Quantification of the time course of CYP3A inhibition, activation, and induction using a population pharmacokinetic model of microdosed midazolam continuous infusion

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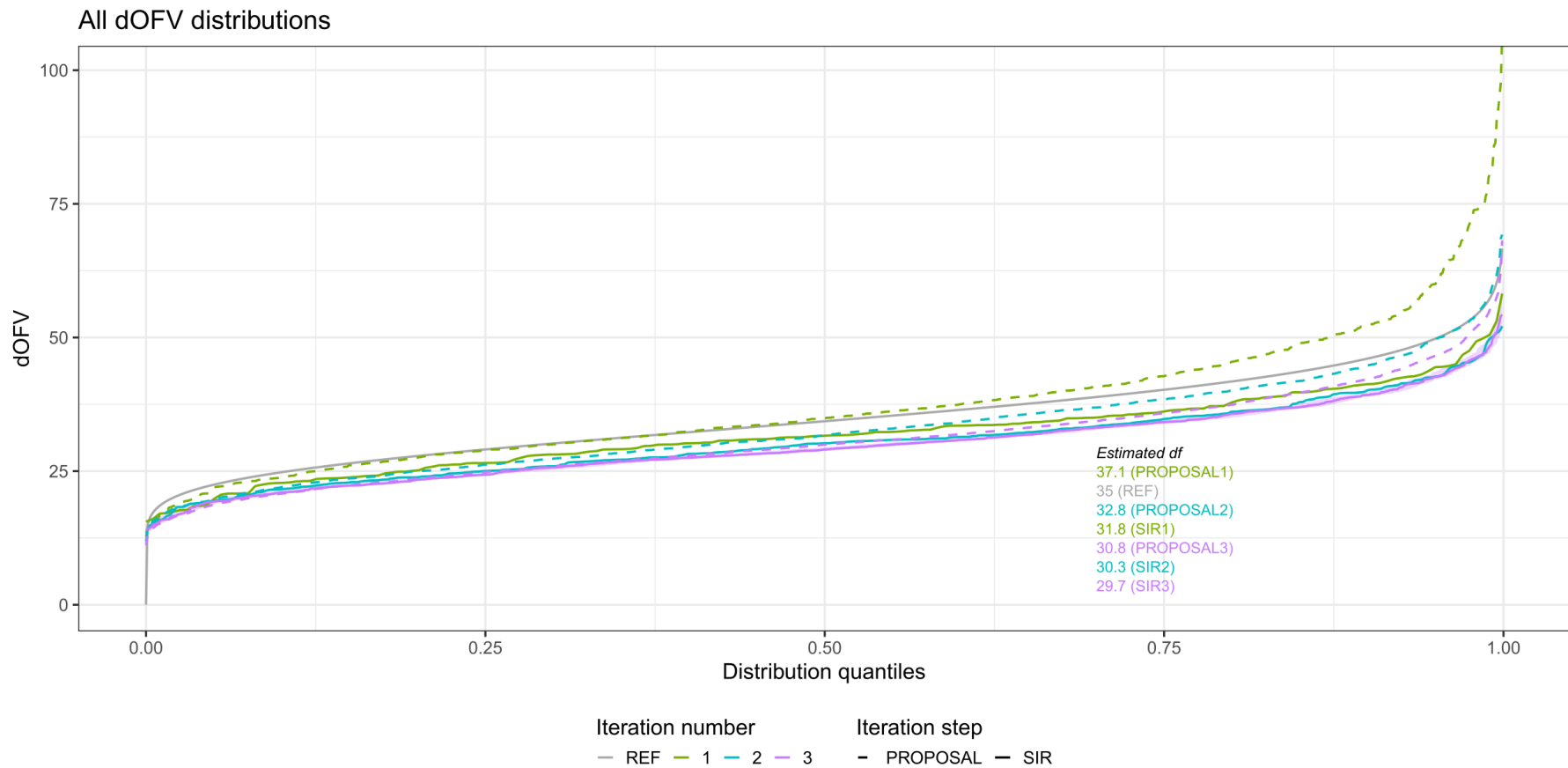
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All dOFV distributions

Estimated df
37.1 (PROPOSAL1)
35 (REF)
32.8 (PROPOSAL2)
31.8 (SIR1)
30.8 (PROPOSAL3)
30.3 (SIR2)
29.7 (SIR3)

