Supplementary Materials: Model-Informed Precision Dosing during Infliximab Induction Therapy Reduces Variability in Exposure and Endoscopic Improvement between Patients with Ulcerative Colitis

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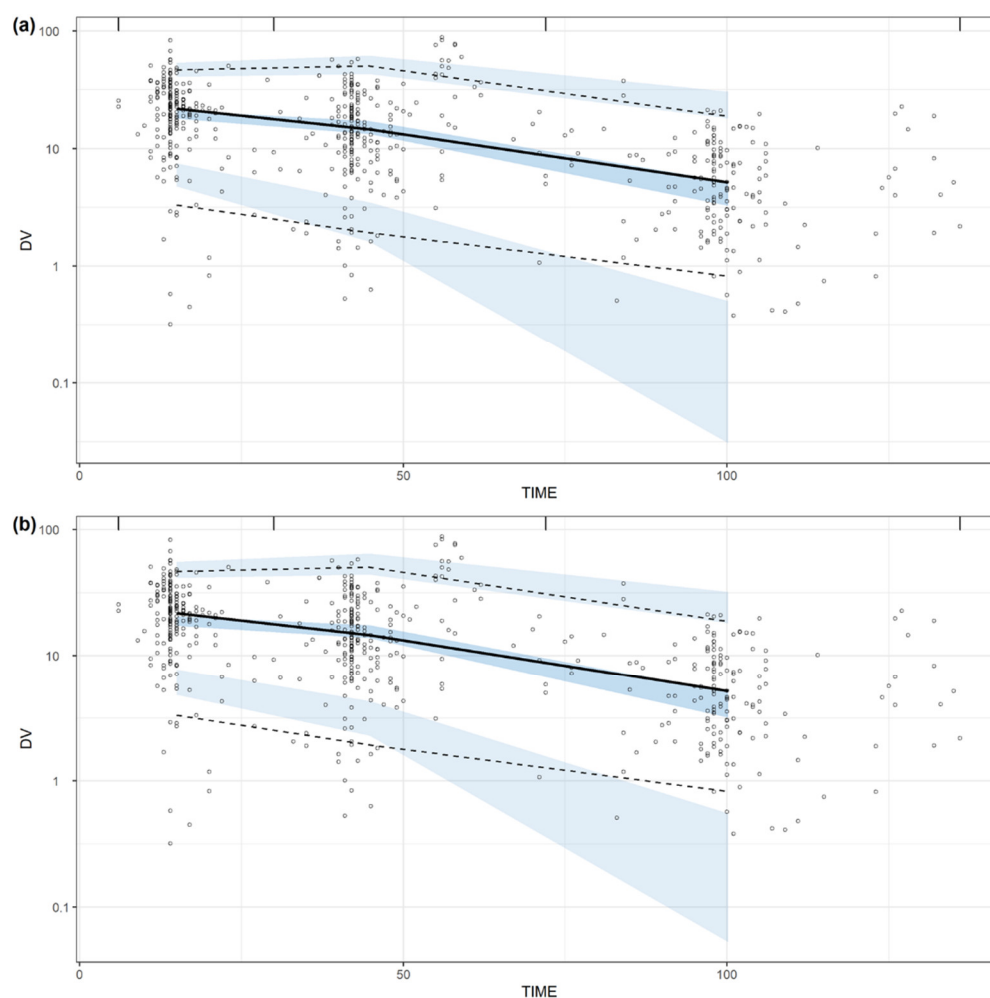

