Supplementary Material

Influence of a short course of ritonavir as used as booster in antiviral therapies against SARS-CoV-2 on the exposure of atorvastatin and rosuvastatin

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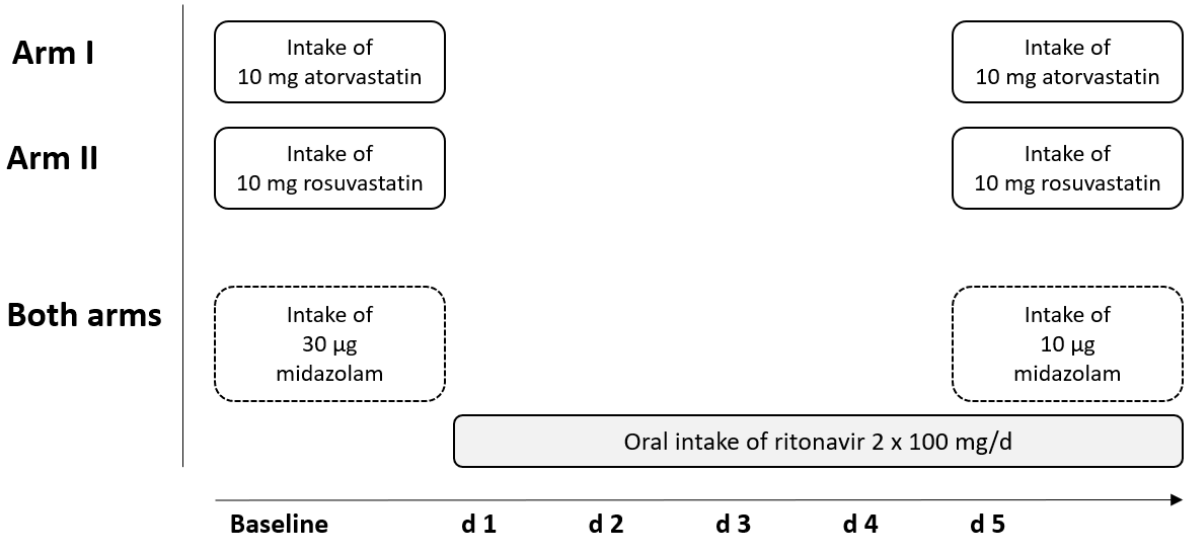
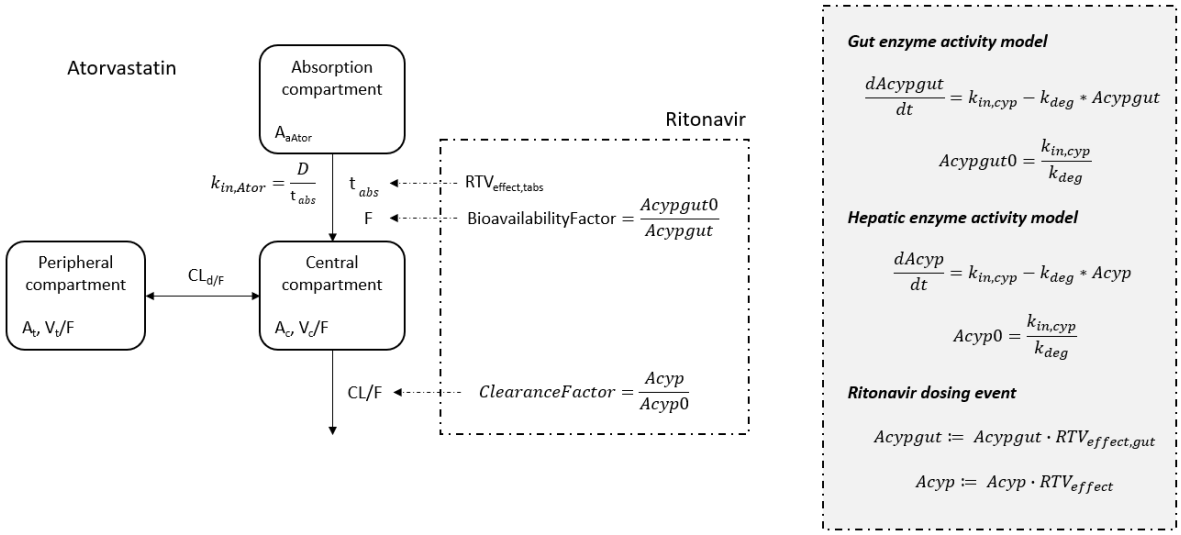
Online Resource Table 1 Atorvastatin population pharmacokinetic parameters from the semi-mechanistic model.

