

Using a model-based approach to address FDA's midcycle review concerns by demonstrating the contribution of everolimus to the efficacy of its combination with low exposure tacrolimus in liver transplantation

Thomas Dumortier*, Michael Looby*, Guido Junge**, Steffen Witte***, Olivier Luttringer*

*Advanced Quantitative Sciences, ** Pharma, *** Integrated Information Sciences, Statistics
Novartis Pharma AG, Basel, Switzerland

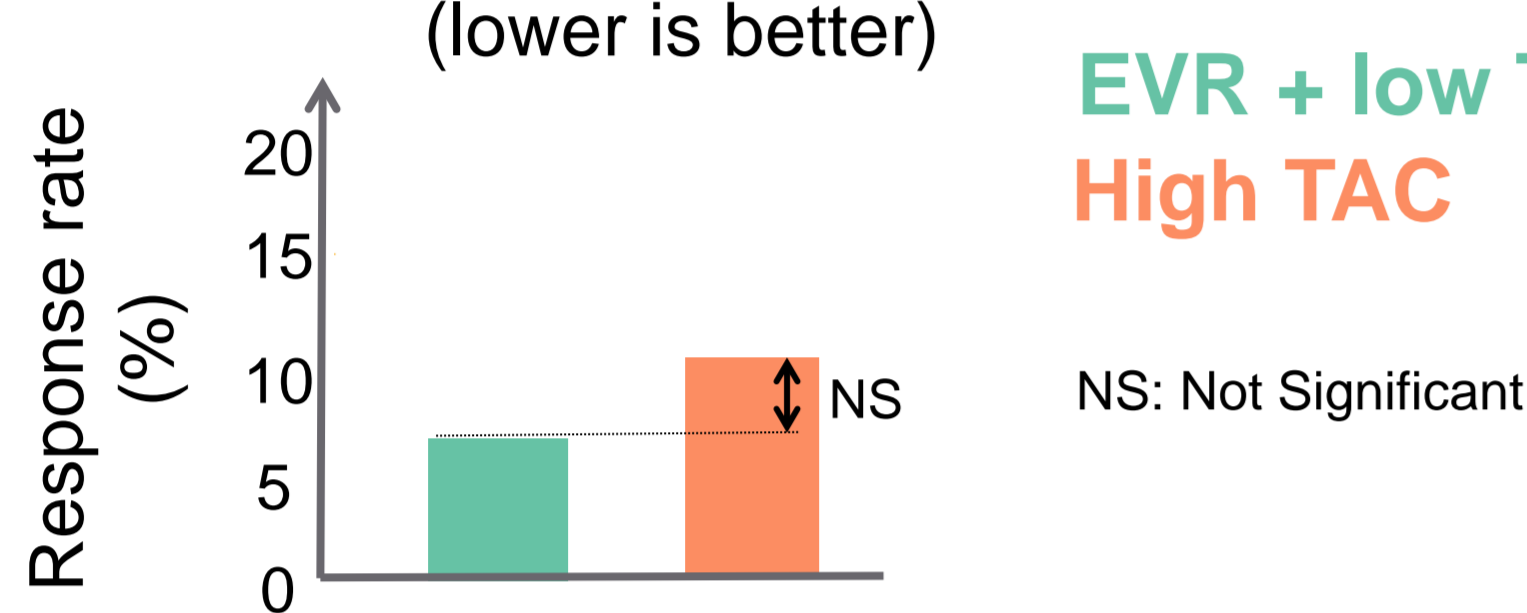


Background

A Phase 3 registration study in liver transplantation showed a favorable benefit-risk profile for everolimus in combination with tacrolimus at low exposure ('EVR + low TAC') compared to the standard of care (TAC at therapeutic exposure, 'high TAC') [1]. Trial outcomes:

- Safety: significantly better renal function
- Efficacy: numerically (but not significantly) lower incidence of composite efficacy events (Figure 1).

