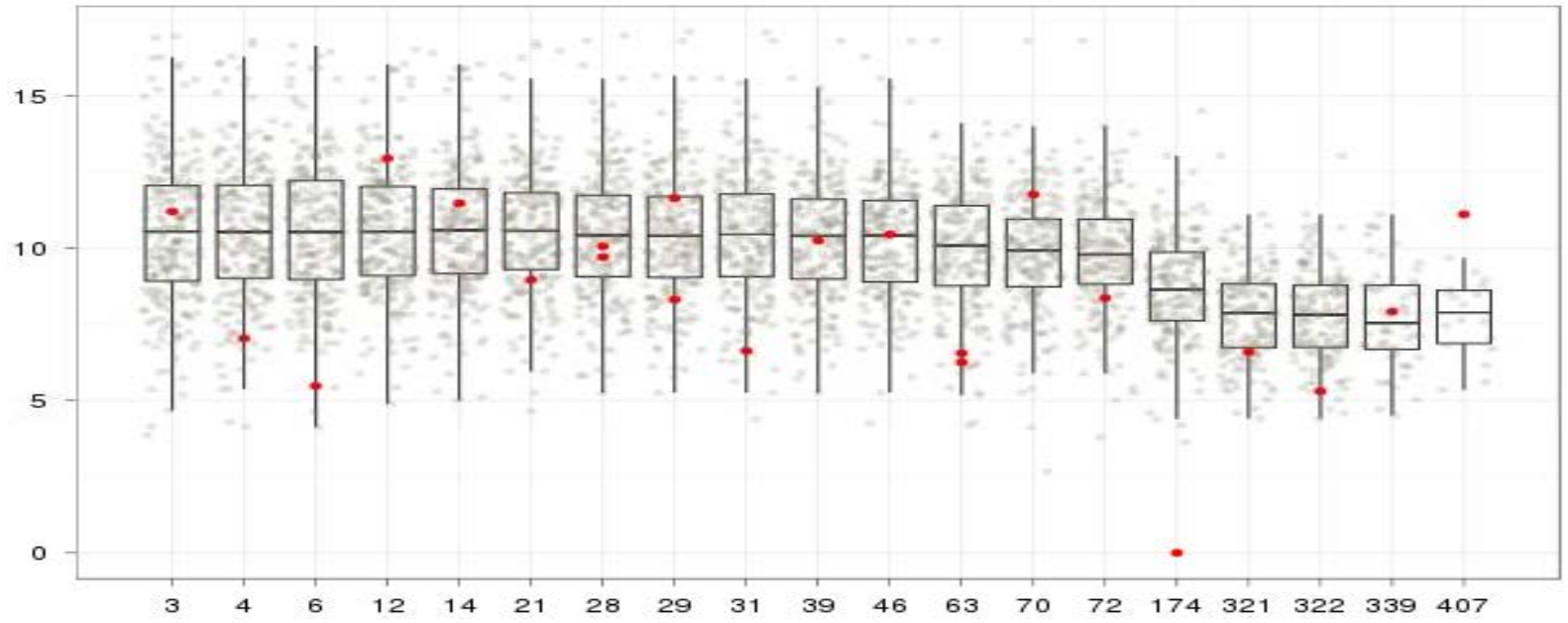


Use of dose-exposure-response model in immunology/transplantation
General considerations + case study

T Dumortier, M Looby, Pharmacometrics, Novartis
Yaning Wang, Pharmacometrics, FDA
London, 5 December 2014

NOVARTIS

Challenges in dose-finding in immunology

- The most active area of pharmaceutical research
- Some challenges
  - Many novel long acting biologics
    - Need to optimize for both dose and regimen
  - Benefit-risk sometimes driven by primary pharmacology with narrow therapeutic window
    - May require dose individualization
  - Multiple targets on overlapping pathways in related but different diseases
    - Suitable for combination therapy. How do we optimize both drugs?
    - Challenges in accounting for impact of comorbidities on benefit-risk
    - Response may be considerably delayed. How do we individualize?
  - Sometimes sub-optimal treatment is not an option
    - May lack placebo control or may not be able to explore whole dose response relationship
- Traditional approaches cannot adequately support dose finding in many cases
  - Model based methods, particularly pharmacometrics based approaches can and do fill the gap
  - However, with the industry there is the perception that such methods are not accepted by Regulatory Authorities
  - Furthermore, lack of experience in the implementation of more complex methods further inhibit adoption
- The case study presents an example of how PMX based methods can bridge the gap

Case study

- FDA's requirement for a combination therapy including a novel agent: To show that the novel agent has an efficacy contribution to the new combination
- This is impossible when there is no 'placebo' efficacy information
- This situation occurred for a sNDA for a combination regimen including everolimus (EVR) in liver transplantation
- The challenge was addressed using a pharmacometric approach combining population PK and time-to-event analyses
- Those analyses proved the efficacy contribution of EVR; the combination regimen was subsequently approved
- This was enable by the use of a rigorous and adequate methodology

sNDA=supplemental New Drug Application
FDA=Food and Drug Administration

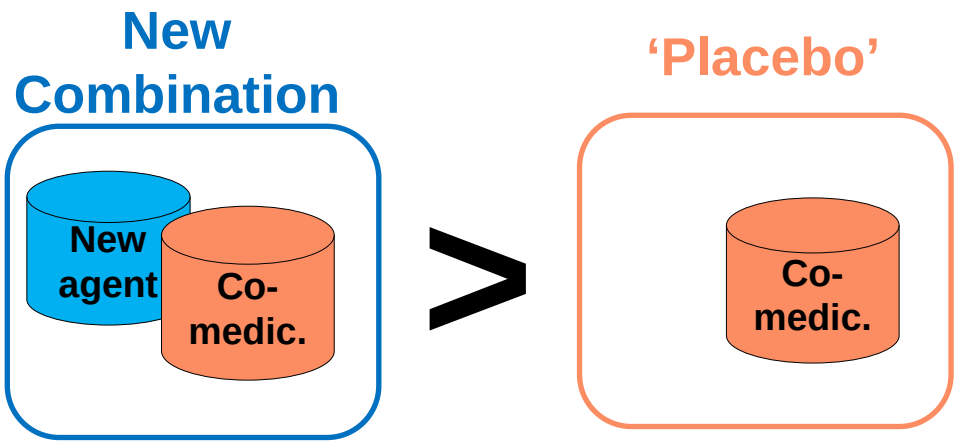
Background

Efficacy requirement for a novel agent in combination

- Regulatory requirement for a combination therapy which includes a novel agent:

  To show that the novel agent has a contribution to the efficacy of the new combination*

- How? by comparing the efficacy of the combination to that of ‘placebo’ (= the combination MINUS the novel agent)



* FDA/CDER/CBER. Food and Drug Administration Center for Drug Evaluation and Research. Guidance for Industry: Codevelopment of Two or More Unmarketed Investigational Drugs for Use in Combination, December 2010.