Parameter	Estimate	Unit	Inter-individual variability (CV %)
V_c/F	2507	[L]	89.5
CL/F	540	[L/h]	79.4
V_t/F	4040	[L]	-
CL_d/F	2387	[L/h]	-
F	1[a]		59.9
t_{abs}	1.20[b]	[h]	-
k_{deg}	0.00866[a]	[1/h]	-
RTV_{effect}	1.00[b]		-
$RTV_{effect,gut}$	0.57		-
$RTV_{effect,tabs}$	1.71[b]		-
Proportional error	0.50		

CL/F: apparent clearance after oral administration; CL_d/F: apparent distribution clearance; CV: coefficient of variation; F: bioavailability; k_{deg}: CYP enzyme degradation-rate constant; RTV_{effect}: ritonavir-induced relative change of CYP activity after a ritonavir dose as used to modify drug elimination; $RTV_{effect,gut}$: ritonavir-induced relative change of CYP activity after a ritonavir dose used to modify bioavailability; $RTV_{effect,tabs}$: ritonavir-induced relative change of zero-order absorption time; t_{abs}: zero-order absorption time; V_c/F: apparent volume of the central compartment; V_t/F: apparent volume of peripheral compartment; [a]: Value fixed according to clinical reasoning or literature results. [b]: Value fixed according to separate analyses.



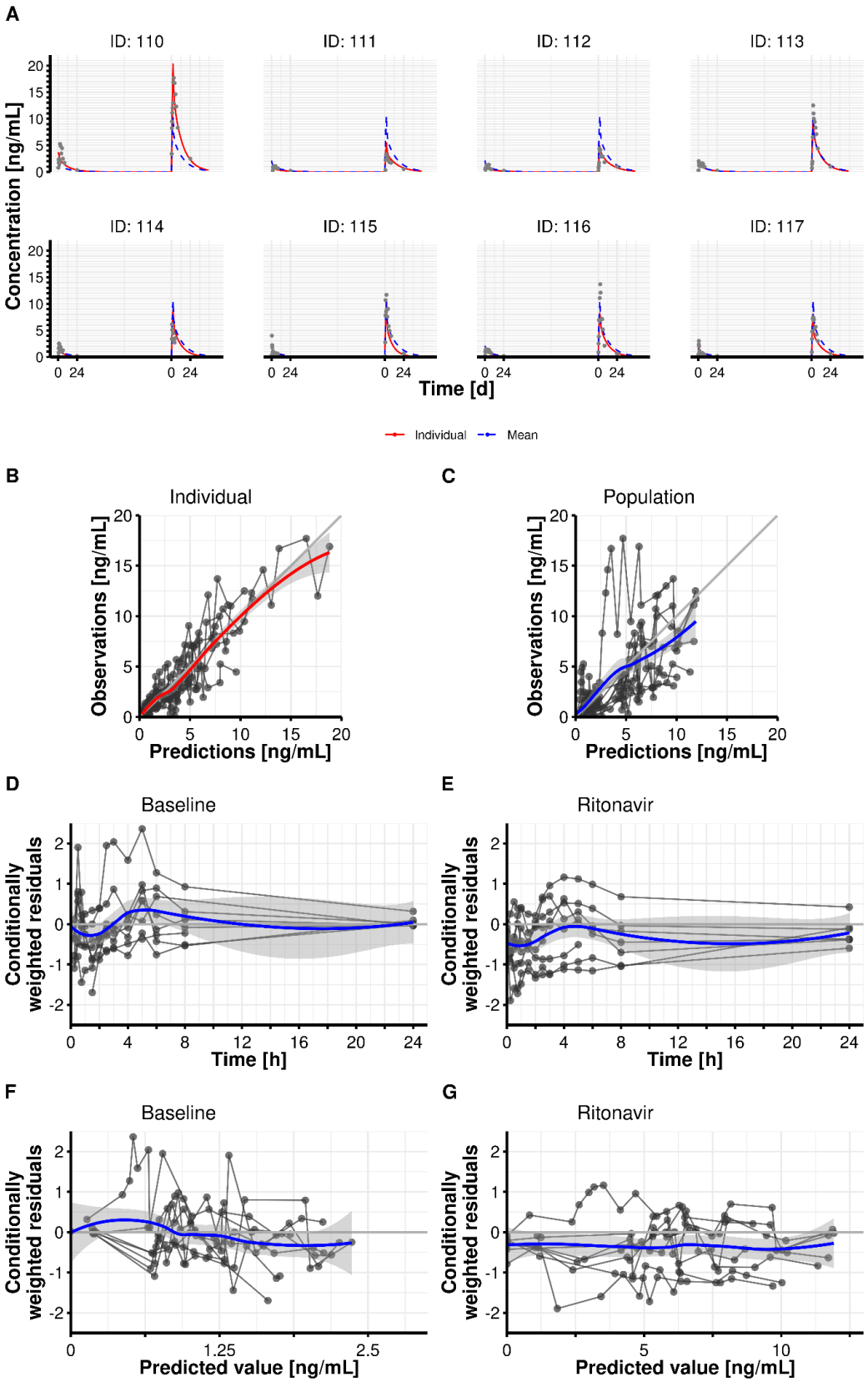
Online Resource 1: Trial design to evaluate the perpetrator effects of a 5-d ritonavir treatment regimen (2 x 100 mg/d) on the single-dose pharmacokinetics of 10 mg atorvastatin or 10 mg rosuvastatin and a microdose of midazolam in eight healthy volunteers per study arm.