Figure S1. Prediction-corrected visual predictive check of the original population pharmacokinetic model **(a)** and the adapted population pharmacokinetic model **(b)**. The solid line connects the observed median prediction-corrected infliximab serum concentrations (mg/L) per bin. The dashed lines connect the 5th and 95th percentiles of the prediction-corrected observations. Shaded areas indicate the 95% confidence interval of the median and 5th and 95th percentiles of the simulated values. The observed prediction-corrected infliximab concentrations are represented by black open circles.
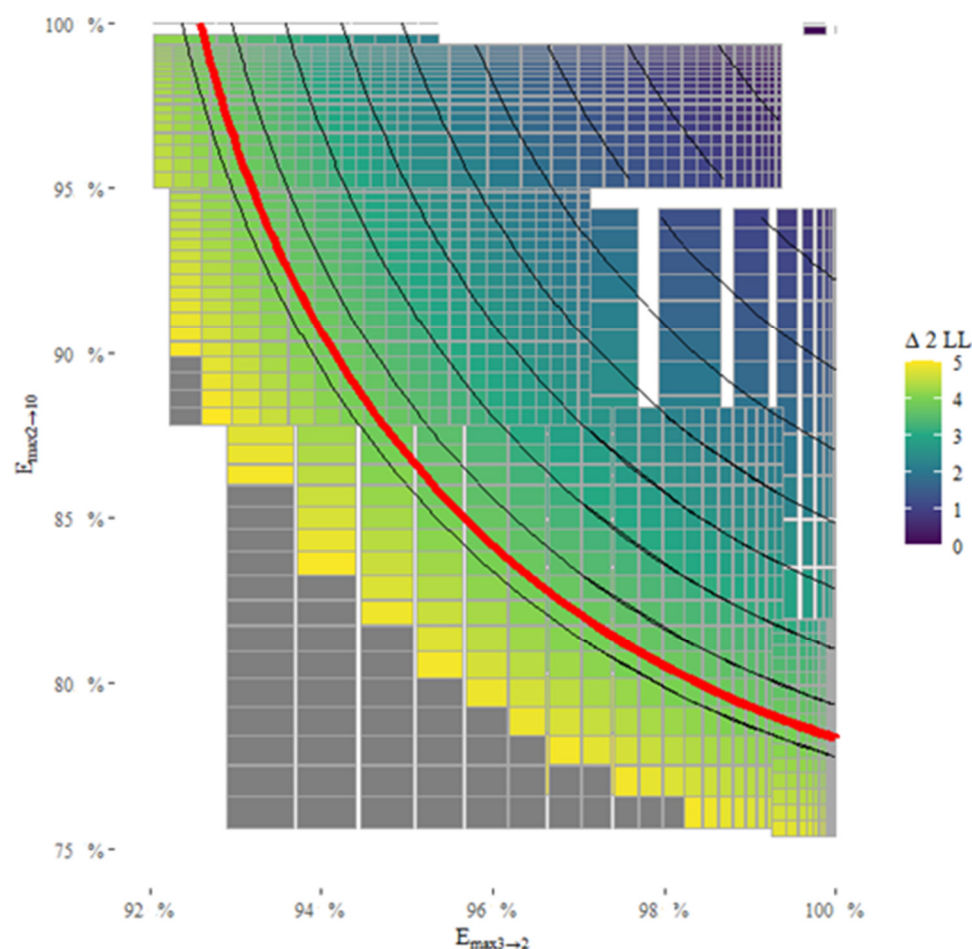
Figure S2. Log-likelihood surface for the exposure-response model. The maximum transition probabilities $E_{max,2\to3}$ and $E_{max,2\to1/0}$ were fixed while associated AUC_{50} values (infliximab exposure metrics associated with a half-maximum transition probability) were estimated. The top right point at 100%–100% represents the original exposure-response model as reported by Dreesen *et al*. [18]. All models top right of the red contour line has a $\Delta2LL <3.84$.

Table S1. Parameter estimates of the original and adapted population pharmacokinetic models.

Parameter	Original Model [18] Estimate	(OFV=2696) (RSE) (%)	Adapted Model Estimate	(OFV=2784) RSE (%)
Typical values				
Elimination rate constant (/d)				
baseline Mayo endoscopic subscore 1 *(/d)*	0.0521	(11)	0.0422	(14)
baseline Mayo endoscopic subscore 2 *(/d)*	0.0543	(3.6)	0.0463	(3.8)
baseline Mayo endoscopic subscore 3 *(/d)*	0.0667	(8.1)	0.0570	(5.0)
albumin	-0.808	(39)		
C-reactive protein	0.0859	(25)		
Volume of distribution (L)	6.34	(3.2)	6.97	(5.0)
fat-free mass	0.544	(29)	0.517	(39)
Corticosteroids [1]	1.33	(6.9)	1.30	(7.7)
Extensive colitis [1]	1.23	(0.019)	1.25	(6.9)
Interindividual variability [2]				
Elimination rate constant (CV%)	29.8	(7.8)	33.4	(5.7)
Volume of distribution (CV%)	26.5	(20)	23.6	(41)
Interoccasion variability				

