx



Probability for adults similarly exposed as children

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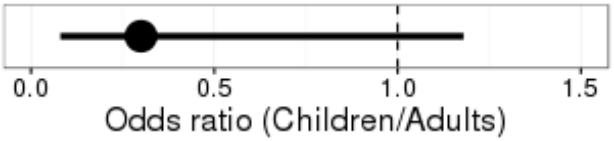
Extrapolation: Analyses results and interpretation

Efficacy results support the adequacy of the regimen

- Paediatric patients had equal or smaller tBPAR rates than adults similarly treated or exposed to EVR
- The results support the conclusion of EVR providing adequate paediatric efficacy

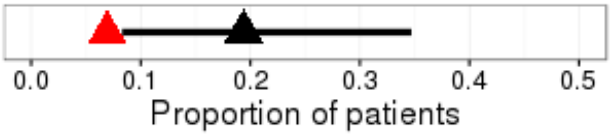
Kidney Tx

Odds ratio (and 95% CI) for EVR-treated patients experiencing tBPAR, between children and adults



Ratios < 1 indicate lower paediatric incidence

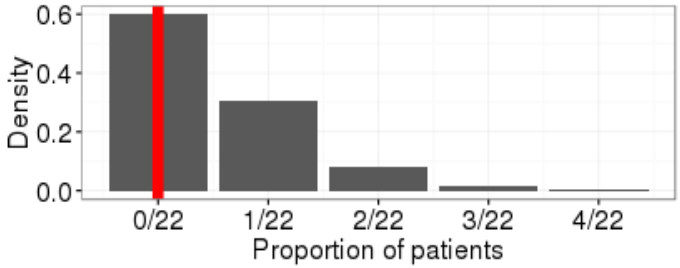
Predictive proportion (and 95% PI) of EVR-treated children experiencing tBPAR, vs observed rate



Red triangle: Observed paediatric rate
Prediction from adult model

Liver Tx

Predictive distribution of EVR-treated children experiencing tBPAR, vs observed rate



Red line: Observed paediatric rate
Prediction from adult model

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Conclusion

- An extrapolation analysis was added to an on-going PIP for the drug everolimus to obtain a rational interpretation of the 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, tailored statistical and pharmacometric methods were used to obtain a valid assessment
  - Although different, both methods addressed similar objectives
- The analyses showed a equal or smaller paediatric rejection rate than those predicted from the adult data suggesting efficacious treatment in children
- These interim analysis and extrapolation analysis results were submitted, and paediatric information was included in the label
- More information will be generated at completion of the PIP studies

For discussion ....

Further guidance needed on the validation criterion

- In order to demonstrate similar efficacy, a specific criterion is required
  - A natural criterion could be equivalence-like
    - boundaries based on the width of the therapeutic windows, and/or
    - relaxed level of confidence based on skepticism regarding the concept
  - It would also be used for proper sample size justification
- Guidelines/principles on how to define this criterion would facilitate extrapolation

