

# PK/PD assessment of tacrolimus nephrotoxicity in liver transplantation

S. Weber, M. Looby, T. Dumortier

Advanced Quantitative Sciences  
Novartis Pharma AG, Basel, Switzerland



## Background

Tacrolimus is often used to prevent rejection events post liver transplantation. However, its main side effect is its nephrotoxicity which may ultimately lead to a loss of kidney function several years post transplant.

It is known that the loss of the kidney function has both acute and chronic components [1,2], whereby reversible acute damage is converted over time into irreversible chronic damage. However, the exact mechanism of action is yet unknown.

## Objectives

The aim of this analysis is to understand the relationship between TAC exposure and the evolution of renal impairment. A model based approach is used to distinguish the time course of acute reversible changes in renal function from chronic irreversible impairment in response to the time course of standard TAC therapy which is constantly adapted in response to safety, tolerability and rejection events.

## Conclusion

- Acute and chronic kidney damage can be differentiated in a PK/PD model
- Conversion of reversible to irreversible kidney damage is predicted to occur on a time-scale of 10 months (given model assumptions)
- Potential therapeutic improvements due to alternate TAC treatments will only become visible several years post-transplant
- Precise long-term GFR predictions require further data and model improvements

## Methods

From Study [3] the TAC treatment arm with N=240 patients were included in the analysis data set. TAC trough concentrations were monitored over a period of up to 2 years. The PK was described by a one-compartment model with a nonlinear bioavailability  $F$ .

The PD response is a decline of GFR over time due to TAC exposure. Clinically three time-scales immediate/transient and long-term effects are empirically known which are captured by a longitudinal model with 3 distinct phases:

- **E1 direct reversible:** Immediate and rapid decline after the liver transplant. This can be described by a direct and *reversible* effect of TAC concentration,  $c(t)$ , on GFR
- **E2 indirect reversible:** Transient and *reversible* decline in the post transplantation recovery phase of a few months where high TAC concentrations are targeted to prevent acute rejection (AR). This somewhat delayed response is described by an effect compartment (EC) concentration  $c^{\dagger}(t)$  with an expected equilibration time in the order of one month.
- **E3 irreversible:** A slow process which converts reversible damage into an *irreversible* damage. This occurs over a time scale of years and is modeled as a response to the cumulative exposure:

$$c_i^{\ddagger}(t) = \sum_{j=0}^{t_j \leq t} \frac{F d_j}{Cl_i}.$$

Each phase is assumed independent of each other (time scale separation) and is scaled by its individual weighting factor  $EC50$ ,

$$d_{ij} = \frac{c_i(t_j)}{EC50_c} + \frac{c_i^{\dagger}(t_j)}{EC50_{c^{\dagger}}} + \frac{c_i^{\ddagger}(t_j)}{EC50_{c^{\ddagger}}} \exp(k_i t_{std}),$$

where  $d_{ij}$  represents a dimensionless PD effect size and the relative contribution of each phase is weighted by its  $EC50$ . Note that E3 has a time dependent  $EC50_{c^{\ddagger}}(t)$  assigned. This accounts for the possibility that the irreversible damage can grow faster in relation to effects other than the total exposure build up rate (determined by the dosing schedule). The three phases are linked together by a Hill function,

$$\log(g_{ij}) = \theta^b + \eta_i^b + \log\left(\frac{\exp(\eta_i^E)}{\exp(\eta_i^E) + d_{ij}}\right).$$

The overall  $EC50$  of the Hill function has been set to 1 on average. Each patient  $i$  is allowed to deviate from the overall scale via the random effect term  $\exp(\eta_i^E)$ . All outcomes were modeled in log-domain with an additive error model. The PK/PD models considered were fit simultaneously with ADVAN4 of NONMEM 7.2.

## Results

### Model development

- Including all 3 effects yields an  $EC50_c$  for the direct effect of approx. 1 ng/ml such that it does not contribute to the dynamical behavior
- Dropping E1 from the model yields no change in the objective function value (OFV). Discarding E2/E3 yields a gain of the OFV by 101/19 points.
- The model with E2 and E3 are in terms of a LRT on the basis of OFV most likely, albeit a model with only E2 is similar in terms of OFV, indicating that E3 is only weakly supported by the data.