Parameter	Original Model [18] *Estimate*	(OFV=2696) *(RSE) (%)*	Adapted Model *Estimate*	(OFV=2784) *RSE (%)*
Elimination rate constant (CV%)	18.7	(17)	6.70	(100)
Residual variability				
Proportional residual error (CV%)	19.2	(9.4)	32.9	(5.8)
Additive residual error (mg/L)	0.300	FIX	0.300	FIX

[1] The corticosteroid and extensive colitis effects were modelled as a fold change compared with the reference of no corticosteroids and no extensive colitis, respectively.

[2] Inter-individual CV% was calculated as sqrt(exp(omega)-1). CV, coefficient of variation; OFV, objective function value; RSE: relative standard error.

NONMEM code of the adapted population pharmacokinetic model

```
$PROBLEM     PopPK analysis of infliximab Induction therapy

$INPUT       ID TIME DV MDV EVID AMT RATE OCC EXTCOL MPRE CRP ALB CS WT HT SEX
             ; EXTCOL: Extensive colitis
             ; MPRE:   Mayo endoscopic score pre-induction
             ; CRP:    C-reactive protein
             ; ALB:    Albumin
             ; CS:     Corticosteroids
             ; WT:     Body weight
             ; HT:     Body height
             ; SEX:    Sex (female 0, male 1)

$DATA        PKCOV.csv IGNORE=@ IGNORE(DV .EQ. 0.15) ; exclude the BLQ data

$SUBROUTINE ADVAN6 TRANS1 TOL=6

$MODEL       COMP=(CENTRAL,DEFDOS,DEFOBS) COMP=(CUMAUC)

$PK BMI=WT/(HT**2)
    IF (SEX.EQ.1) THEN
                    FFM= (9.27*1000*WT)/((6.68*1000)+(216*BMI)) ;male
                ELSE
                    FFM= (9.27*1000*WT)/((8.78*1000)+(244*BMI)) ;female
                ENDIF

FLAG1=0
FLAG2=0
FLAG3=0
FLAG4=0

IF (OCC .EQ. 1) FLAG1=1
IF (OCC .EQ. 2) FLAG2=1
IF (OCC .EQ. 3) FLAG3=1
IF (OCC .EQ. 4) FLAG4=1

MPRE1=0
MPRE2=0
MPRE3=0
MPRE4=0

IF (MPRE.EQ.-99) MPRE1=1
IF (MPRE.EQ.1)   MPRE2=1
IF (MPRE.EQ.2)   MPRE3=1
IF (MPRE.EQ.3)   MPRE4=1

TVK = (MPRE1*THETA(4) + MPRE2*THETA(3) + MPRE3*THETA(2) + MPRE4*THETA(1))
TVV = THETA(6) *(THETA(5)**CS) *((FFM/52)**THETA(7)) *(THETA(8)**EXTCOL)

K   = TVK * EXP(ETA(1) +FLAG1*ETA(3)+FLAG2*ETA(4)+FLAG3*ETA(5)+FLAG4*ETA(6))
V   = TVV * EXP(ETA(2))

CL = V*K
S1 = V

$DES DADT(1) =  -K*A(1)
     DADT(2) =  A(1)/S1
     CAUC = A(2) ; cumulative AUC

$ERROR IPRED = F
       IRES  = DV-IPRED
       Y     = IPRED*(1+ERR(1))+ERR(2)
       IWRES = IRES/(SQRT(IPRED**2*SIGMA(1,1)+SIGMA(2,2)))

$THETA (0, 0.057)  ; KE MPRE3
       (0, 0.0463) ; KE MPRE2
       (0, 0.0422) ; KE MPRE1
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```
      (0, 0.617)  ; KE MPRE-99
      (1.3)       ; CS on V
      (6.97)      ; TVV
      (0.517)     ; FFM on V
      (1.25)      ; EXTCOL on V

$OMEGA 0.106.       ;ETA(1)
       0.5          ;ETA(2)
$OMEGA BLOCK(1) 0.054 ;IOV
$OMEGA BLOCK(1) SAME
$OMEGA BLOCK(1) SAME
$OMEGA BLOCK(1) SAME

$SIGMA 0.103
       0.09 FIX

$ESTIMATION MAXEVAL=9999 NOABORT PRINT=1 NSIG=2 METHOD=1 INTER LAPLACE
$COVARIANCE

$TABLE ID DV TIME MDV EVID PRED IPRED RES WRES CWRES IWRES K CL V ONEHEADER NOPRINT NOAPPEND
FILE=PKCOV.sdtab
$TABLE ID K CL V ETA(1) ETA(2) ETA(3) ETA(4) ETA(5) ETA(6) FIRSTONLY NOAPPEND NOPRINT
FILE=PKCOV.patab
$TABLE ID EXTCOL MPRE CS SEX ONEHEADER NOPRINT FILE=PKCOV.catab
$TABLE ID CRP ALB WT HT ONEHEADER NOPRINT FILE=PKCOV.cotab
```