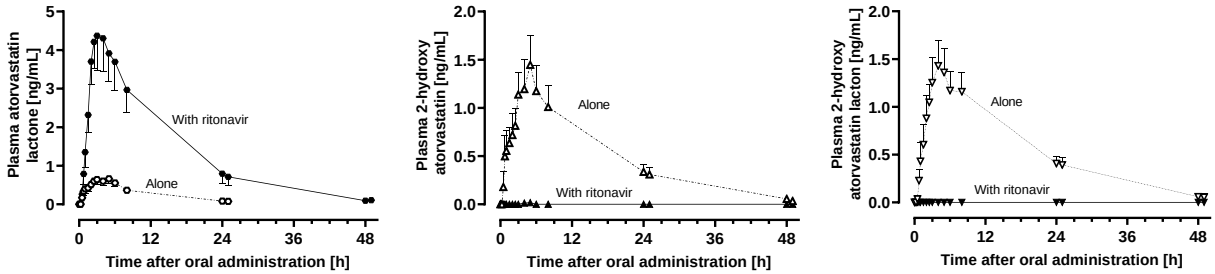
Online Resource 2: Final atorvastatin pharmacokinetic model. AaAtor: amount in absorption compartment; A_c and A_t: amount in central and peripheral compartments; Acyp0 and Acypgut0: relative activity of hepatic and intestinal CYP-enzyme before intervention (set at 1); Acyp and Acypgut: relative activity of hepatic and intestinal CYP-enzyme (initial values set at 1); C_c: plasma concentration; CL_d/F, apparent distribution clearance; CL/F, apparent clearance after oral administration; k_{deg}: 1st-order degradation rate constant; $k_{in,Ator}$: zero-order absorption rate constant; $k_{in,cyp}$: hepatic/ intestinal CYP synthesis rate; RTV_{effect}: ritonavir-induced relative change of CYP activity after a ritonavir dose as used to modify drug elimination; $RTV_{effect,gut}$: ritonavir-induced relative change of CYP activity after a ritonavir dose used to modify bioavailability; $RTV_{effect,tabs}$: ritonavir-induced relative change of zero-order absorption time; t_{abs}: zero-order absorption time; V_c/F: apparent volume of the central compartment V_t/F: apparent volume of peripheral compartment.

Online Resource 3: Code of the pharmacokinetic atorvastatin model fitted with the nlmixr2 package and simulated with the rxode2 package (second part). Apparent zero-order absorption time (and its modulation by ritonavir) were considered as fixed values in the data frame and event tables, respectively.

