Population Pharmacokinetics and Exposure–Response Analysis of PMX001 in Acute Severe Ulcerative Colitis

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2026-01-02

Introduction

Acute severe ulcerative colitis affects a quarter of patients with ulcerative colitis, either at initial presentation or later in the course of the disease. Acute severe ulcerative colitis represents a medical emergency, with 36% of patients experiencing multiple episodes during their lifetimes, and about 40% requiring colectomy, along with significant morbidity. Corticosteroids are the primary treatment for acute severe ulcerative colitis, yet one in three patients fails to respond. Infliximab and cyclosporin emerged as the second-line rescue treatment options after corticosteroid failure, but with colectomy rates plateauing at about 10%, there is an unmet medical need.

Objectives

The primary aim of this study was to characterize the population pharmacokinetics of PMX001 in adult patients with acute severe ulcerative colitis. In addition, the analysis sought to identify and quantify the influence of key clinical and demographic covariates on PMX001 exposure. Finally, the study explored the relationship between PMX001 exposure metrics and colectomy-free survival, with the goal of understanding how drug exposure may impact clinical outcomes in this critically ill patient population.

Methods

Population pharmacokinetic modeling was conducted using NONMEM (version 5.4.0), with model execution and workflow management supported by Pirana and Perl-speaks-NONMEM

(PsN). Data processing and visualization were performed in R (version 4.5.2).

Below-limit-of-quantification (BLQ) observations were handled using the M7+ method, selected over M3 due to computational and time constraints, as well as minimal anticipated impact on parameter estimates in this dataset. Model development followed an iterative approach comprising at least three iterations. This approach was executed for both the base and the covariate model development.

Covariate selection was performed using the SCM+ algorithm implemented in PsN, evaluating covariates such as antidrug antibody (= immunogenicity, `ADA`), age, serum albumin concentration (`ALB`), body weight (`BW`), serum creatinine concentration (`CREAT`), and sex. Model robustness and parameter precision were assessed through nonparametric bootstrap analysis with 2000 replicates; in cases of computational limitations, 1000 replicates were used, which provide comparable precision. Predictive performance was evaluated using visual predictive checks (VPC) based on 200 simulated datasets.

Running Code

```
data <- read.table("dataset.txt",
                   sep = " ",         # space-separated
                   na.strings = ".", # treat "." as NA
                   header = TRUE)

LLOQ <- 1                            # mg/L

data <- data %>%
  mutate(DOSE = as.numeric(DOSE),
         EVID = case_when(
           is.na(CONC) & DOSE!=0 ~ 1,
           CONC>=0 ~ 0,
           is.na(CONC) & is.na(DOSE) ~ 2),
         BLQ = case_when(
           CONC<1 ~ 1,
           CONC>=1 ~ 0,
           is.na(CONC) ~ 0))

data <- data %>% group_by(ID) %>%
  fill(c(BW),.direction = "downup") %>%
  fill(c(ALB),.direction = "downup") %>%
  fill(c(CREAT),.direction = "downup") %>%
  ungroup()
```

```r
data <- data %>%
  group_by(ID) %>%
  arrange(TIME, .by_group = TRUE) %>%
  mutate(ADA = case_when(
    ID %in% 71:75 ~ as.integer(cumany(ADA == 1)),
    TRUE          ~ ADA)) %>%
  ungroup()


data$DOSE = data$DOSE * data$BW # dose (mg) = dose (mg/kg) * body weight (kg)

write.table(data, file = "dataset_clean.txt", quote = FALSE, sep = " ", na = ".")
write.csv(data, file = "dataset_clean.csv", quote = FALSE, na = ".", row.names = FALSE)
```

```r
datacor <- data %>%
     select(ADA, AGE, ALB, BW, CREAT, COL, SEX)
rcorr(as.matrix(datacor), type = "spearman")$r %>%
  signif(digits = 3)
```

```
          ADA     AGE      ALB       BW   CREAT      COL      SEX
ADA    1.0000 0.01860  0.01920 -0.13200 -0.1500 -0.00650 -0.0324
AGE    0.0186 1.00000  0.09270  0.01920  0.1690  0.00324  0.0620
ALB    0.0192 0.09270  1.00000 -0.05100 -0.1180  0.00658  0.1050
BW    -0.1320 0.01920 -0.05100  1.00000  0.0922 -0.00759  0.3480
CREAT -0.1500 0.16900 -0.11800  0.09220  1.0000 -0.01440  0.1120
COL   -0.0065 0.00324  0.00658 -0.00759 -0.0144  1.00000 -0.0131
SEX   -0.0324 0.06200  0.10500  0.34800  0.1120 -0.01310  1.0000
```

```r
rcorr(as.matrix(datacor), type = "spearman")$P %>%
  signif(digits = 3)
```

```
           ADA      AGE      ALB       BW CREAT   COL      SEX
ADA         NA 4.59e-02 3.97e-02 0.00e+00 0.000 0.486 5.22e-04
AGE   0.045900       NA 0.00e+00 3.98e-02 0.000 0.729 3.05e-11
ALB   0.039700 0.00e+00       NA 4.66e-08 0.000 0.481 0.00e+00
BW    0.000000 3.98e-02 4.66e-08       NA 0.000 0.416 0.00e+00
CREAT 0.000000 0.00e+00 0.00e+00 0.00e+00    NA 0.122 0.00e+00
COL   0.486000 7.29e-01 4.81e-01 4.16e-01 0.122    NA 1.62e-01
SEX   0.000522 3.05e-11 0.00e+00 0.00e+00 0.000 0.162       NA
```

```r
length(unique(data$ID))
```

```
[1] 75
```