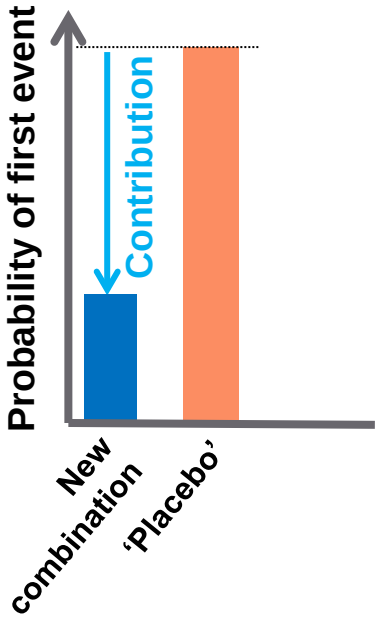
NOVARTIS

Background

Efficacy contribution can be proved via direct/indirect comparison

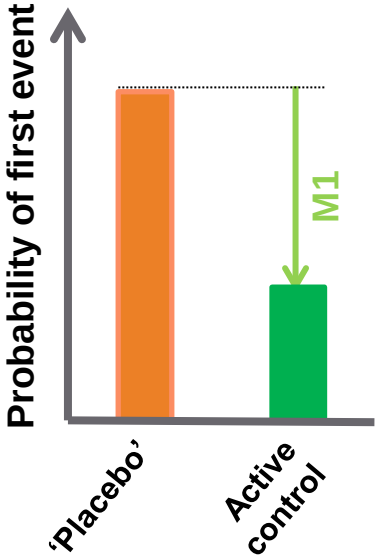
DIRECT

‘Placebo’ controlled study

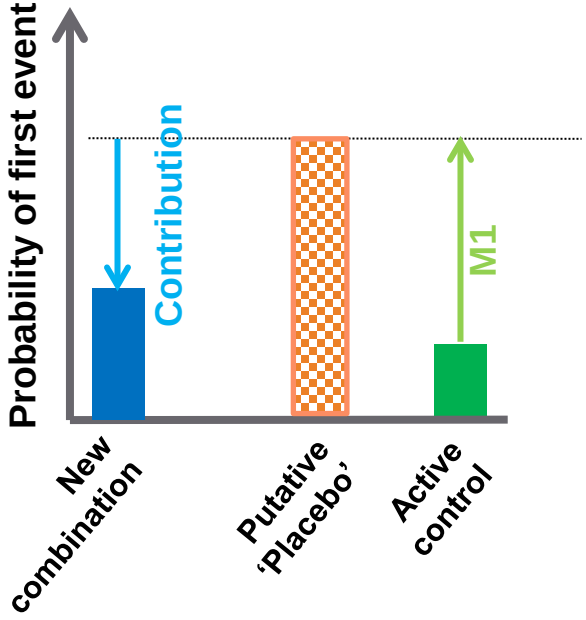


INDIRECT

Historical data



Non inferiority (NI) study



*M1 is “what is thought to be the whole effect of the active control relative to placebo in the NI study” **

* FDA/CDER/CBER. Food and Drug Administration Center for Drug Evaluation and Research. Guidance for Industry: Non-inferiority clinical trials (Draft).

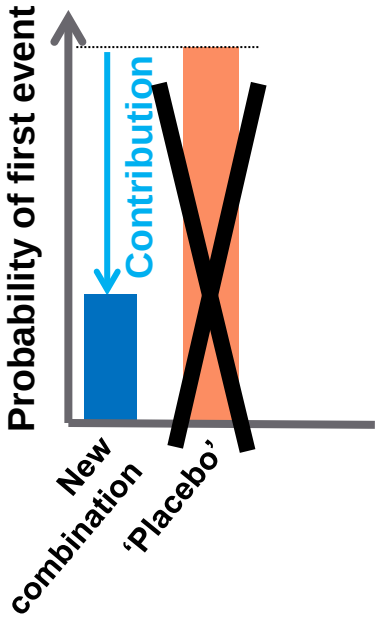
NOVARTIS

Challenge

Issue when no available efficacy information for 'placebo'

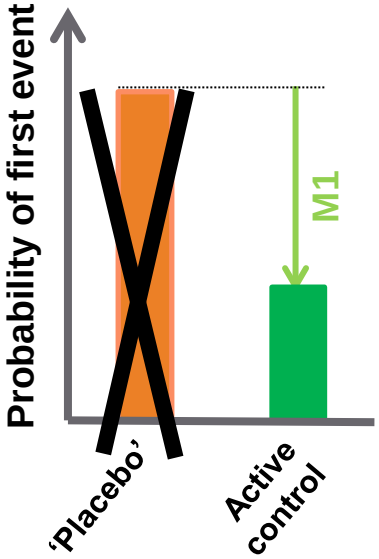
DIRECT

'Placebo' controlled study

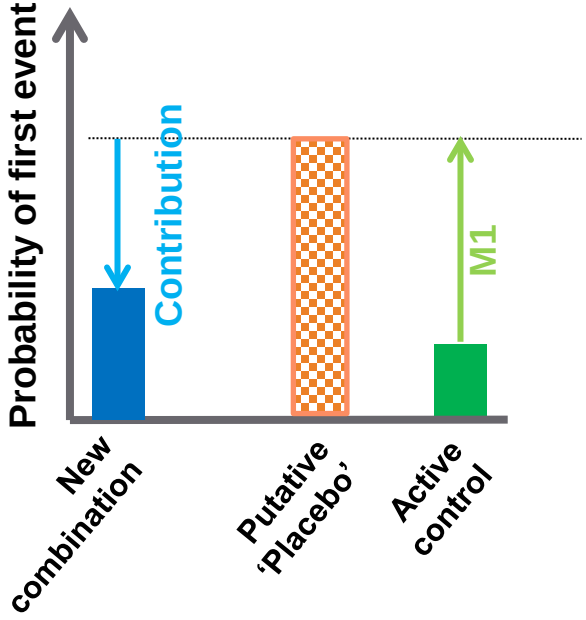


INDIRECT

Historical data



Non inferiority (NI) study



*M1 is "what is thought to be the whole effect of the active control relative to placebo in the NI study" **

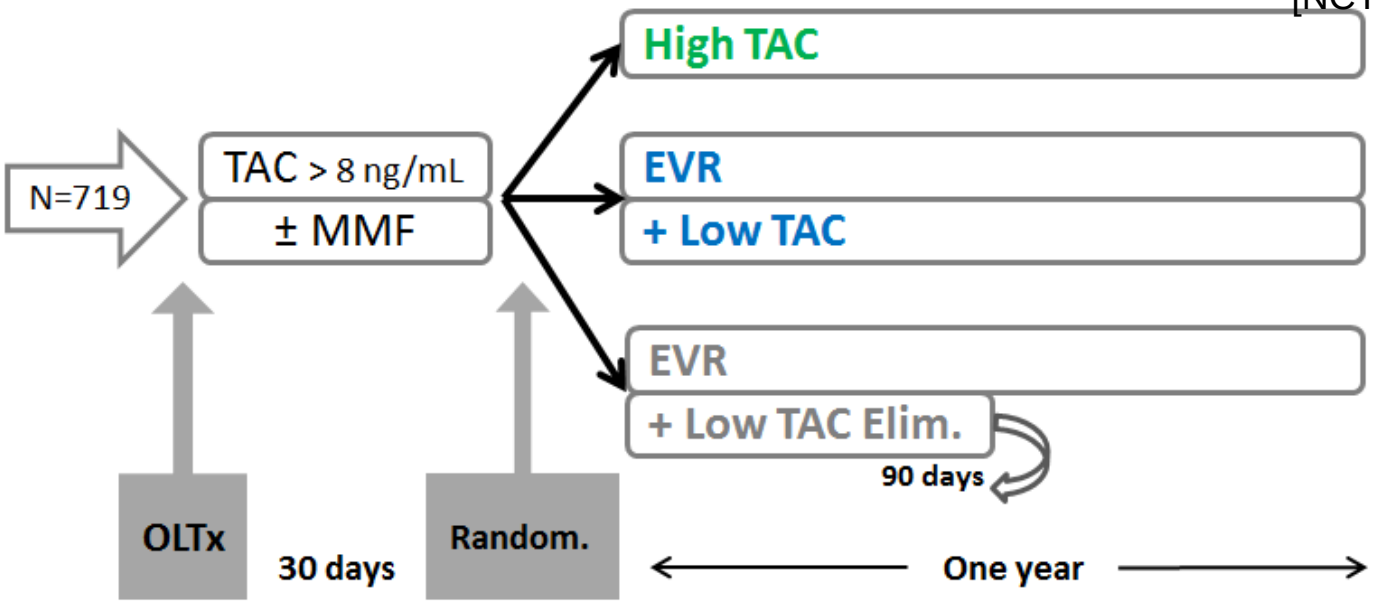
* FDA/CDER/CBER. Food and Drug Administration Center for Drug Evaluation and Research. Guidance for Industry: Non-inferiority clinical trials (Draft).