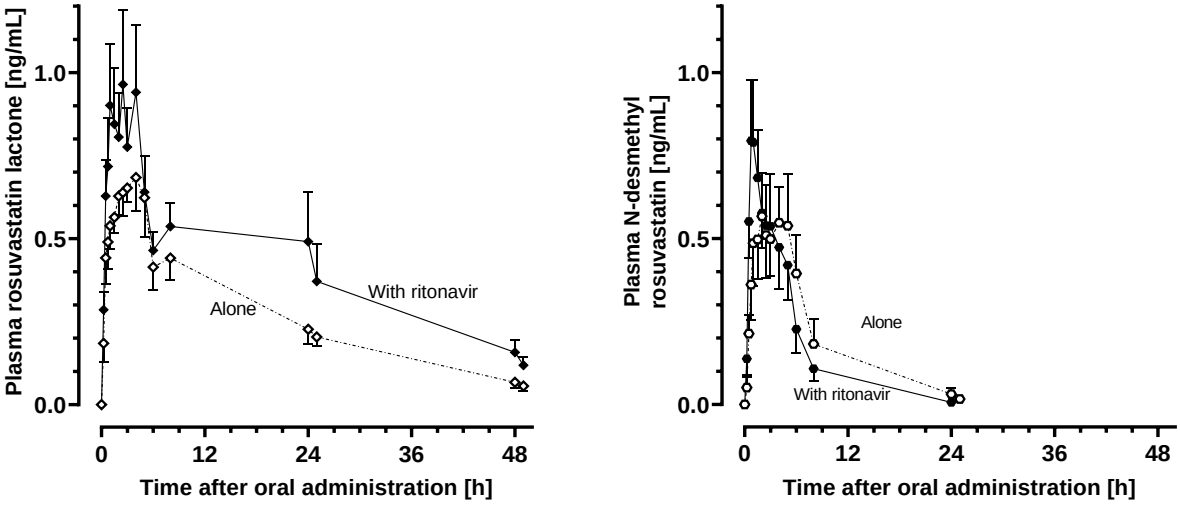
```
nlmixr2_model <- function() {
# parameter definition and inital estimates (starting values)
  ini({
   # central volumen of distribution (fixed to baseline estimate)
      tVc <- fix(log(exp(fit_alone$fixef['tVc']))); label("Vc")
   # (systemic) clearance (fixed to baseline estimate)
      tCl <- fix(log(exp(fit_alone$fixef['tCl']))); label("Cl")
   # peripheral volumen of distribution (fixed to baseline estimate)
      tVt <- fix(log(exp(fit_alone$fixef['tVt']))); label("Vt")
   # inter-compartmental clearance (fixed to baseline estimate)
      tCld <- fix(log(exp(fit_alone$fixef['tCld']))); label("Cld")
   # bioavailability (fixed to 1)
      tf <- fix(log(1)); label("F")
   # RTV effect on (remaining) systemic clearance (fixed to Null effect, no further influence
detectable)
      tRTVeffect <- fix(log(1)); label("RTVeffect")
   # RTV effect on first-pass (gastro-intestional clearance)
      tRTVeffectgut <- c(log(0.5), log(0.8), log(0.9)); label("RTVeffectgut")
   # Inter-individual variability (IIV)
      eta.f ~ 0.3
      eta.Vc ~ 0.6
      eta.Cl ~ 0.5
   # proportional error model
      prop.err <- 0.4
  })
# model block with the error specification and model specification
  model({
   # model-defined initial values of state variables
      Acyp(0)<-1;
      Acypgut(0)<-1;

   # Parameters and IIV
      Vc <- exp(tVc + eta.Vc)
      Cl <- exp(tCl + eta.Cl)
      Vt <- exp(tVt)
      Cld <- exp(tCld)
      f <- exp(tf + eta.f)
      RTVeffect <- exp(tRTVeffect)
      RTVeffectgut <- exp(tRTVeffectgut)

   # parameter calculations
      kdeg <- 0.00866;
      R0=kdeg;

   # output as concentration
      Cc = Ac / Vc;
      Ct = At / Vt;

   # ATV Pharmakokinetic model
      # dosing compartment (used for zero-order absorption)
         d/dt(AaAtor) = 0
      # central compartment
         d/dt(Ac) = - ((Cl *(Acyp))*Cc) + (AaAtor * f *(1/Acypgut)) - (Cld * Cc) + (Cld * Ct)
      # peripheral compartment
         d/dt(At) = (Cld * (Cc - Ct))

   # CYP activity model: (time-dependent) covariate influence of RTV administration
      d/dt(RTV_adminis) = 0;
      d/dt(Acyp) = (R0-(kdeg*(Acyp))) - (Acyp - (Acyp*RTVeffect^(RTV_adminis)));
      d/dt(Acypgut) = (R0-(kdeg*(Acypgut))) - (Acypgut - (Acypgut*RTVeffectgut^(RTV_adminis)));

   # output (dependent) variable
      ATV <- Cc * 1000;
      ATV ~ prop(prop.err)
  })
}
```