Iteration number   Iteration step
— REF — 1 — 2 — 3   - PROPOSAL — SIR

Fig S1 Diagnostic plot for the midazolam and 1'-hydroxymidazolam model showing that SIR settings were appropriate. Proposal is above the Chi square and SIR dOFV is below the Chi square distribution
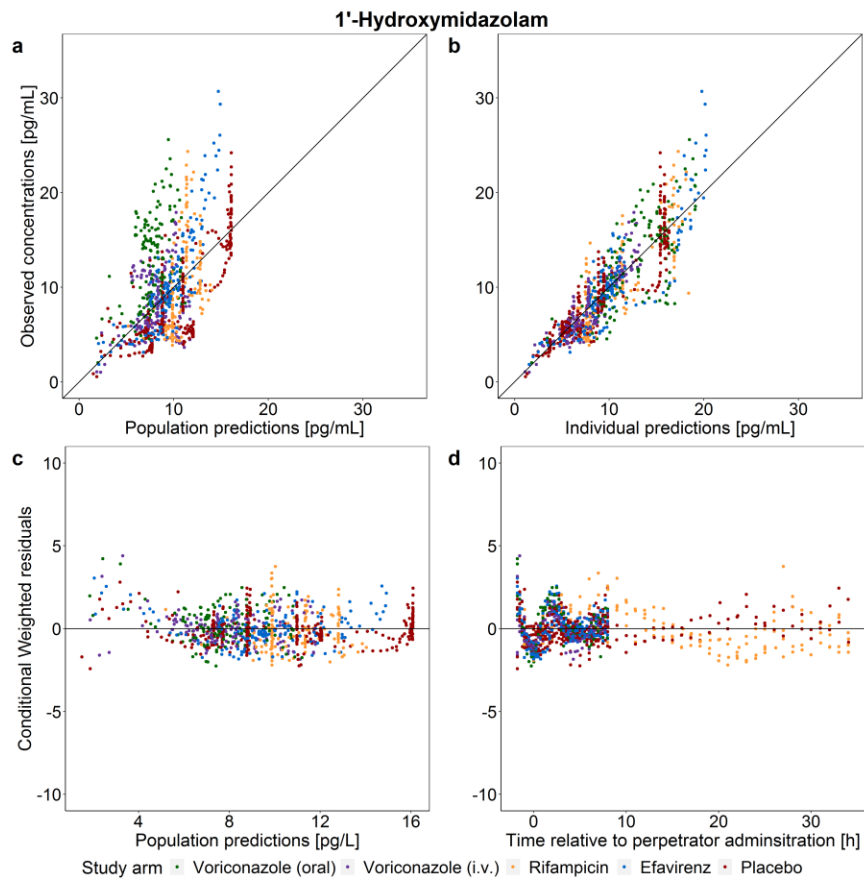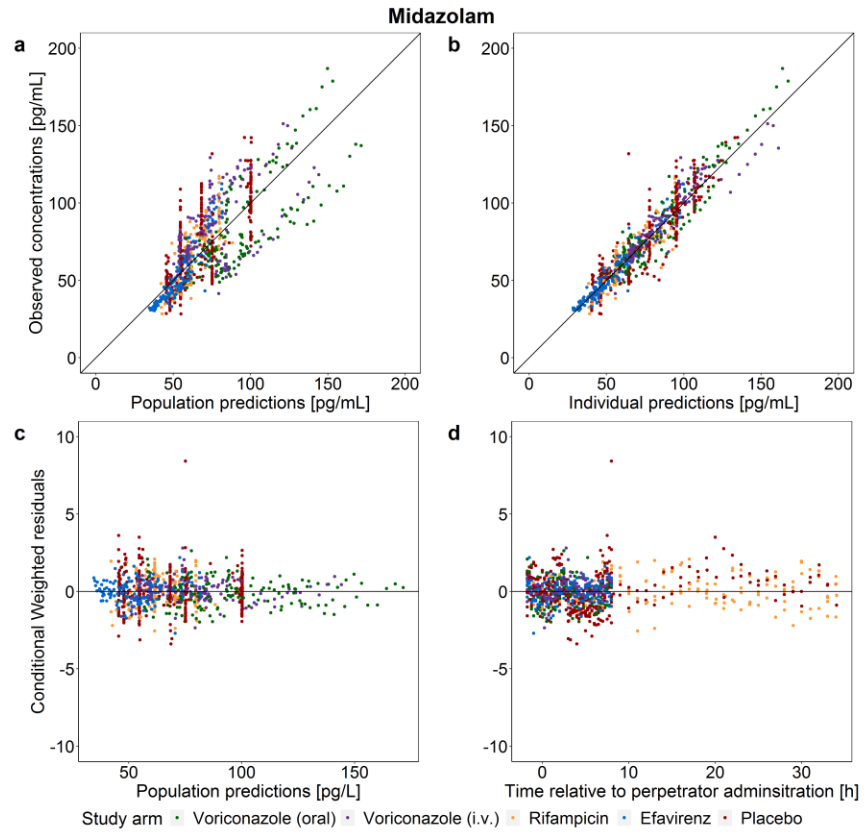
Midazolam