NOVARTIS

Case study: Liver transplantation - Phase III

Non-inferiority study with 2 EVR based combinations and active control

[NCT00622869]



- No efficacy information for Low TAC ('placebo')
  - Non-inferiority margin decided based on clinical consideration
- Therapeutic drug monitoring: **Low TAC: 3-5 ng/mL**; **High TAC: 8-12 ng/mL till Month 3 then 6-10 ng/mL**; EVR: 3-8 ng/mL

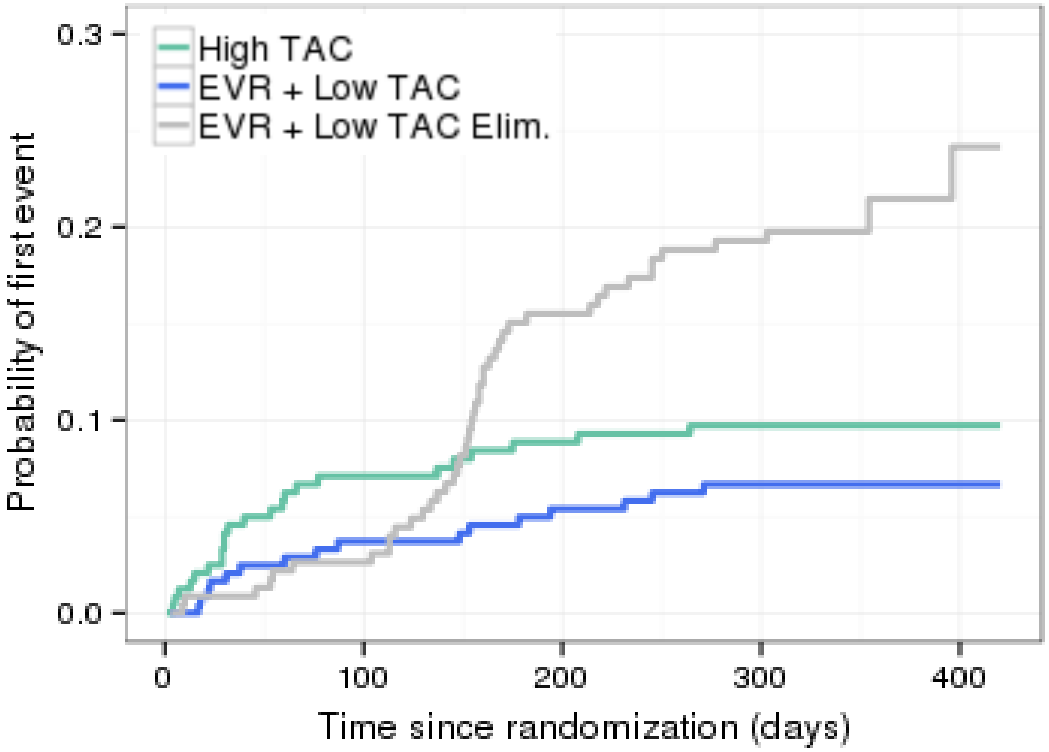
NOVARTIS

Case study: Efficacy results

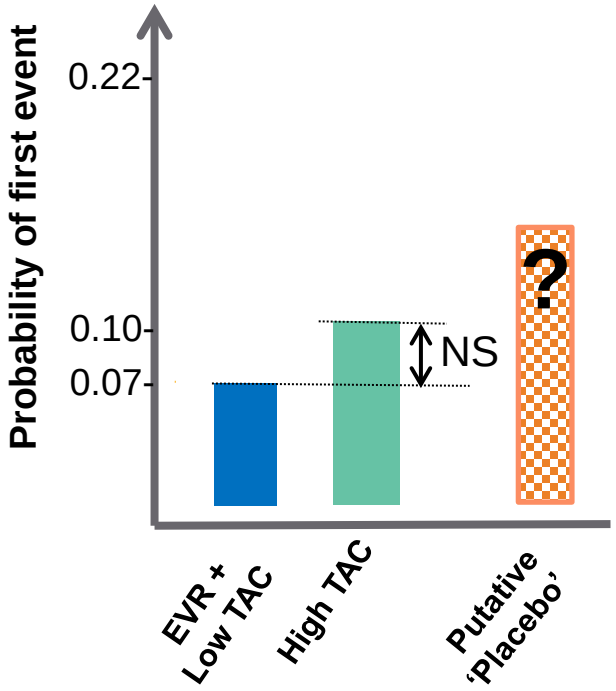
Numerical superiority of EVR + Low TAC. But no information about efficacy contribution of EVR

Probability of first rejection event

Kaplan-Meier estimates



Month 12 results



NS = non-significant

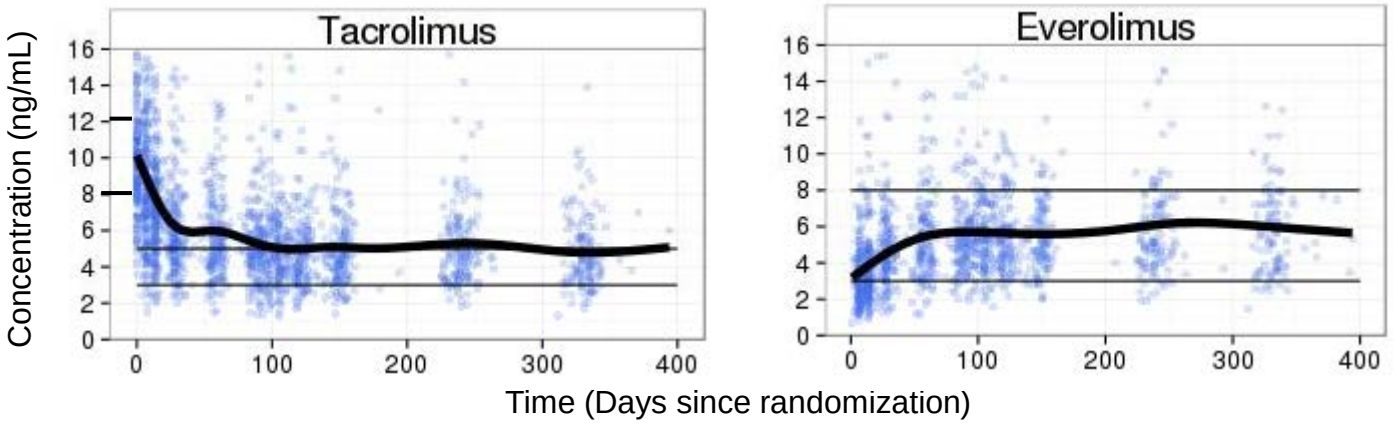
NOVARTIS

What is ‘placebo’ in a TDM context?