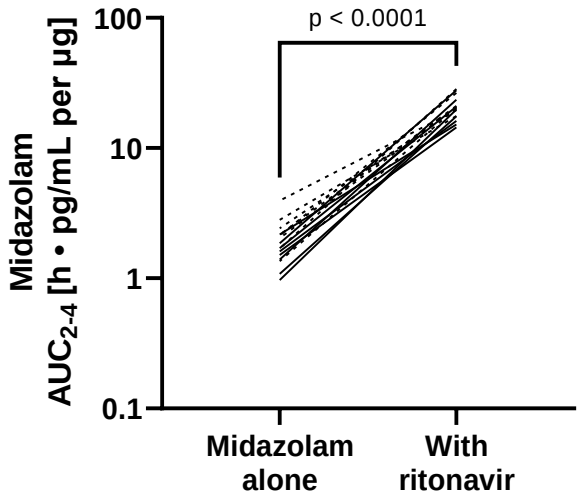
Online Resource 4: Model diagnostics for (visual) inspection of goodness of fit for the final pharmacokinetic model of atorvastatin concentrations (A: Individual and population fits; B/C: Observed versus predicted values of individual and population fits; D/E: Residuals versus time during baseline and under ritonavir treatment; F/G: Residuals versus predicted values during baseline and under ritonavir treatment).



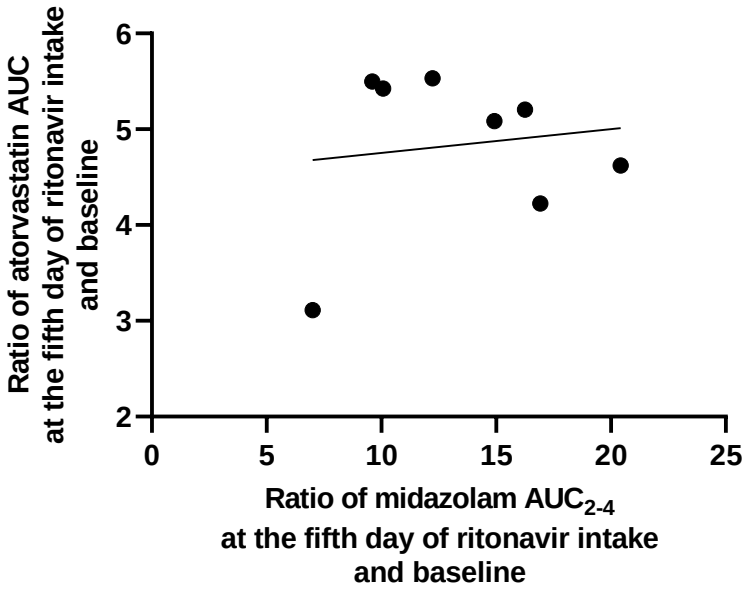
Online Resource 5: Mean (± SEM) plasma concentration-time profiles of atorvastatin lactone (left), 2-hydroxy atorvastatin acid (middle) and 2-hydroxy atorvastatin lactone (right) before and on the fifth day of ritonavir administration (2 x 100 mg/d) in eight healthy volunteers.



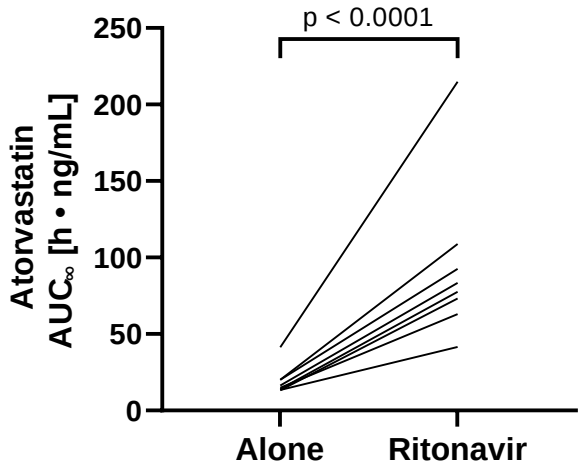
Online Resource 6: Mean (± SEM) plasma concentration-time profiles of rosuvastatin lactone (left) and N-desmethyl rosuvastatin (right) before and on the fifth day of ritonavir administration (2 x 100 mg/d) in eight healthy volunteers.