Acknowledgements

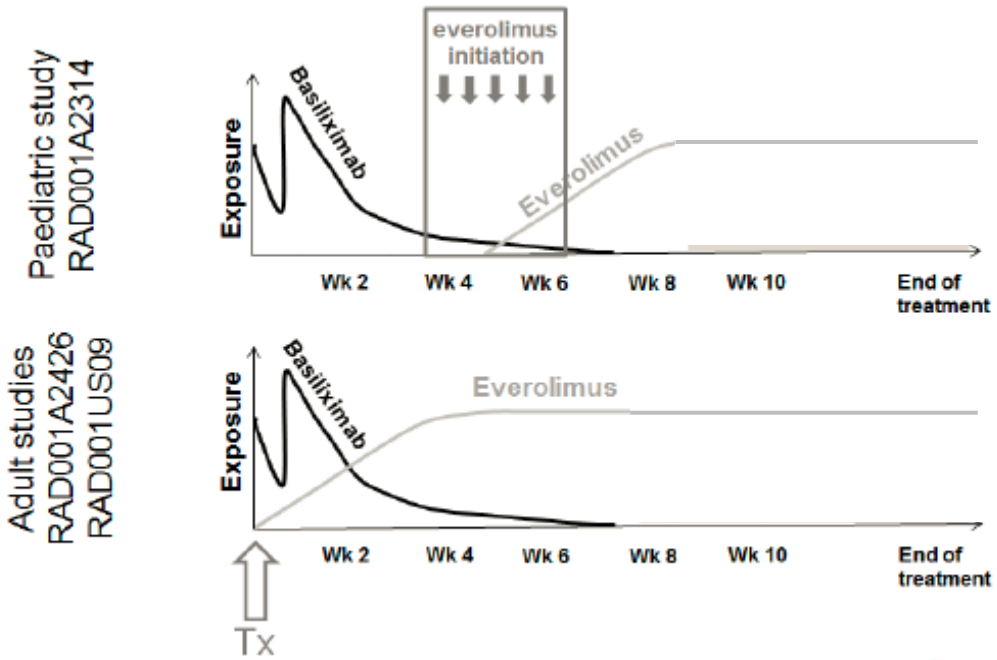
- S Ballerstedt, B Bornkamp, F Bretz, O David, M Fink, M Looby, J Ng, O Sander, H Schmidli, JL Steimer (Novartis)

Backup Slides

Use of PKPD extrapolation in kidney Tx

Design differences requires characterizing the relative efficacy contribution of many risk factors, expectedly difficult given their correlation and absence of putative placebo arm

Time course of induction therapy and everolimus concentration, in adult and paediatric studies



Low EVR associated with

	Adult study	Paediatric study
Induction	HIGH	LOW
CS	HIGH	LOW
TAC	HIGH	MODERATE
Baseline risk	HIGH	LOW

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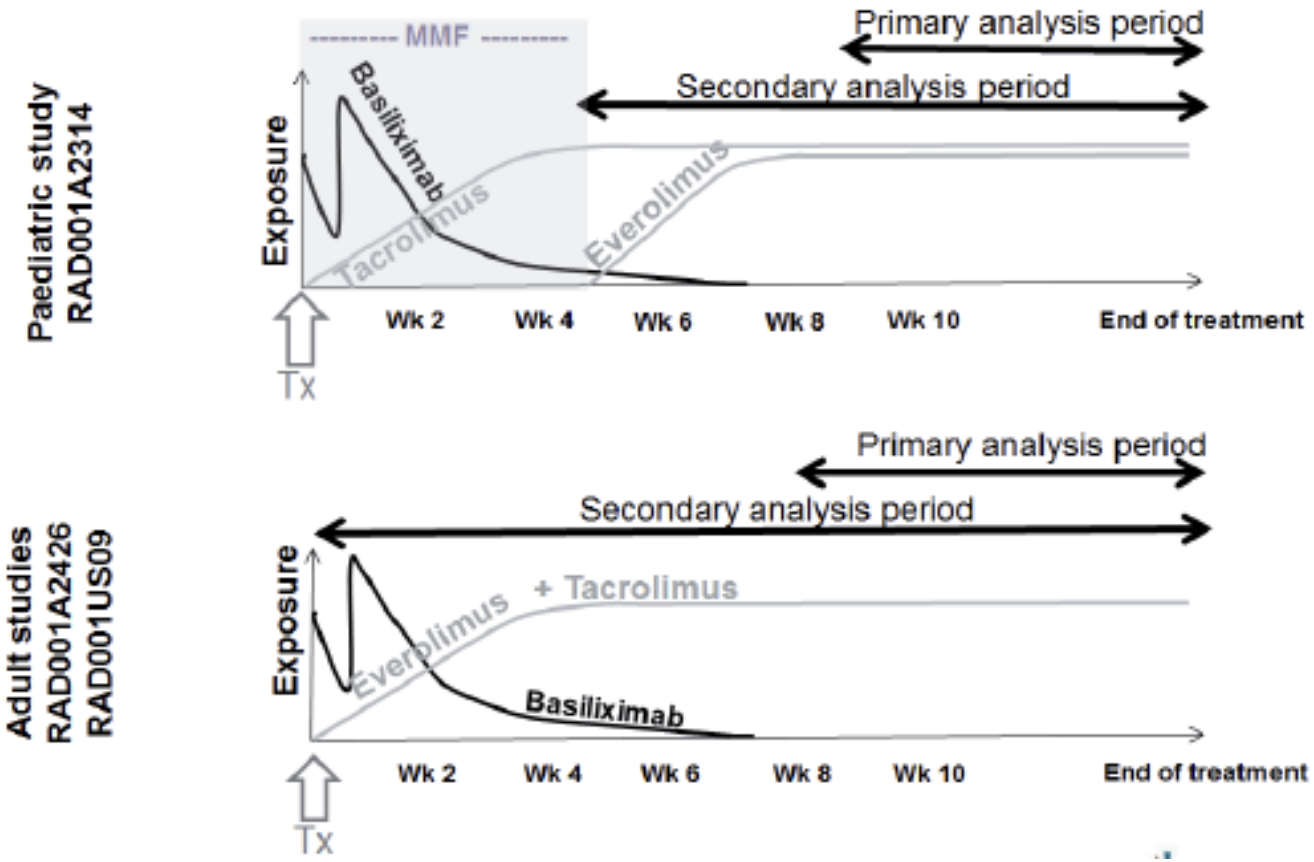
Use of PKPD extrapolation in kidney Tx