Study arm • Voriconazole (oral) • Voriconazole (i.v.) • Rifampicin • Efavirenz • Placebo

1'-Hydroxymidazolam

Study arm • Voriconazole (oral) • Voriconazole (i.v.) • Rifampicin • Efavirenz • Placebo

Fig S2 Basic goodness-of-fit plots (a) observations versus population predictions, b) observations versus individual predictions, c) conditional weighted residual versus population predications, d) conditional weighted residuals versus time relative to perpetrator administration of midazolam (top) and 1'-hydroxymidazolam (bottom) model, color-coded by study arm. Dots represent the data points; the solid black line is the line of identity of slope 1 or zero. *I.v.* intravenous.
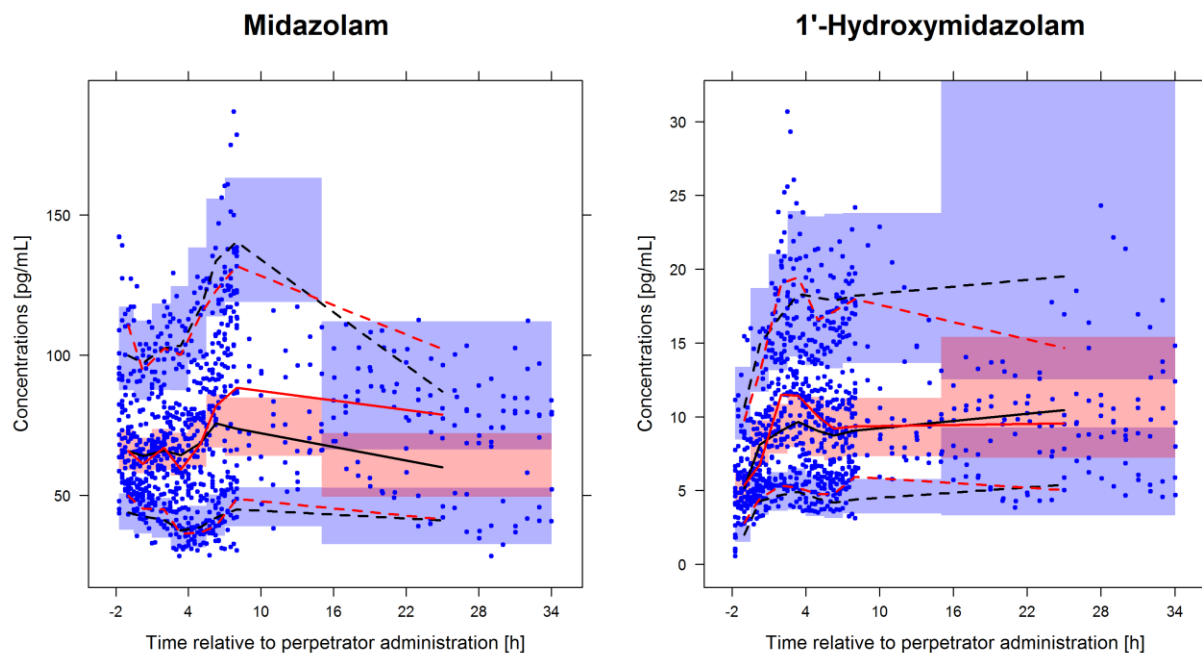