Figure 1: Composite efficacy events rate at Month 12 (lower is better)

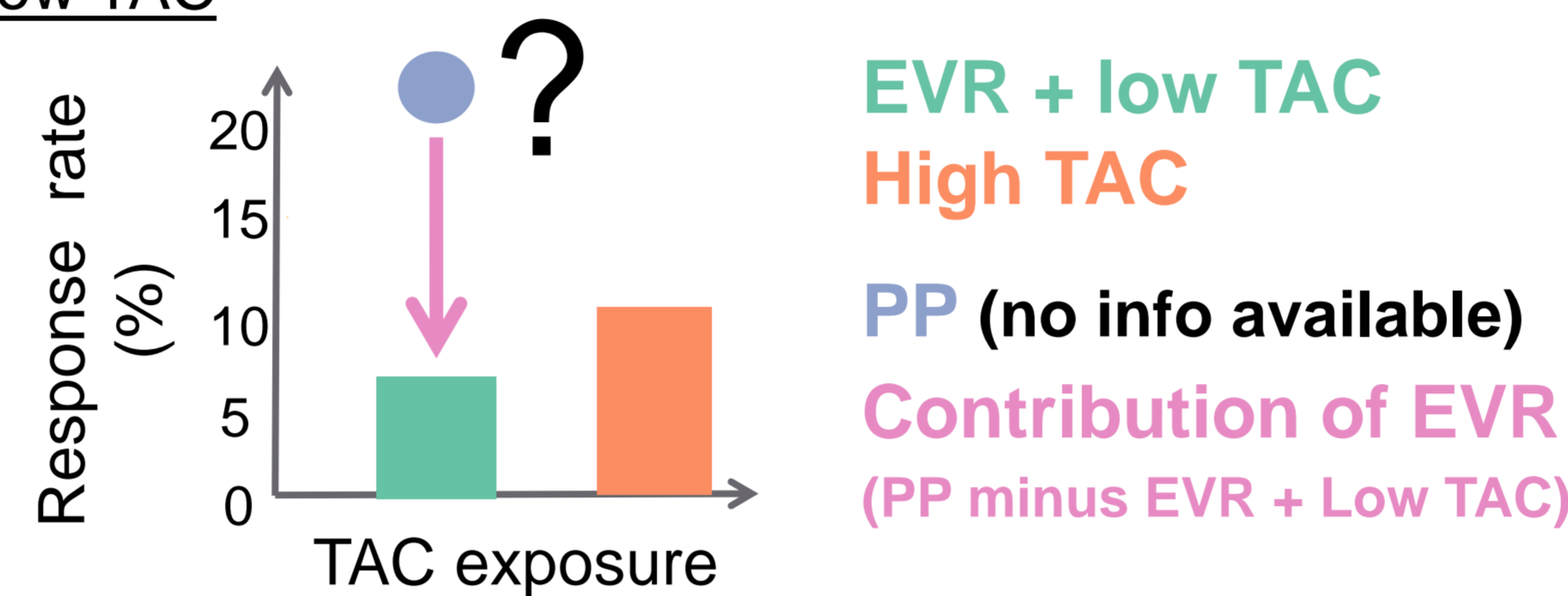


FDA's Challenge

"The submitted data does not include sufficient information to assess the significance of the contribution of EVR to the efficacy of EVR + low TAC"

Note: The absence of information about the efficacy of 'Putative Placebo' ('PP': TAC alone, at same (low) exposure as in EVR + low TAC), in the study or in previous studies, precludes from an easy assessment of the contribution of EVR.

Figure 2: Contribution of EVR to the efficacy of EVR + low TAC



Objectives

To assess the contribution of EVR to the efficacy of EVR + low TAC in absence of information regarding the efficacy of PP.