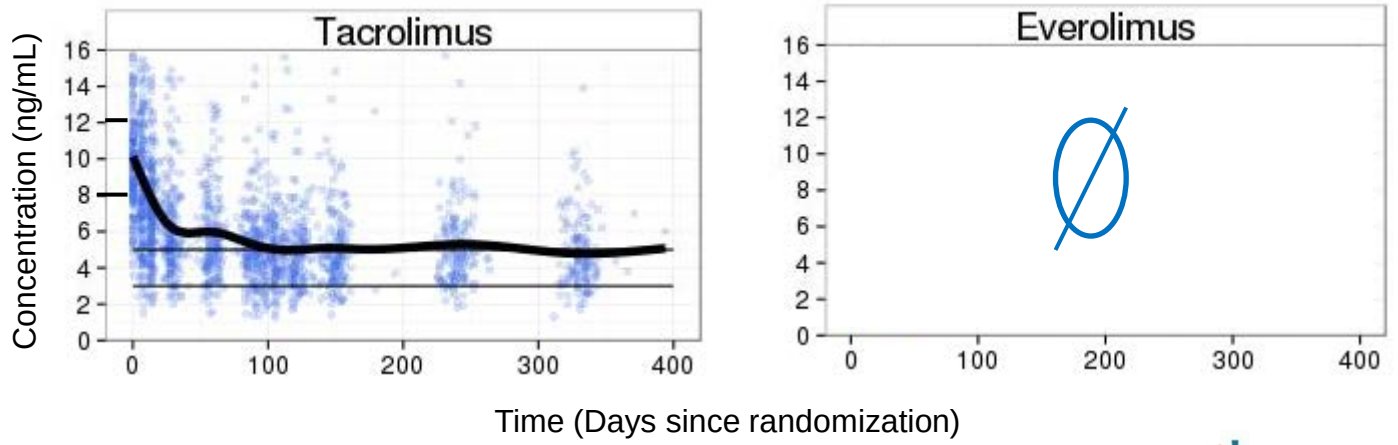
Putative ‘placebo’: *same TAC exposure as in the EVR + Low TAC arm but no EVR exposure*

Concentration over time

EVR + Low TAC



Putative ‘Placebo’

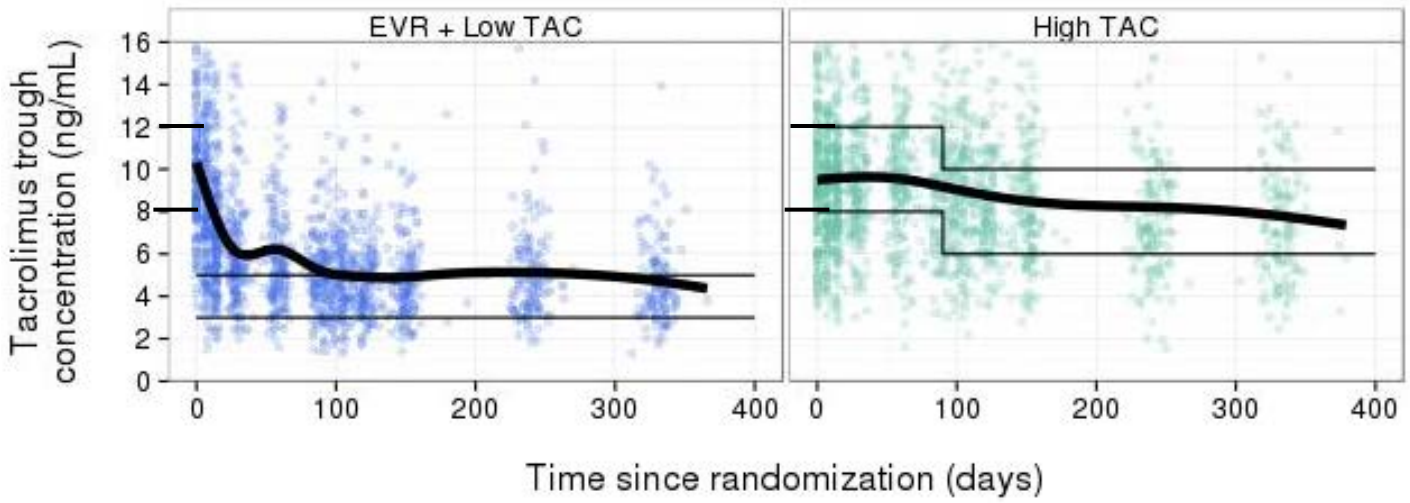


NOVARTIS

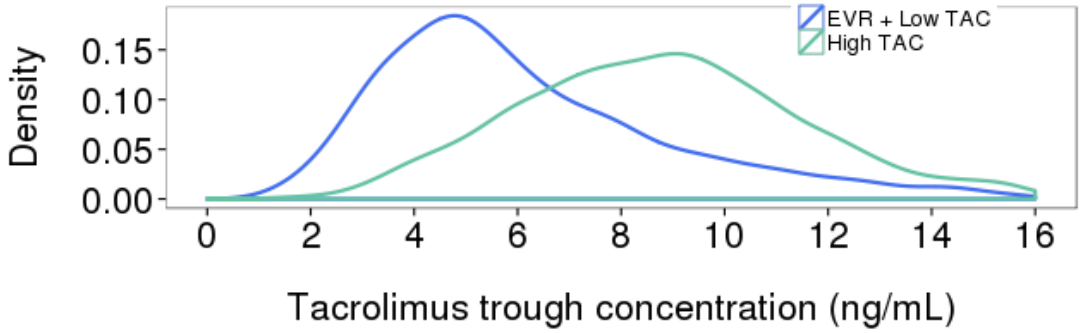
Solution – I

Adequate exposure data, possibility to use an exposure-response analysis to predict the putative 'placebo' efficacy