NONMEM code of the adapted exposure-response model

```
$PROBLEM MPRE==2,3, CAUC drives change

$INPUT ID DV C14 CAUC14 MPRE MPST CDOS CAUC TIPD
       ; TIPD: Time to PD assessment (post-induction endoscopy)

$DATA PKPD.csv IGNORE=@ IGNORE(MPRE.EQ.1) IGNORE(TIPD.LE.30) IGNORE(TIPD.GE.132)

$PRED PKMETRIC = CAUC
      EMAX1=1/(1+exp(-THETA(6)))
      EMAX2=1/(1+exp(-THETA(7)))

; transition 3 -> 2
X5032  = THETA(1) + ETA(1)
SL32   = THETA(2)
DF32   = (PKMETRIC/X5032)**SL32
D32    = EMAX1*DF32/(1+DF32)

; transition 2 -> 10
X50210 = THETA(3)
SL210  = THETA(4)
DF210  = (PKMETRIC/X50210)**SL210
D210   = EMAX2*DF210/(1+DF210)

; fraction of patients at 3 and 2 before treatment
P3B    = THETA(5)
P2B    = 1 - THETA(5)

FP33   = (1 - D32)
FP32   = D32 * (1 - D210)
FP310  = D32 * D210

FP23   = (1 - D32)
FP22   = (1 - D210 - (1 - D32))
FP210  = D210

FCHK1  = FP33+FP32+FP310+FP23+FP22+FP210-1 ; -1 compensates for 2 initial states

; fractions in respective bins
IF (DV.EQ.32)              Y=P3B *FP32    ; 3 -> 2
IF (DV.EQ.31.OR.DV.EQ.30)  Y=P3B *FP310   ; 3 -> <2
IF (DV.EQ.33)              Y=P3B *FP33    ; 3 -> 3
IF (DV.EQ.23)              Y=P2B *FP32    ; 2 -> 3
IF (DV.LT.22)              Y=P2B *FP210   ; 2 -> <2
IF (DV.EQ.22)              Y=P2B *FP22    ; 2 -> 2

FX3   = P3B*FP33 + P2B*FP23
FXN3  = 1-FX3

FX2   = P3B*FP32 + P2B*FP22
FXN2  = 1-FX2

FX10  = P3B*FP310 + P2B*FP210
FXN10 = 1-FX10

$THETA (0, 295, 1000)   ; X5032
       1 FIX            ; SL32
       (0, 1380, 10000) ; X50210
       1 FIX            ; SL210
       (0, 0.516, 1)    ; prob at 3
       <<REPLACE_DURING_LIKELIHOODPROFILING>> ; EMAX1
       <<REPLACE_DURING_LIKELIHOODPROFILING>> ; EMAX2

$OMEGA 0 FIX

$ESTIMATION MAX=9990 SIGDIG=3 METH=1 LIKE LAPLACE NUMERICAL NOABORT
$COVARIANCE
```

tdmore **R code for the sensitivity analysis**
```
<please see separate files – PDSensitivity.zip>
```

tdmore **R code for the simulations**
```
<please see separate files – simulation.zip>
```