### Model diagnostics

The histograms of the  $\Phi^{-1}$ (NPDE) distributions in the time spans early high (0-1 month), transient high (1-4 month), transient steady (4-16 month) and late steady (16- $\infty$ ) are expected to be uniformly distributed in the 0-1 interval:

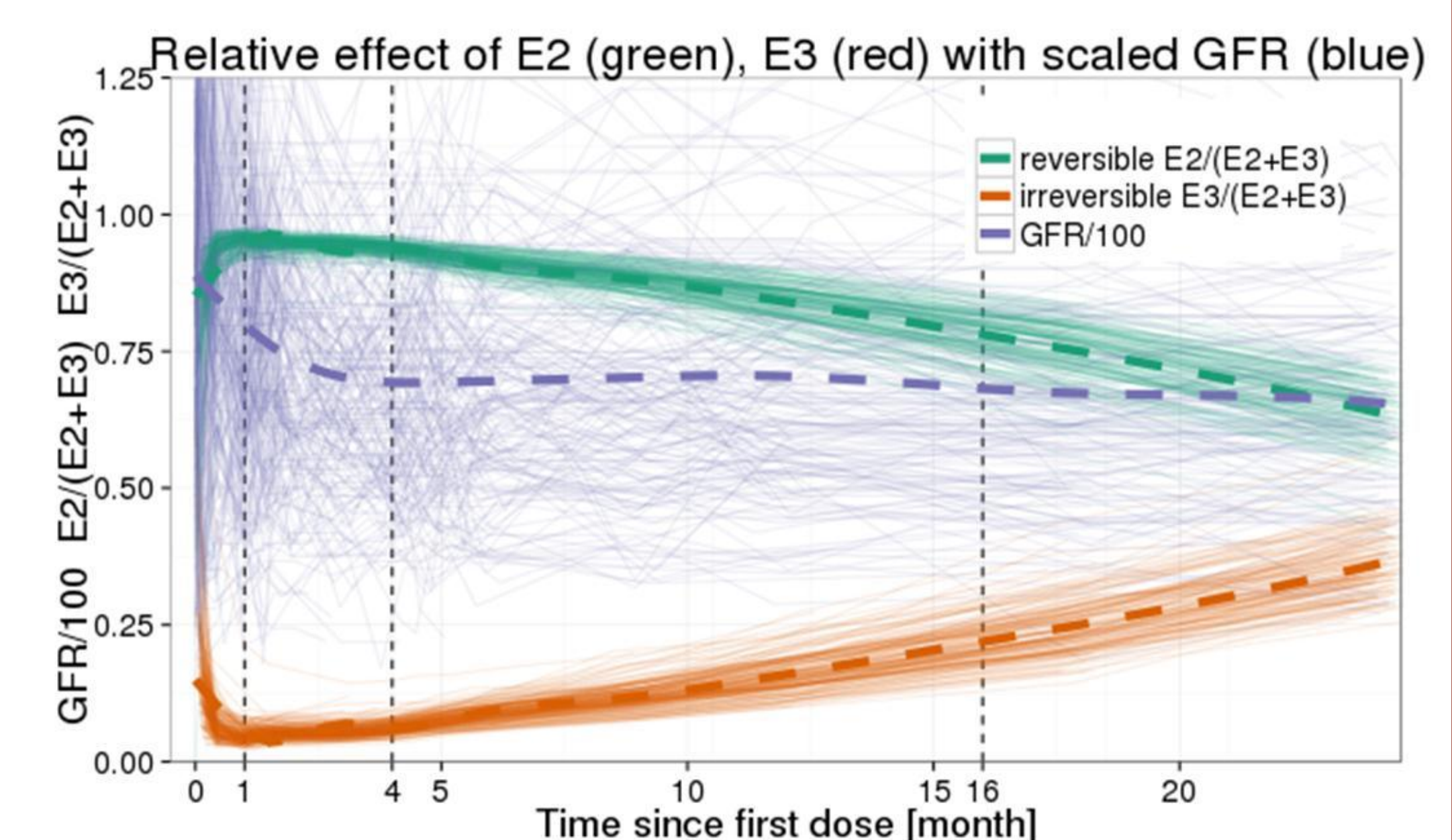