TAC Concentration over time



TAC Concentration Density

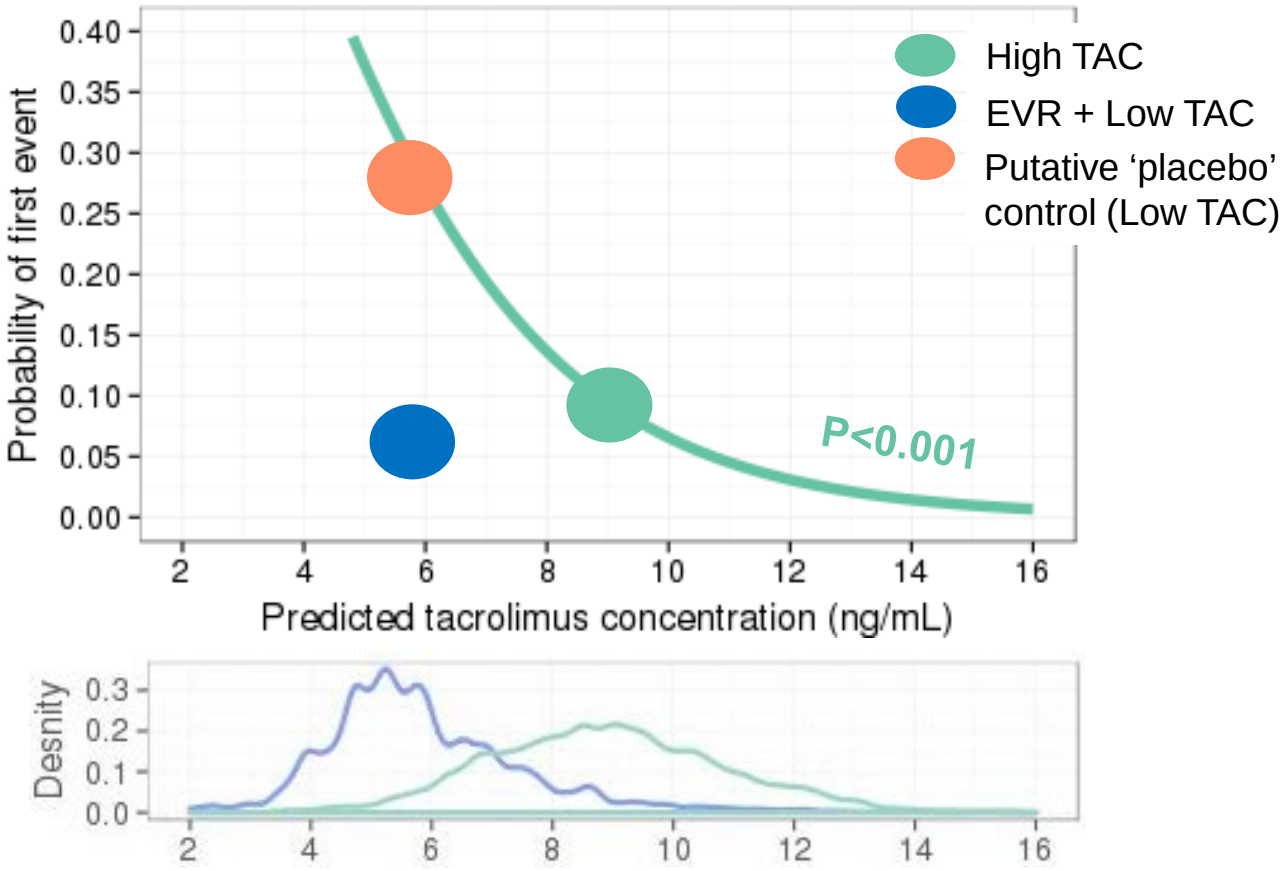


NOVARTIS

Solution - II

Using an adequate PK/PD methodology,
A) a very significant TAC concentration effect was detected

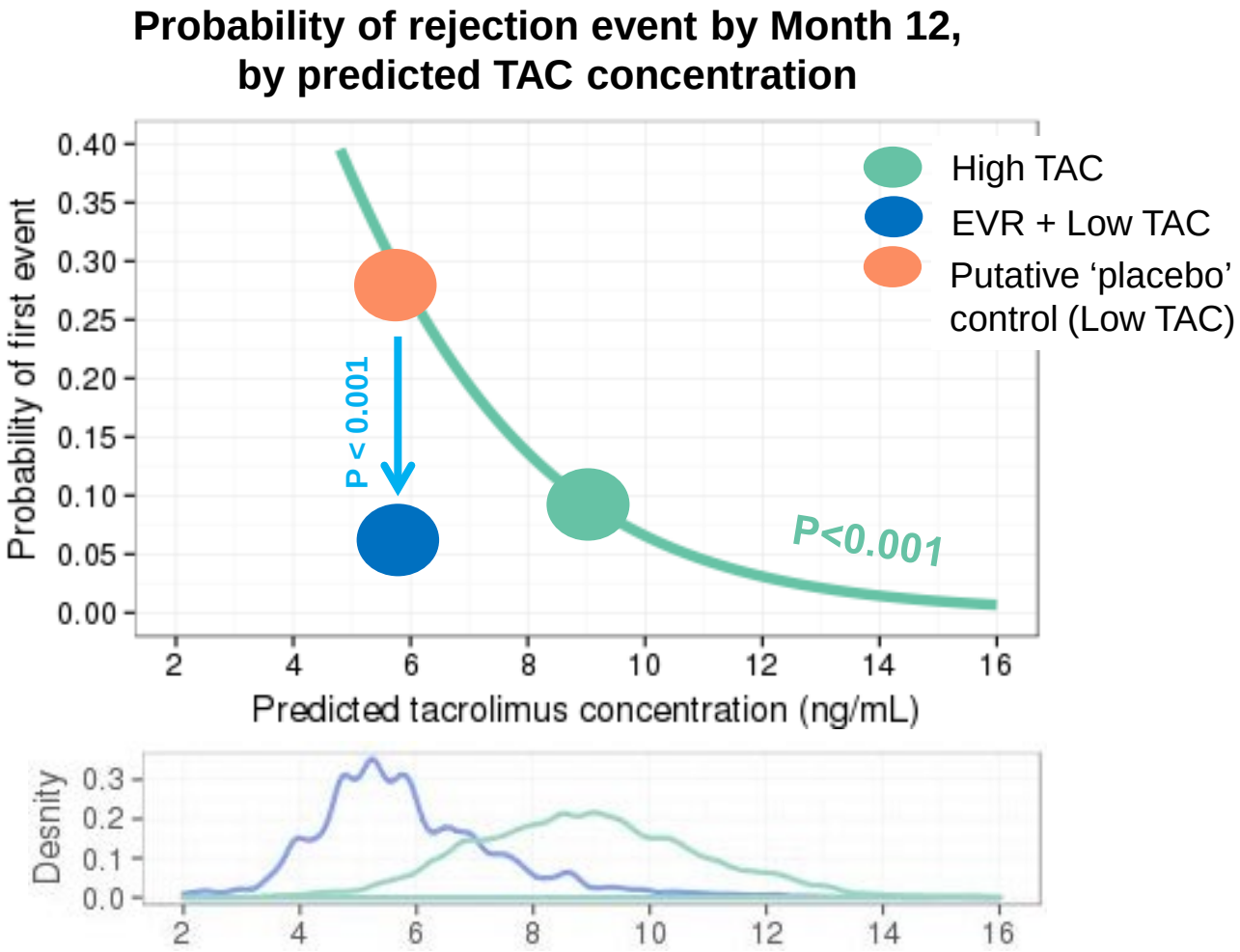
Probability of rejection event by Month 12, by predicted TAC concentration