Difficulty → low likelihood of success on the secondary analysis period.
Use only steady state data for the primary analysis, but very low tBPAR incidence



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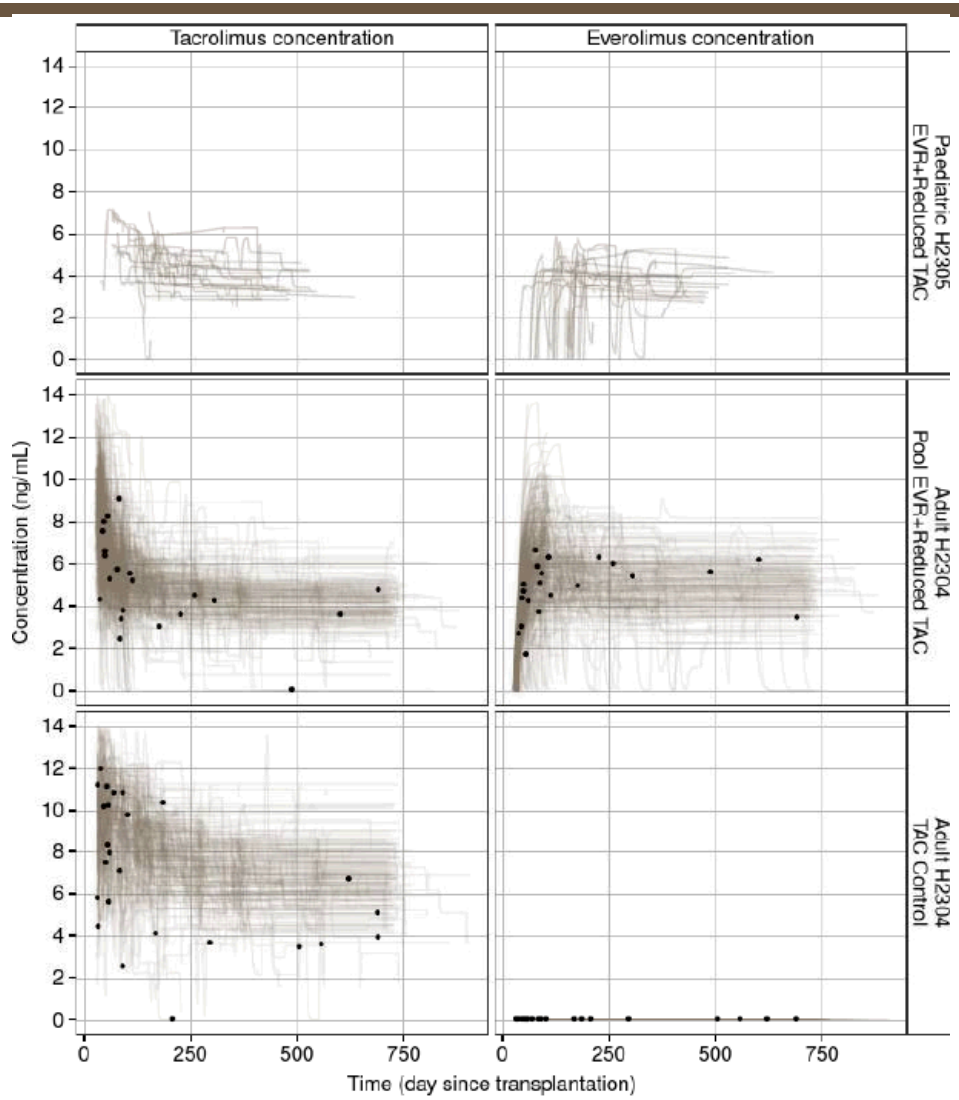
Liver adult and paediatric results