Model File

```
;; 1. Based on: run02
;; 2. Description: PMX001 2CMT LINEAR M7+ (COV MODEL)
;; x1. Joshua I., Ali K.
;; 2025-12-29

$PROBLEM PMX001 Two Compartment

$INPUT DUMMY=DROP ID TIME WEEK DOSE=AMT RATE CONC=DV ADA BW ALB SEX AGE CREAT COL EVID BLQ

$DATA dataset_clean.csv IGNORE=@

$ABBR DERIV2=NO

$SUBROUTINES
ADVAN13 ; general nonlinear model
TOL=9   ; tolerance for $DES, higher TOL: more accurate, but slower computation
        ; TOL=9 -> DES will aim for accuracy of 1E-9 for each integration step

$MODEL
NCOMP=2                      ; number of compartments
COMP=(DOSE, DEFDOSE, DEFOBS) ; first (central) compartment
COMP=(PERIPH)                ; second (peripheral) compartment

$PK
;; time after last dose
IF (EVID.EQ.1) LASTDOSE = TIME
TAD = TIME - LASTDOSE

;; typical values
 TVCL = THETA(1)
 TVV1 = THETA(2)
 TVV2 = THETA(3)
  TVQ = THETA(4)

;; covariate determined from SCM+ based on base model
IF(ADA.EQ.0) V1ADA = 1               ; Most common
IF(ADA.EQ.1) V1ADA = ( 1 + THETA(5))
V1COV = V1ADA

;; individual values
```

```
   CL = TVCL * EXP(ETA(1))
   V1 = TVV1 * EXP(ETA(2)) * V1COV
   V2 = TVV2
    Q = TVQ

;; derived parameters
  K10 = CL/V1
  K12 = Q/V1
  K21 = Q/V2

;; scaling factors
   S1 = V1/1 ; scale prediction based on DOSE (mmol) and CONC (mmol/L)
   S2 = V2/1

$THETA ; values are determined in 3 iterations
(0.01,  1.32,   3)   ; CL (L/d) [1]
(0.01,  4.7,    8)   ; V1 (L) [2,3]
(0.01,  0.232,  1)   ; V2 (L)
(0.001, 0.0574, 1.5) ; Q  (L/d)
(-1,    7.86,   20)  ; V1ADA

$DES DADT(1) = -K10*A(1) -K12*A(1) +K21*A(2) ; ODE for central    compartment
     DADT(2) =            K12*A(1) -K21*A(2) ; ODE for peripheral compartment

$ERROR
IPRED = F
LLOQ = 1  ; (mg/L)

;; residual error standard deviations
PROP_SD = SIGMA(1)
ADD_SD  = SIGMA(2)

;; BLQ inflation for M7+ censoring method
IF (BLQ.EQ.1) ADD_SD = ADD_SD + LLOQ

;; final residual error
W = SQRT(ADD_SD**2+PROP_SD**2)

IF (W.LE.0.000001) W=0.000001 ; Protective code

IRES=CONC-IPRED
IWRES=IRES/W
```

```
Y = IPRED * (1 + EPS(1)) + EPS(2)

$OMEGA ; interindividual variability
0.539  ; IIV CL
0.235  ; IIV V

$SIGMA          ; residual variability
0.131           ; EPS(1), proportional
0.000000005 FIX ; EPS(2); additive, required by M7+ censoring method

$EST
METHOD=1 INTERACTION; FOCE-I
MAXEVAL=9999
SIG=3
PRINT=5

$COVARIANCE PRINT=E UNCONDITIONAL MATRIX=S

$TABLE ; output table
ID TIME TAD DV EVID PRED IPRED WRES IWRES RES IRES CWRES CL V1 V2 Q K10 K12 K21 ADASEX COL BW

;; REFERENCES
;; 1) https://www.ncbi.nlm.nih.gov/books/NBK557889/
;; 2) https://pmc.ncbi.nlm.nih.gov/articles/PMC8301575/
;; 3) https://ascpt.onlinelibrary.wiley.com/doi/abs/10.1016/j.clpt.2004.12.212
```