NOVARTIS

Solution - II

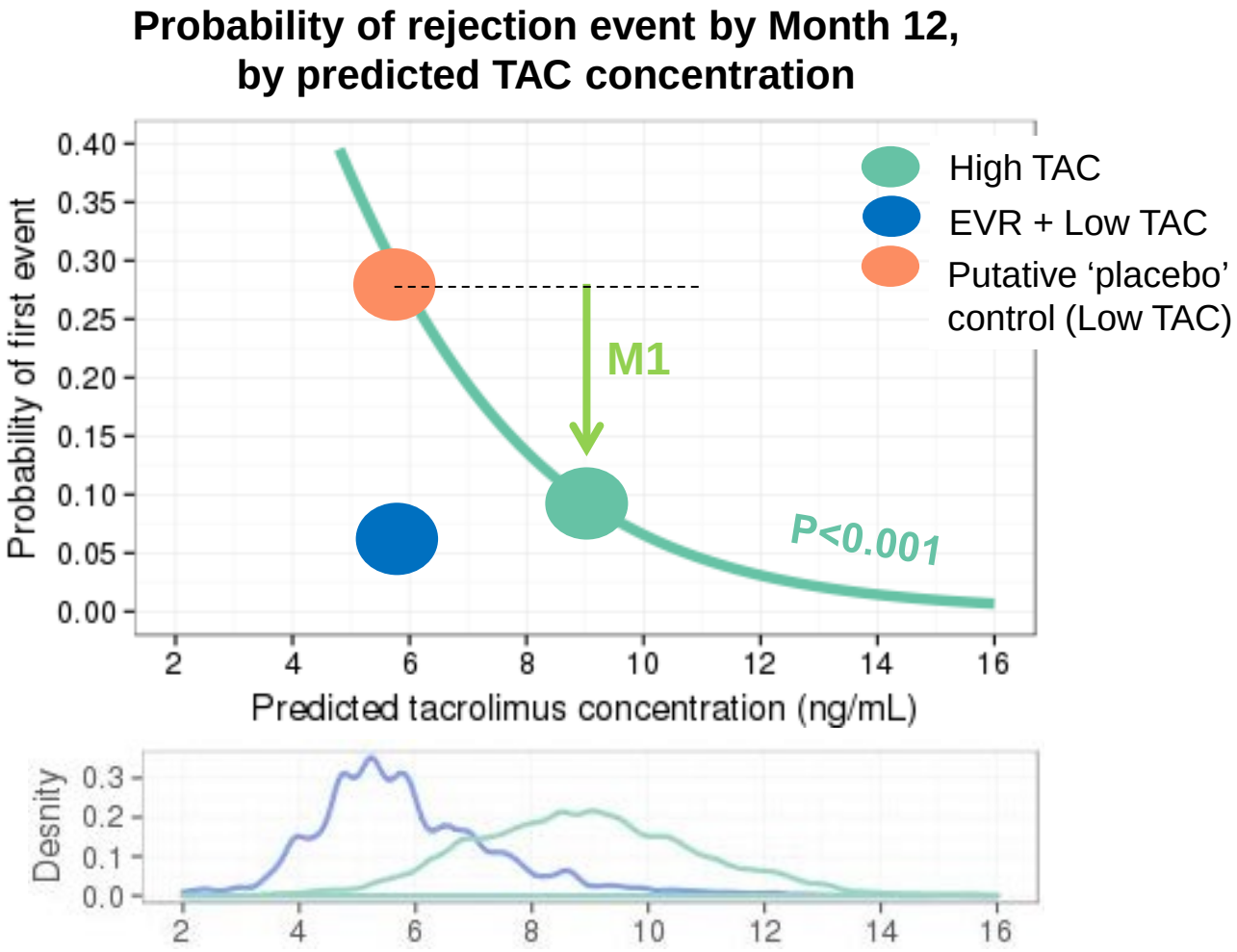
B) a very significant contribution of EVR to the efficacy of the combination was detected



NOVARTIS

Solution - II

or C) a non-inferiority margin could be calculated for further non-inferiority analysis



NOVARTIS

Impact

The modeling work has been key to the approval of the combination

- The modeling report (major amendment to the sNDA), triggered an additional 90 day extension to the review
- Subsequent FDA's Pharmacometric review:
  - Similar approach + additional analyses
  - Some differences in the interpretation
  - Similar conclusions
- The sNDA was eventually approved, without requests for REMS or post approval commitment study
- EVR + Low TAC is the first drug combination approved in liver transplantation in 10 years

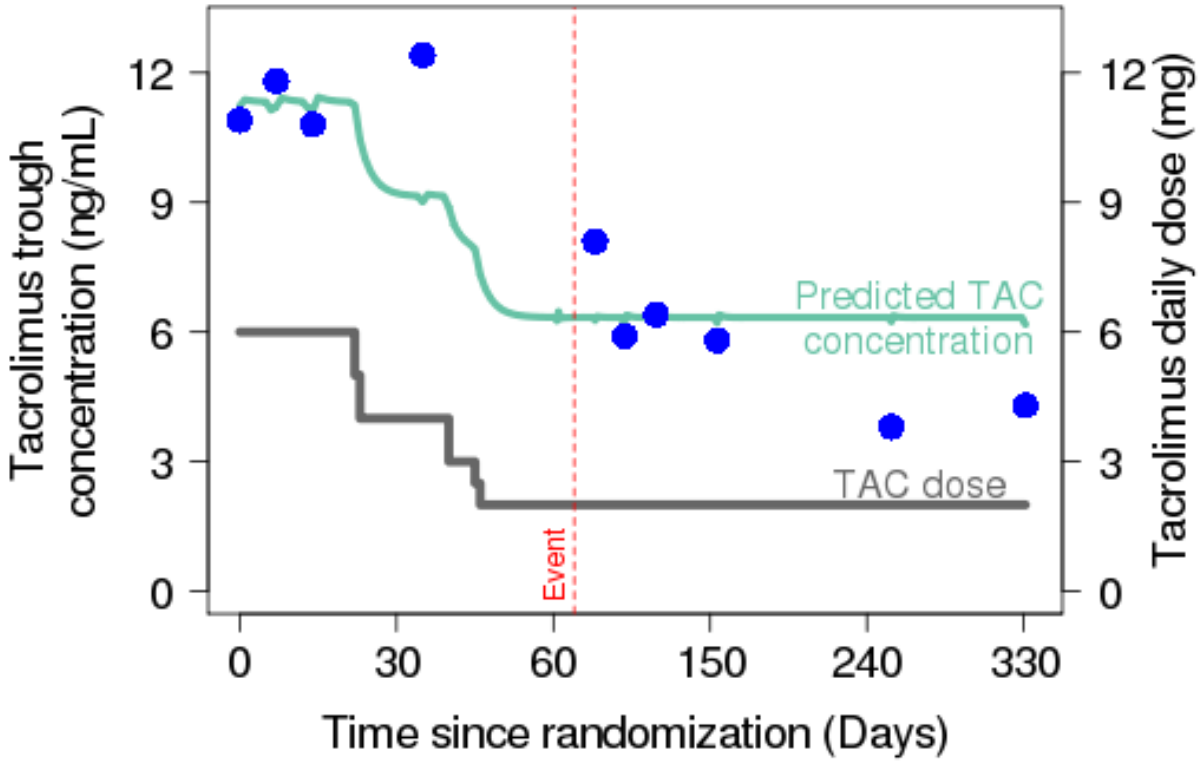
Methodological aspects

- Several features specific to immunology/transplantation had to be addressed
  - Absence of placebo, or dose-response information
  - Non steady-state exposure
  - Sparse PK sampling
  - Individual dose adjustments
- ... Addressed using
  - A population PK model coupled with a time-to event model
  - An assessment of causality of the exposure-response relationship

Sparse PK sampling, non 'steady state' exposure

Requires a population PK analysis to provide a realistic approximation of the true (unknown) tacrolimus concentration

Example of one study subject :