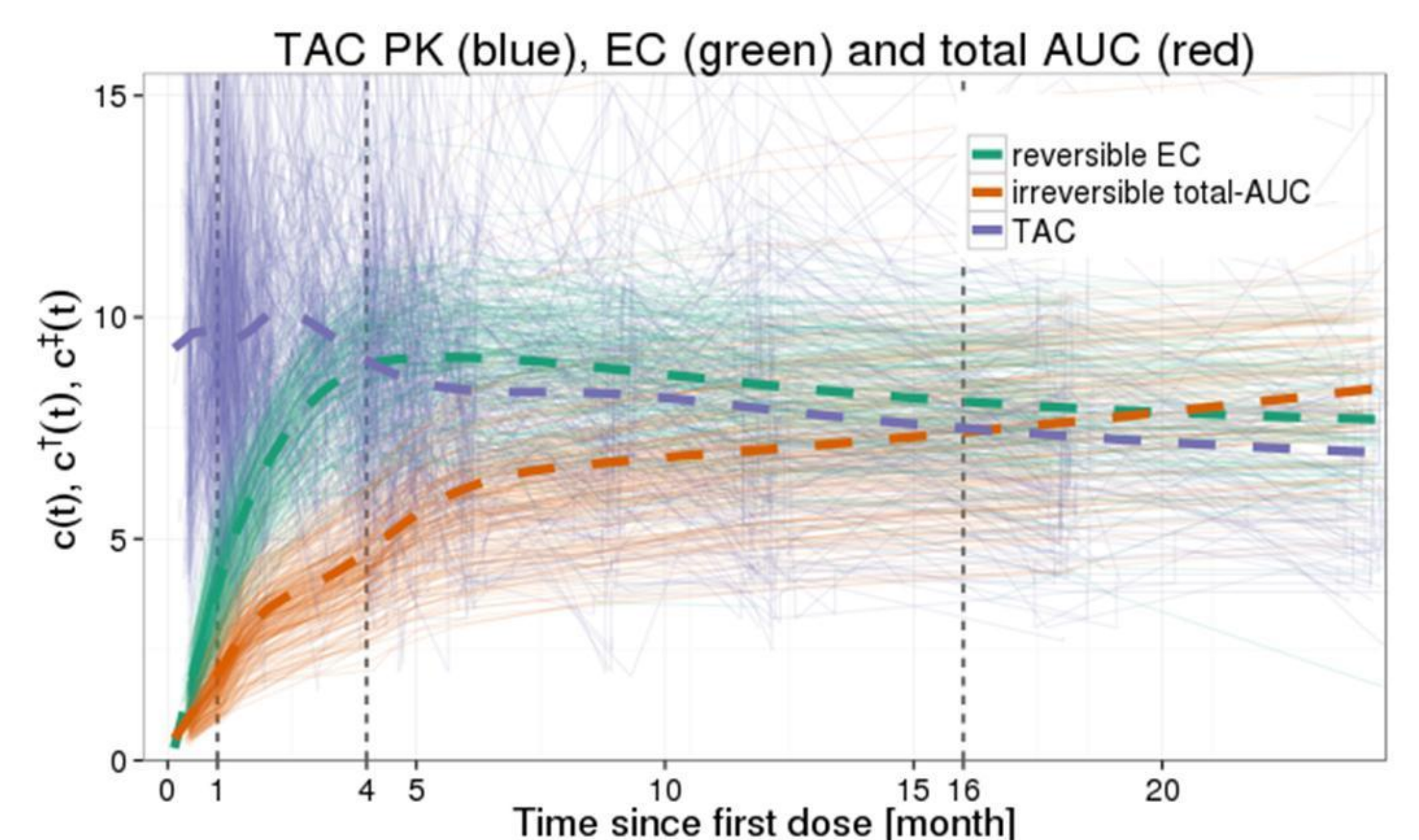
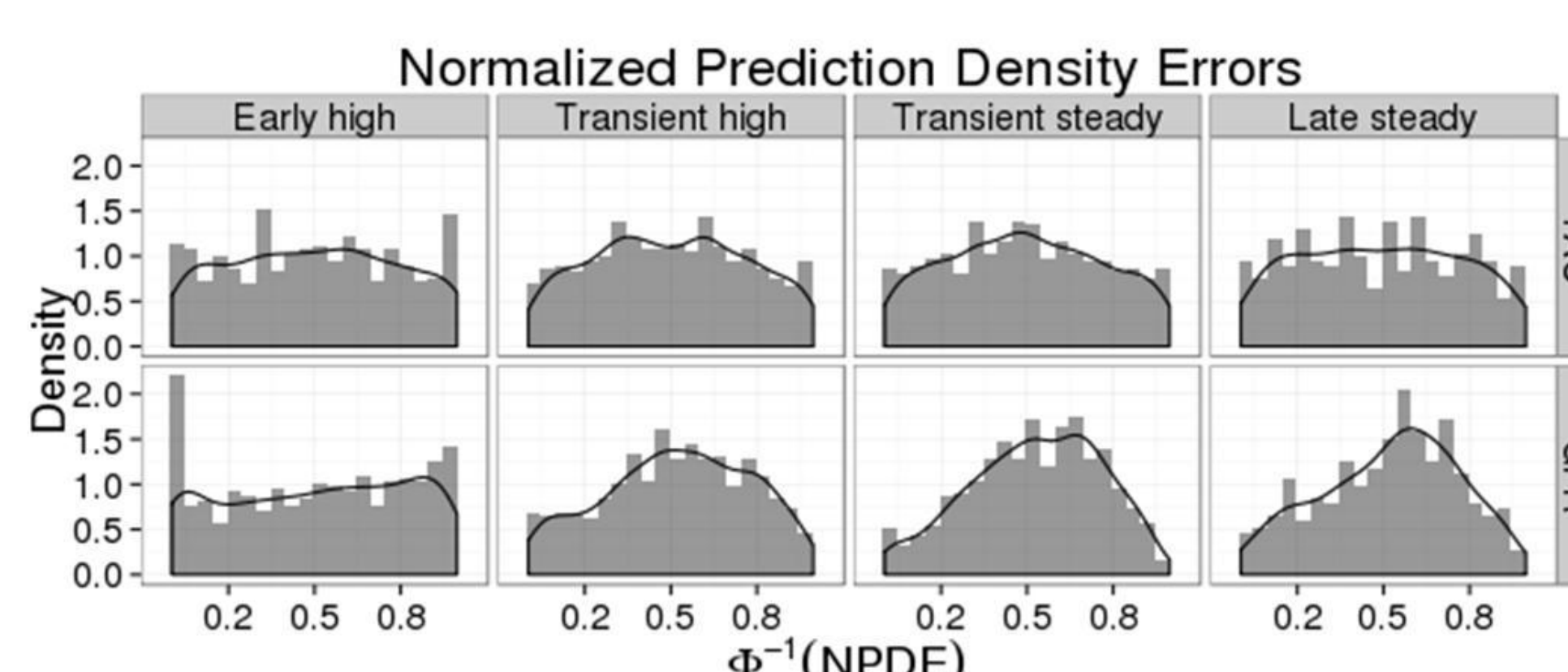
- The PK fit shows an excellent agreement over the complete observation time
- PD fit shows a slight bias and a possible disagreement between the data and the assumed error model for the transient/late steady phase