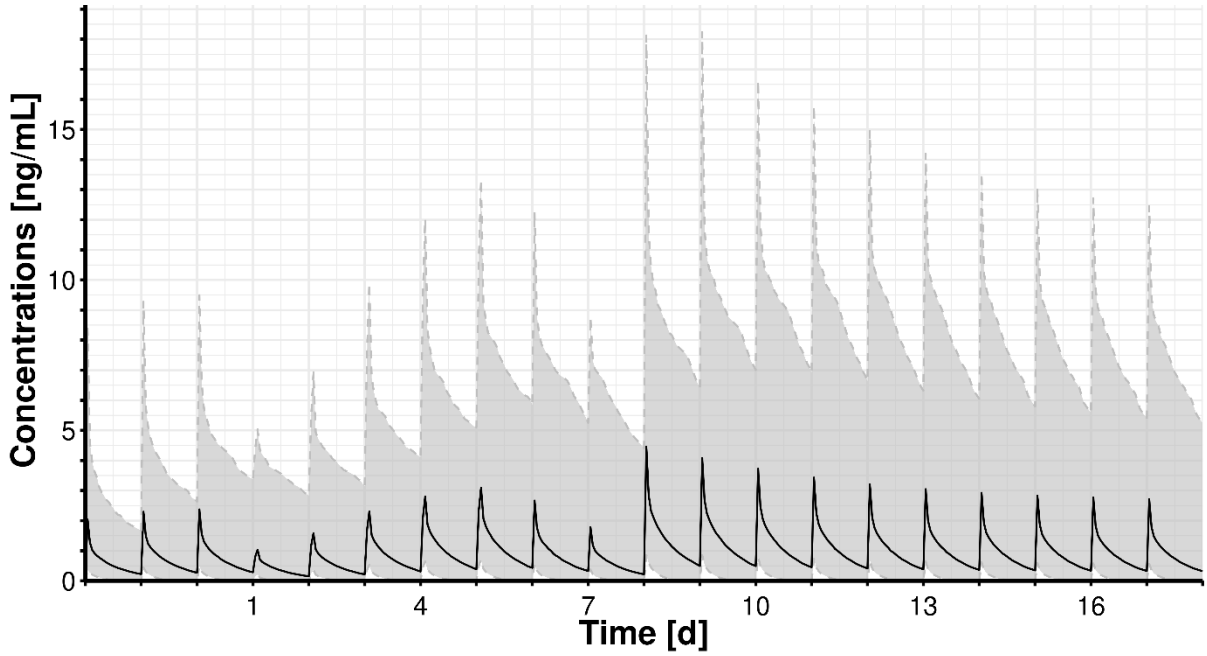
Online Resource 7: Change in midazolam AUC_{2-4} before and on the fifth day of ritonavir (2 x 100 mg/d) in 16 healthy volunteers. Solid lines show participants of the atorvastatin group and dashed lines show participants of the rosuvastatin group. AUC_{2-4}: area under the concentration-time curve from 2-4 h normalized to 1 µg for the two different doses administered.



Online Resource 8: Regression of individual midazolam AUC ratios of the increase at the fifth day of ritonavir intake ($r^2 = 0.02$. $p = 0.75$) as a marker mainly influenced by CYP3A4 activity with the ratio of the atorvastatin AUC increase.



Online Resource 9: Impact of 5 d of ritonavir (2 x 100 mg/d) on the exposure of atorvastatin after administration of a single dose of 10 mg to eight healthy volunteers. AUC_{∞}: area under the concentration-time curve extrapolated to infinity.



Online Resource 10 Simulation with inter-individual variability in 1000 virtual patients most practical dosing regimen (e) according to Figure 5. The solid line marks the median trajectory, while 95 % of all predicted values fall within the grey-shaded region (dashed lines indicate upper and lower bounds).