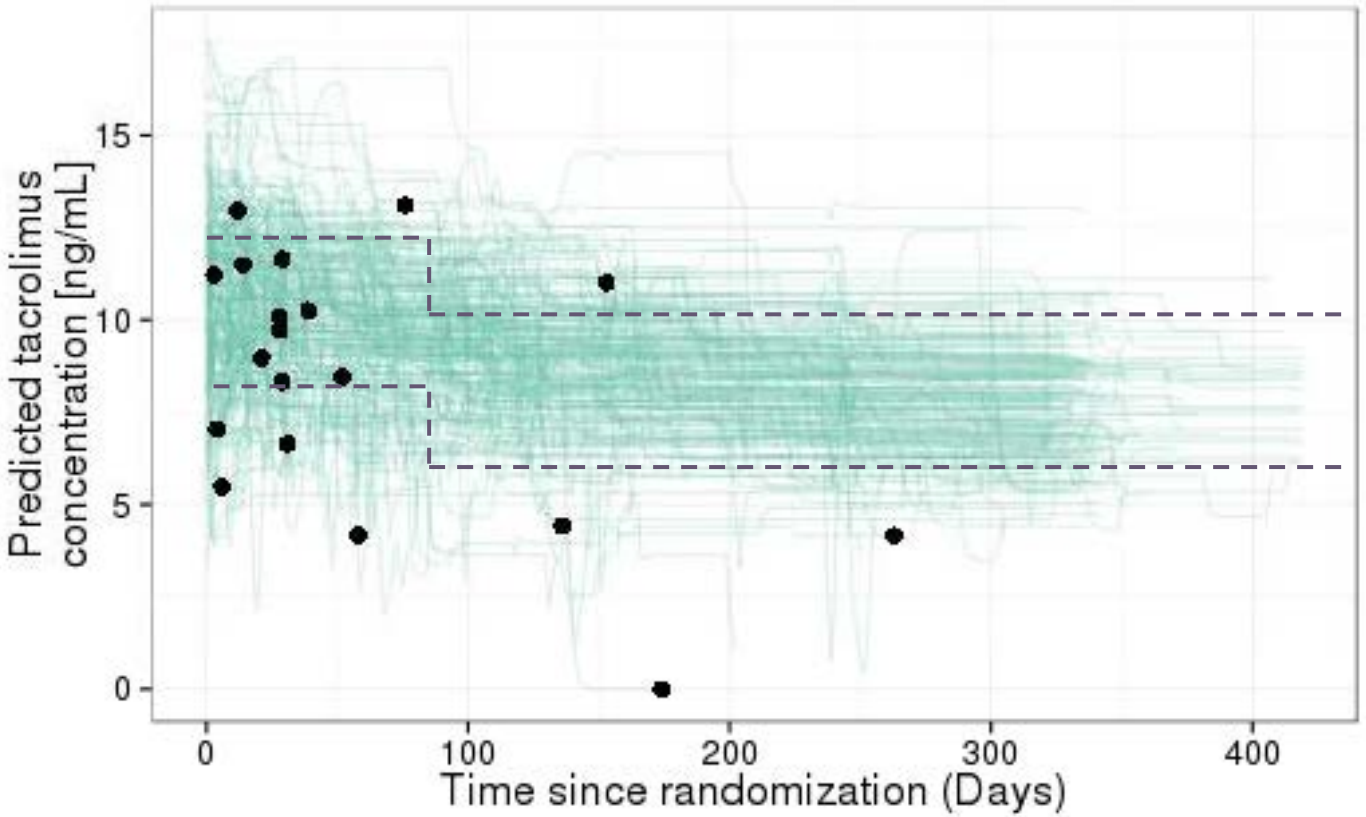


NOVARTIS

Non ‘steady state’ exposure

Requires a time-to event method to account for systematic decrease in exposure and time-varying baseline hazard

Predicted TAC exposure over time, and rejection event (High TAC arm)



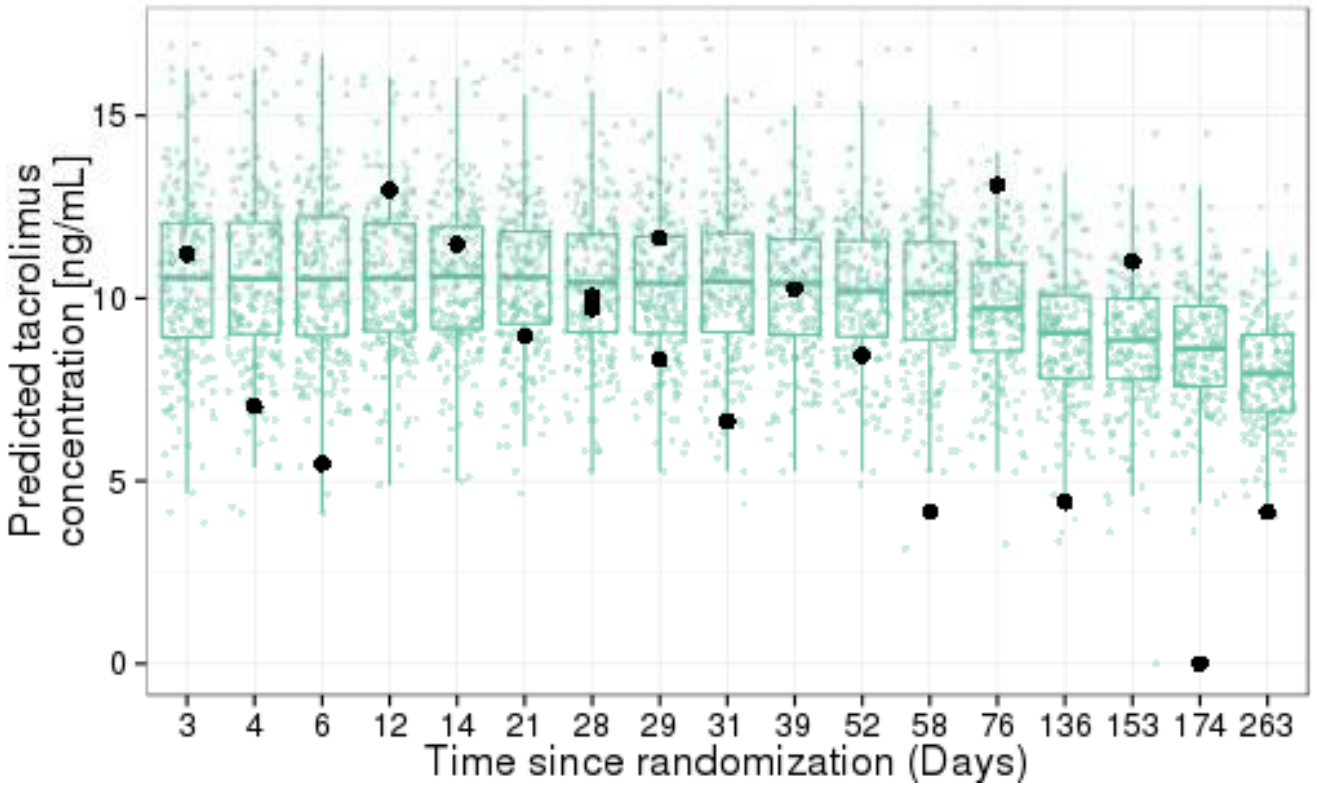
Curve = predicted TAC concentration for one subject of the High TAC arm (N=245)
Dot (●) = predicted TAC concentration on Day of event (N=22 subjects)

NOVARTIS

Non ‘steady state’ exposure

An E-R relationship appears when looking in a time-match fashion, in order to account for time-varying baseline risk

Predicted TAC exposure at event days, and rejection event (High TAC arm)



Dots (●) = predicted TAC concentration on each day with events (N=245 subjects),
Box-plot = corresponding distribution
Dots (●) = predicted TAC concentration on Day of event (N=22 subjects)