Conclusion

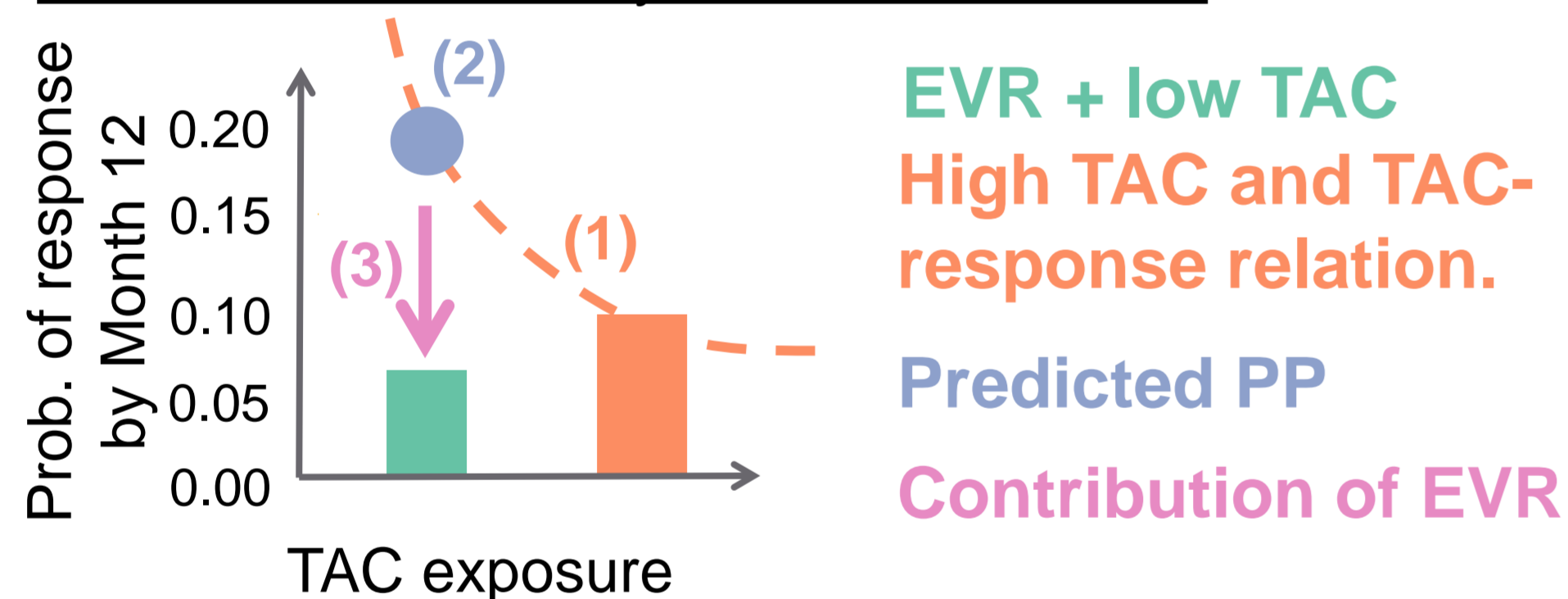
- The contribution of EVR to the efficacy of EVR + low TAC could be assessed by means of model-based analyses
- The significance of the contribution was demonstrated
- EVR + low TAC was approved by the FDA.

Methods

The contribution of EVR to the efficacy of EVR + low TAC can be estimated from the relationship between TAC exposure and efficacy response (composite efficacy endpoint), as follows:

- (1) Assess the TAC exposure-response relationship
- (2) Predict the efficacy of PP from this relationship
- (3) Estimate the contribution of EVR.

Figure 3: Sequential estimation of the contribution of EVR to the efficacy of EVR + low TAC



Systematic/frequent changes in TAC dose (>10 changes on average by subject) require to use:

- A time-to-event (response) analysis allowing the hazard of response to vary as a function of the time-varying TAC exposure

The hazard of response is modeled by means of a Cox model:

$$h(t) = h_0(t) \cdot e^{\beta \times TAC(t) + \delta \times 1_{EVR}}$$

Where $h_0(t)$ and $TAC(t)$ are time-varying baseline hazard and TAC exposure, and 1_{EVR} is a flag indicating treatment with EVR (yes/no: 1/0)

The probability of response by Month 12 (Y-axis of Figures 3 and 5) is derived as:

$$P = 1 - e^{-\int_0^{12} h(s) ds}$$

- A population PK model to get an accurate prediction of the individual time-varying TAC exposure