Larger incidence in the 2-3 months following Tx, regardless of the higher TAC concentration



Predicted concentration

Predicted concentration on day before event

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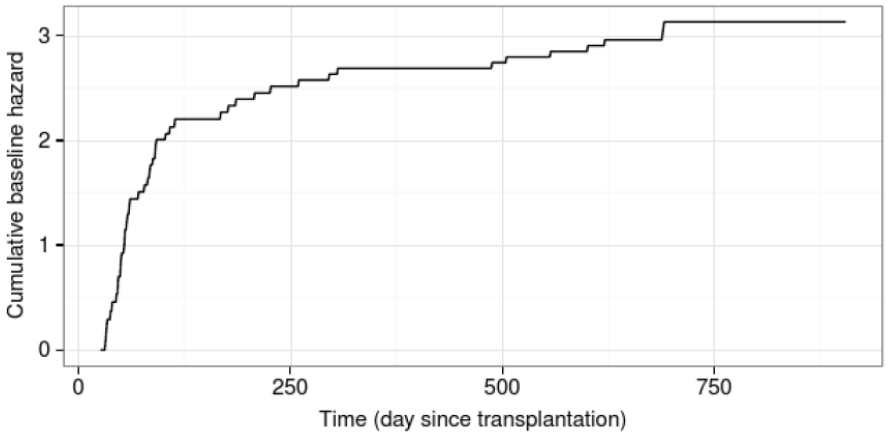
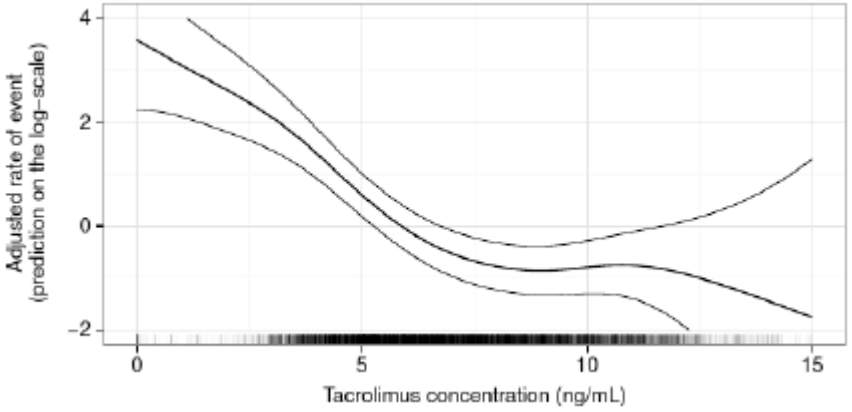
Liver adult results