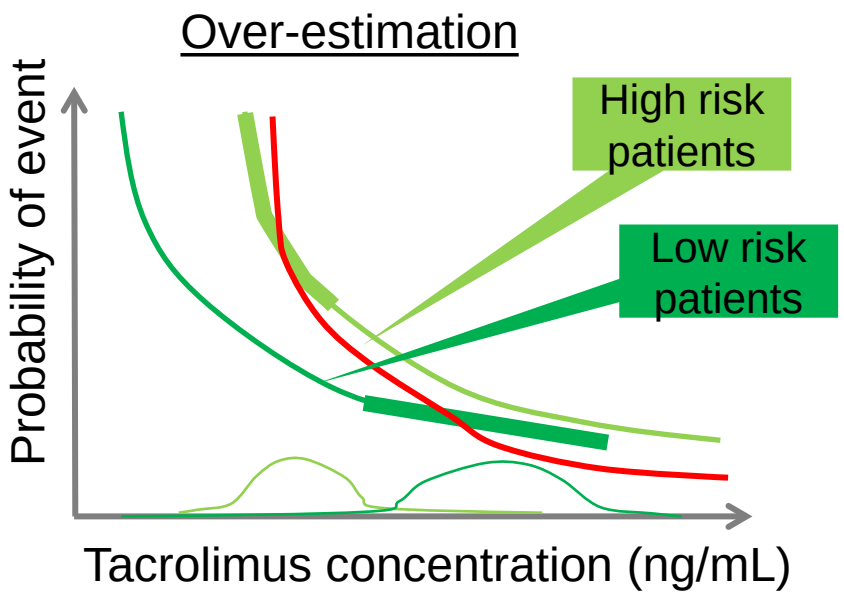
NOVARTIS

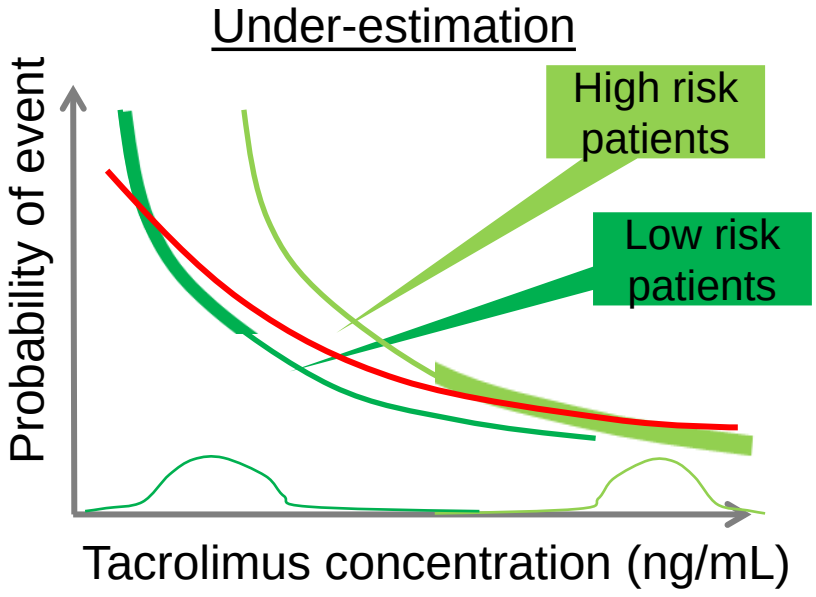
Individual dose adjustments

TAC concentration not randomized. This can cause a biased estimate of the exposure-response relationship

- There are baseline prognostic factors for rejection events
- The TAC concentration is not randomized

  → Investigators could target different levels depending on prognostic factor
- **Not accounting for those factors result in biased inference**



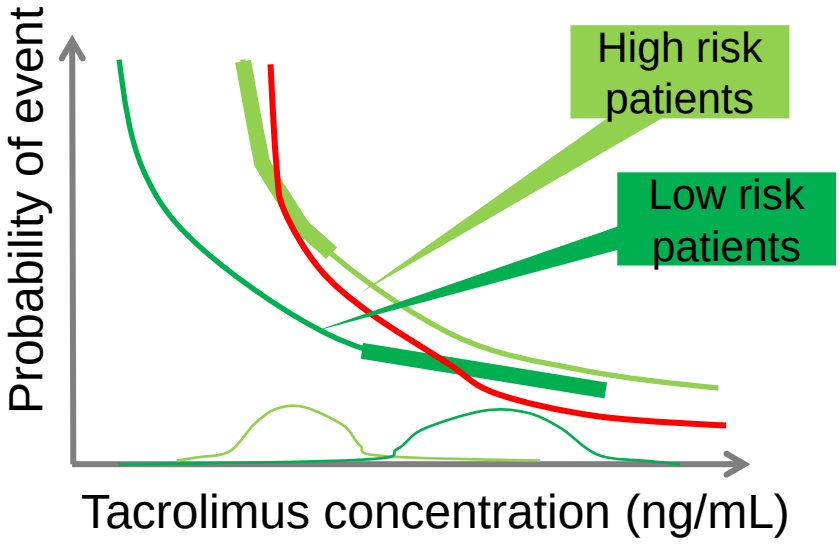


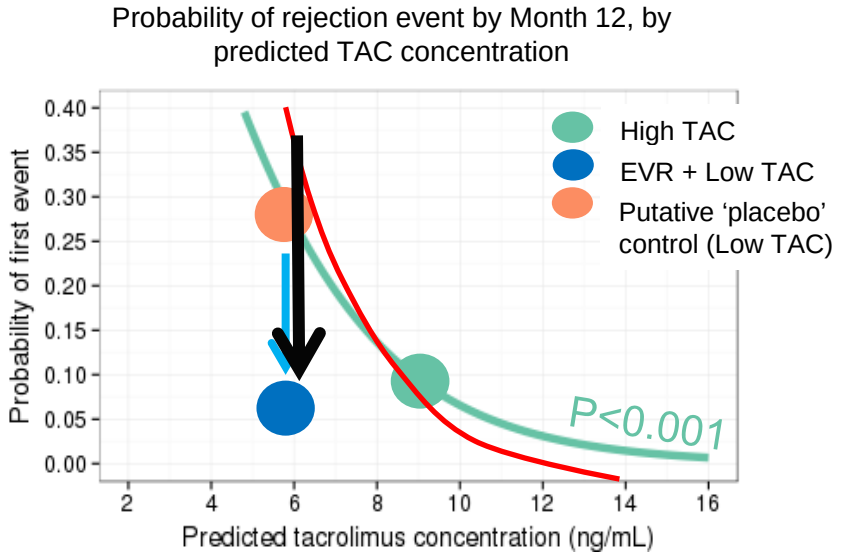
NOVARTIS

Individual dose adjustments

Presence of anti conservative bias must be ruled out; this was investigated by FDA's Pharmacometrics group

- Overestimated E-R relationship
  - not expected: investigators 'assigning' low concentration to patients at risk (based on baseline prognostic factors)
  - would result in overestimation the efficacy contribution of EVR → Anti-conservative
    - **ABSOLUTELY NEED TO BE RULED OUT**





NOVARTIS

Individual dose adjustments

No confounding factors resulting in relevant anti-conservative bias

- Presence of anticonservative bias was investigated by FDA's pharmacometric department for 3 potential prognostic factors:
  - Diagnostic of "HCV positive"
  - eGFR at randomization
  - MMF use prior to randomization (Yes/No)
  - Analysis method: includes the baseline prognostic factors as additional covariate in the hazard model
- All analyses show conservative results (flatter exposure-response relationship without covariate adjustment)
- Those sensitivity analyses led to a conservative estimate of M1, which was used to interpret the primary efficacy analysis

Conclusion

- A novel PMX based approach was used retrospectively to support the regulatory submission of a new combination transplant therapy
- The method was able to provide evidence of efficacy of the individual components of the treatment that could not have been done with traditional methods
- Support for the methodology within the Regulatory Authority helped gain acceptance and approval
- The example demonstrates that there is significant room for improvement in the application of dose finding methodologies