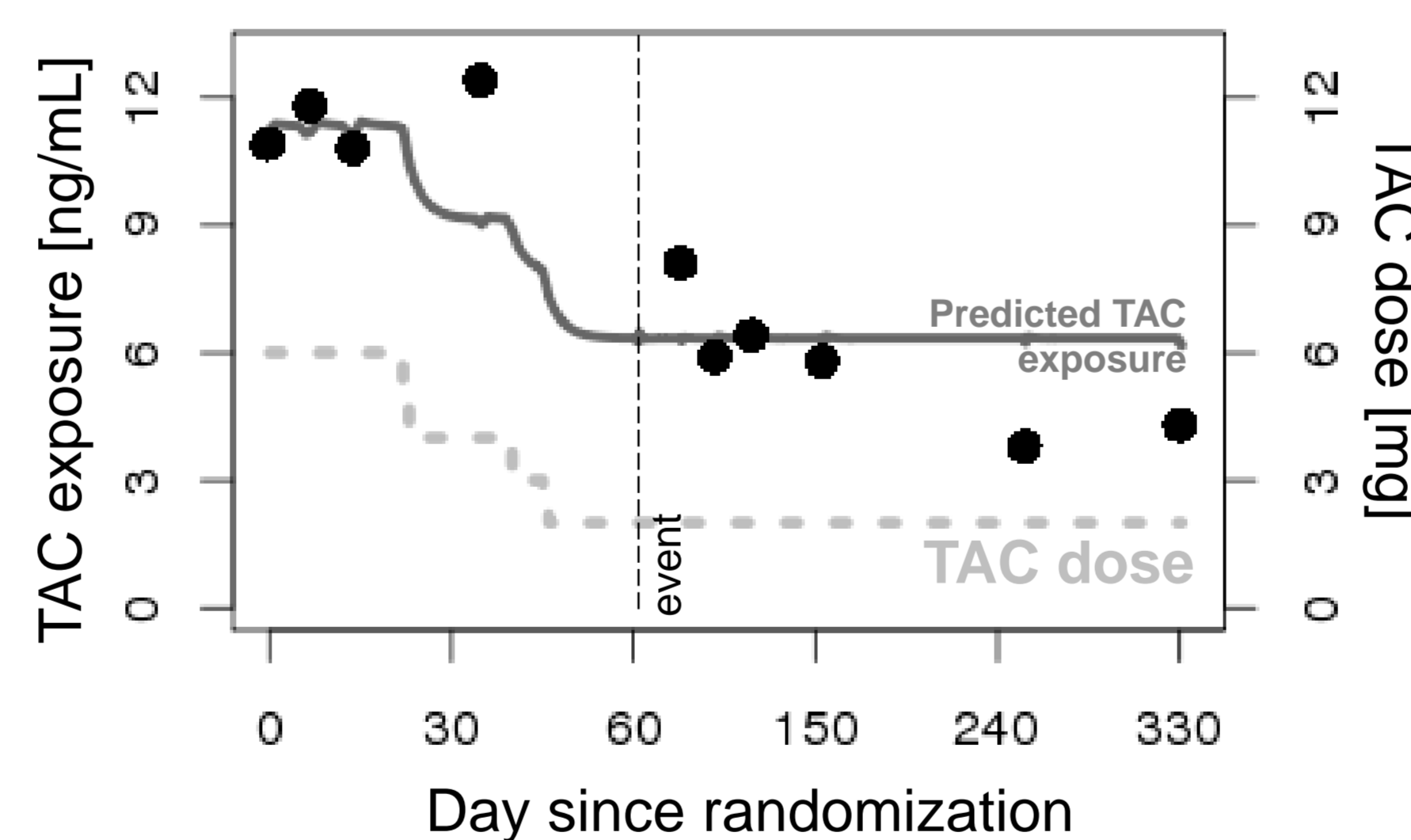
The PK model structure and the absorption rate constant parameters, which can't be estimated from the collected through PK samples, are obtained from the literature [2]; the rest of the parameters are estimated from the data.