### TAC PK profile

- High starting regimen during the first 4 month of 8-12ng/mL and later low dosing of 6-10ng/mL.
- The equilibration rate constant of the EC corresponds to a doubling time of 1.2 month (95% CI 0.8 – 1.8)
- Shortly after the dosing regimen is changed to the lower regime at month 4, the EC is in equilibrium with the central TAC compartment.

### Relative contribution of effects

- Immediate acute GFR impairment is replaced by the irreversible effect E3.
- The doubling time of the rate constant associated with the weight of the irreversible PD effect is 9.5 month (95% CI 6.5 – 15.0).
- The build-up of the irreversible effect due to long-term treatment is much slower, the typical dose/CI ratio to the  $EC50_{c^{\ddagger}}$  is  $< 10^{-3}$ .



Model parameters in the PK/PD model with effect E2 and E3. «l» indicates log, RSE given in % of mean.

| Parameter                           | Definition                      | Est.     | RSE  | Ref.   |
|-------------------------------------|---------------------------------|----------|------|--------|
| Bioavailability $F_{rel}$           | $(d/d_{ref})^{\theta^F-1}$      | 0.40     | 5.6  |        |
| Reference dose $d_{ref}$            | 5                               |          |      | mg     |
| Absorption rate $k_a$               | 4.5                             |          |      | 1/h    |
| Clearance $Cl_i/F$                  | $\theta^{Cl} \exp(\eta_i^{Cl})$ | 37.79    | 2.3  | L/h    |
| Volume $V/F$                        | $\theta^V$                      | 2642     | 23.4 | L      |
| EC microrate $l(k_{eff})$           | $\theta^{eff}$                  | -0.55    | 36.7 | 1/mo.  |
| $lEC50_c$                           | $\theta^c$                      | $\infty$ |      | ng/mL  |
| $lEC50_{c^{\dagger}}$               | $\theta^{c^{\dagger}}$          | 3.69     | 3.3  | a.u.   |
| $lEC50_{c^{\ddagger}}$              | $\theta^{c^{\ddagger}}$         | 6.0      | 9.9  | mg h/L |
| $EC50_{c^{\ddagger}}$ growth $lk_i$ | $\theta^{k_i}$                  | -0.14    | 169  | 1/y    |
| Baseline IGFR                       | $\theta^b + \eta_i^b$           | 4.43     | 0.01 |        |
| Cl pop. var.                        | $\omega^{Cl}$                   | 0.19     | 7.4  |        |
| IGFR pop. var.                      | $\omega^b$                      | 0.3      | 5.1  |        |
| $lEC50$ pop. var.                   | $\omega^E$                      | 0.95     | 8.6  |        |
| Residual TAC var.                   | $\sigma^{TAC}$                  | 0.31     | 2.5  |        |
| Residual GFR var.                   | $\sigma^{eGFR}$                 | 0.21     | 3.2  |        |

## References:

- [1] Naesens, M. et al., CJASN, 4 (2), p. 481, 2009
- [2] Staatz, C. E. and Tett, S. E., Clin Pharmacokinet, 43 (10), p. 623, 2004

- [3] De Simone et al., Am J Transplant. 12(11), 3008, 2012
- [4] Antignac, M. et al., Eur J Clin Pharmacol, 64, p. 409, 2005

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