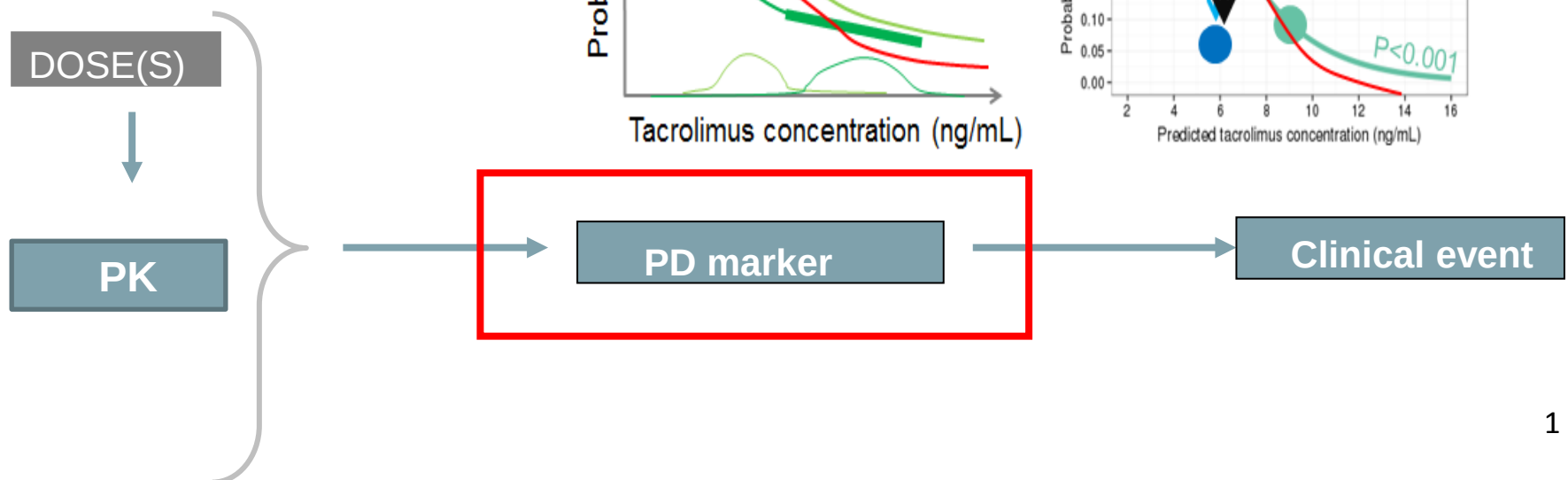
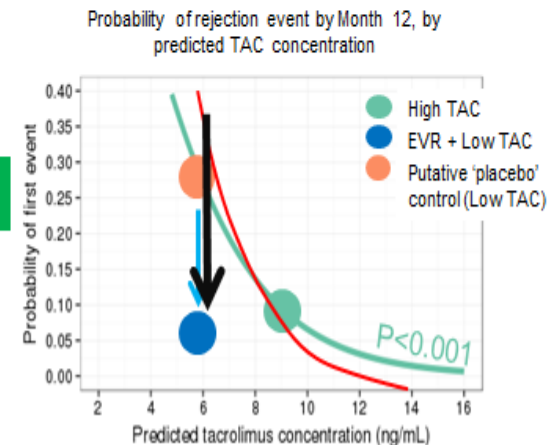
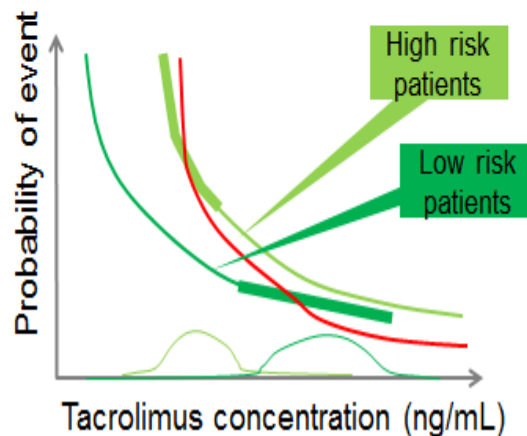


Presence of anti conservative bias must be ruled out; this was investigated by FDA's Pharmacometrics group

- 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**



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