Baseline hazard higher after Tx, strong effect of TAC concentration but only treatment effect of EVR (not shown)

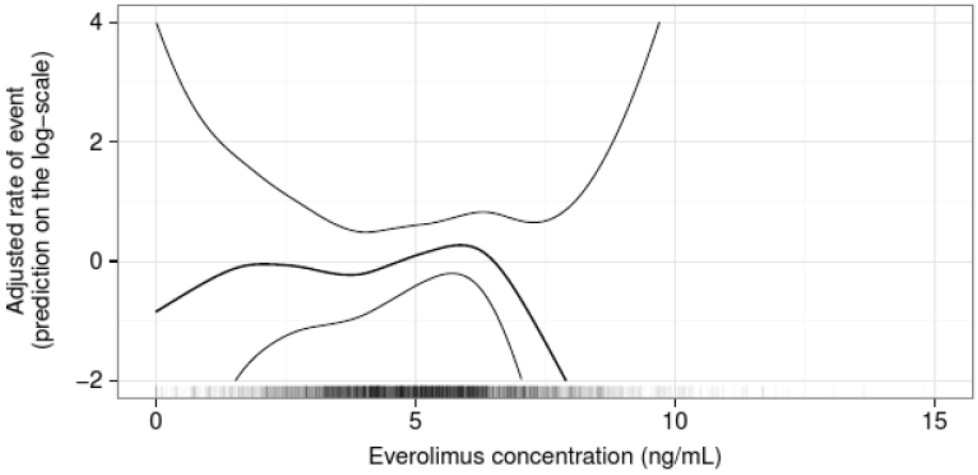
Cumulative baseline hazard



Relationship between TAC conc. and adjusted rate of event



Relationship between EVR conc. and adjusted rate of event



(Grambsch 1995)

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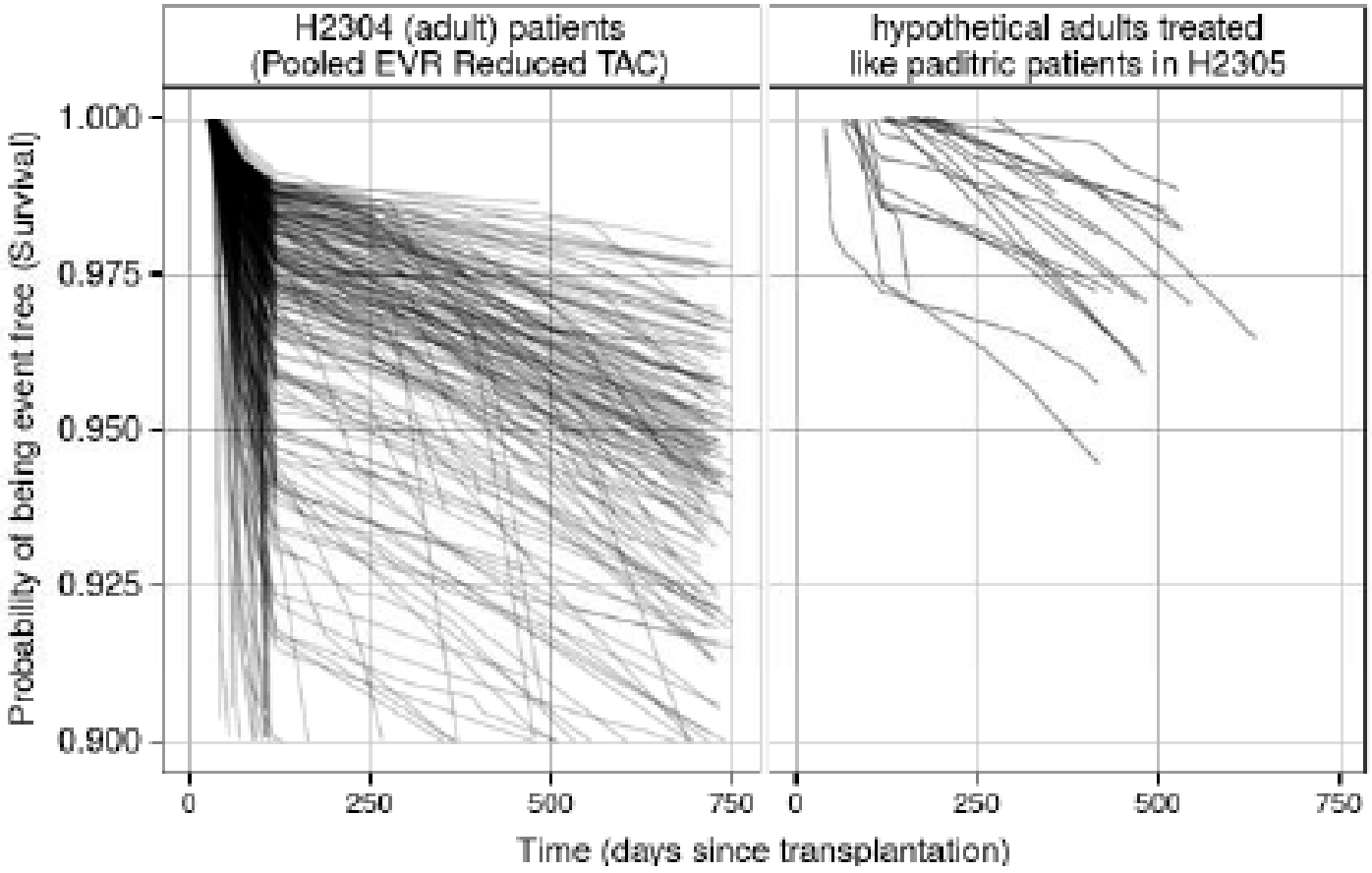
Liver adult results