Rationale for model-based prediction of TAC exposure

The model-based prediction provides an accurate estimate of time-varying TAC exposure by combining the sparse trough concentration data (1-12 samples by subject) with the TAC dosing history.

As an example (one subject of the study), Figure 4 shows that the predicted (dark grey curve) but not the observed (black dots) TAC exposure allows an accurate prediction of the TAC exposure on the day of response event (vertical dashed black line, on Day 64) as reflecting the stepwise decrease in dose (light grey dotted step curve) which starts on Day 23.

Figure 4: Observed + predicted TAC exposure and dose history for one subject of the study



Results

There is an inverse relationship between predicted TAC exposure and response, as seen with (green curve) and without (brown curve) treatment with EVR (Figure 5). This relationship is statistically significant ($p < 0.001$)

The probability of response in PP is estimated to be 27% (grey dot)

The contribution of EVR to the efficacy of EVR + low TAC is represented by the pink arrow. Expressed on the hazard ratio scale (without/with EVR), the contribution of EVR is statistically significant ($p < 0.001$; figure 6).

Figure 5: TAC exposure-response relationships + putative placebo + Contribution of EVR

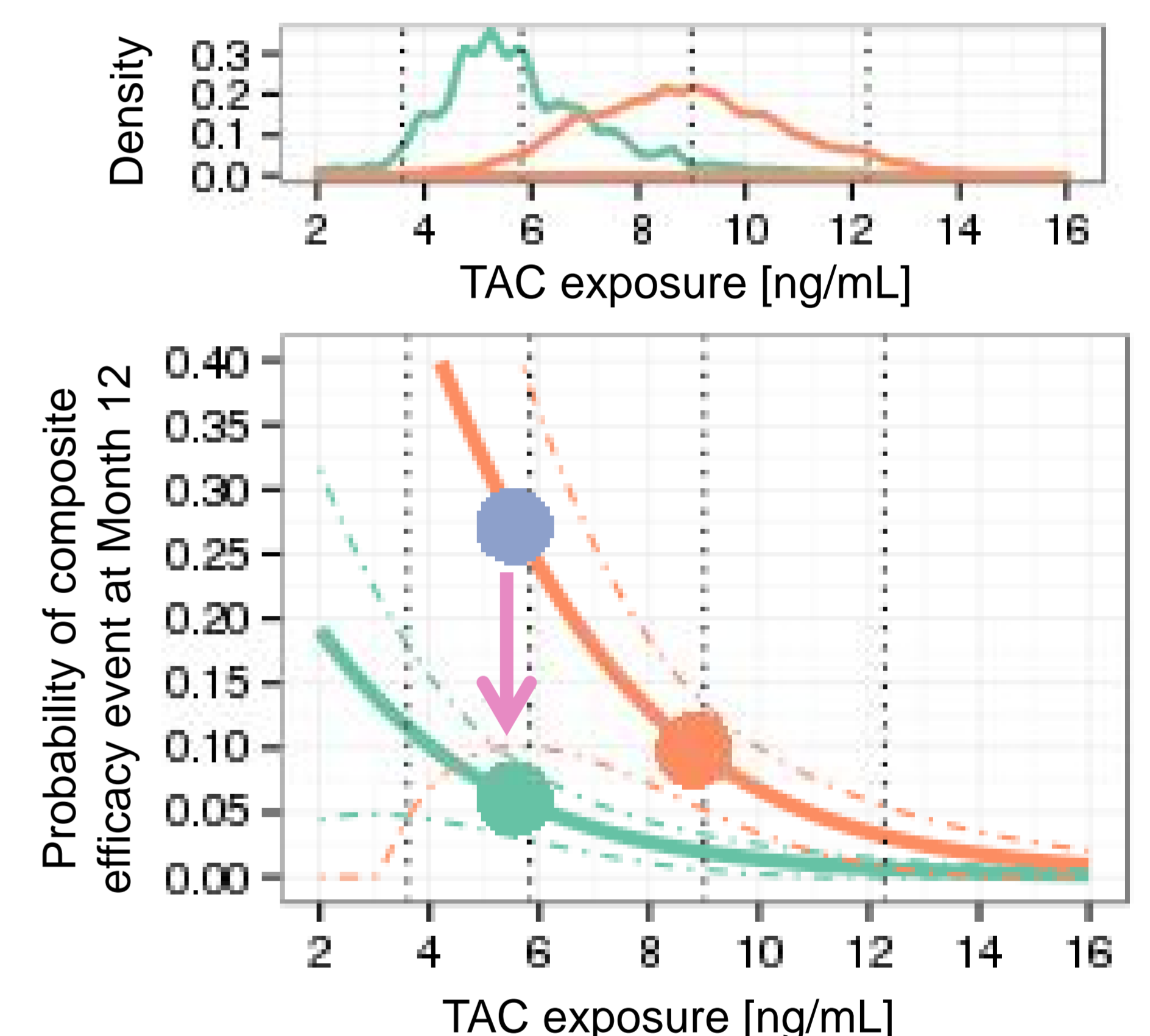
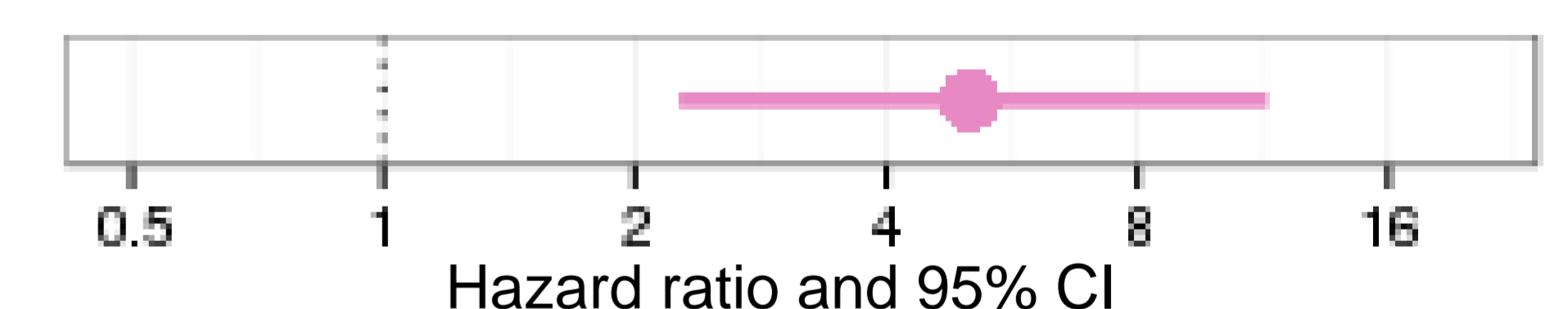