Fig S3 Visual predictive check (1000 simulations) of the midazolam and 1'-hydroxymidazolam model. Dots represent the measured concentrations, solid red and black lines represent the median of the observed and simulated concentrations, respectively. The upper and lower dotted red and black lines represent the 10th and 90th percentiles of the observed and simulated concentrations, respectively. Shaded areas represent the 95% confidence interval of the simulated percentiles. The number of bins was set to 8 with equal number of observations.
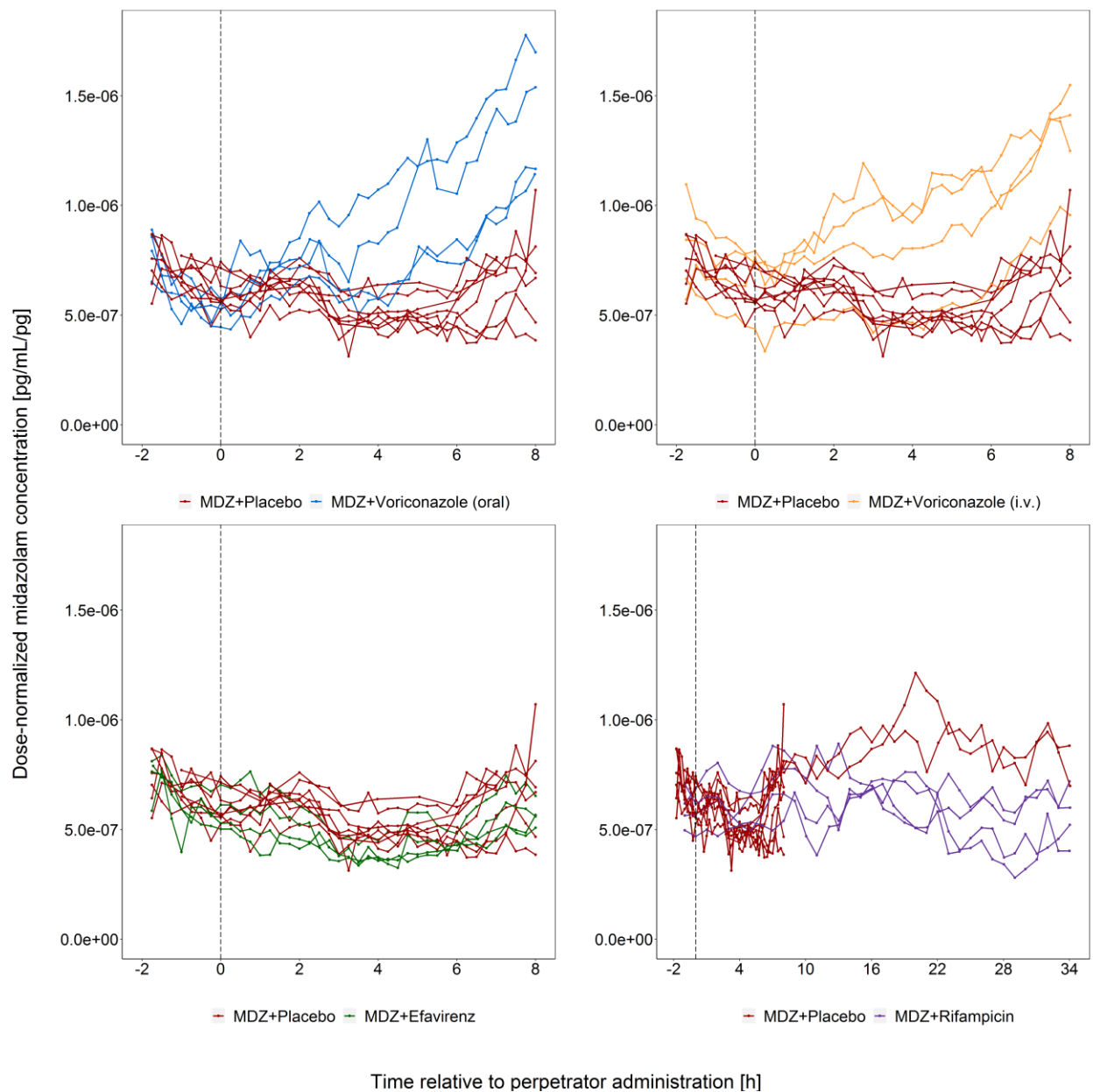
Fig S4 Dose-normalized midazolam concentration versus time relative to perpetrator administration, per study arm, color-coded by administered perpetrator or placebo. Dashed vertical line: Time of perpetrator administration. *I.v.* intravenous