Mostly starting after the high risk period, adults treated as paediatric patients have a slowly decreasing survival



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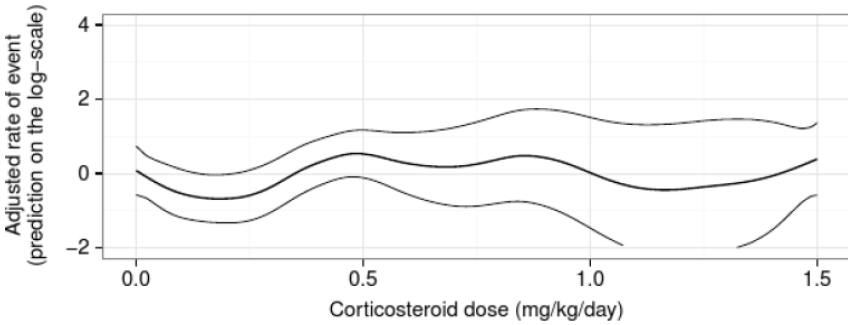
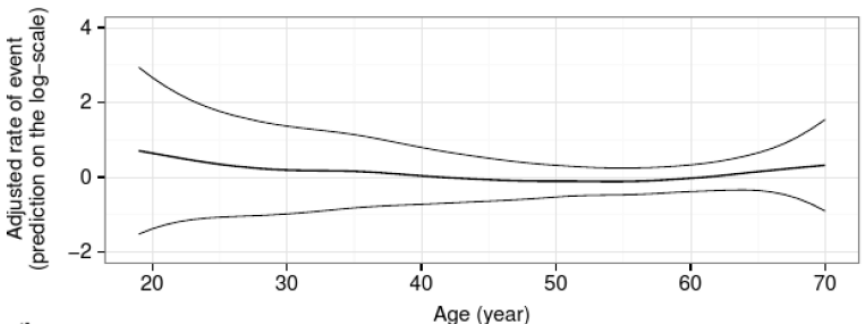
Liver adult results

No effect of CS or age on tBPAR event rate

Effect of CS dose on event



Effect of age on event



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