Figure 6: Hazard ratio (without/with EVR) for the Probability of composite efficacy event at Month 12



Discussion

- Although TAC is approved in liver transplantation, its exposure-efficacy relationship has not been fully characterized, nor is known the efficacy of low TAC alone.
- Consequently, it is not possible to determine the contribution of EVR to the efficacy of its combination with low TAC using standard methods such as non-inferiority [3].
- By combining the whole dose and concentration history in a model-based approach, it is possible to account for the frequent changes in therapy and to provide an accurate estimate of exposure which serves as precise basis for the exposure-response analysis.
- Using this methodology, that TAC exposure-response and then the contribution of EVR to the efficacy of EVR + low TAC was successfully characterized.

References: [1] De Simone: Everolimus With Reduced Tacrolimus Improves Renal Function in De Novo Liver Transplant Recipients: A Randomized Controlled Trial. American Journal of Transplantation 2012; 12: 3008–3020. [2] Bruce, 2004: Population pharmacokinetics of tacrolimus in liver transplant patients, available from URL: <http://www.page-meeting.org/page/page95/abstract/abstract.html> (accessed 1 May 2012). [3]: FDA/CDER/CBER. Guidance for Industry: Non-inferiority clinical trials (Draft) FDA/CDER/CBER, March 2010. Available at: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM202140.pdf> (accessed 1 July 2011).

Acknowledgments: Clarisse Chavanne, Patrick Lupien, Guenter Heimann, Amy Racine