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

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Introduction

Acute severe ulcerative colitis (ASUC) 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 ciclosporin 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 (popPK) 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

Data Preparation

```
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),
         CONC_M7 = ifelse(CONC < 1, 0, CONC))

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


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)
```

Data from a Phase 1/2 study of the investigational medicinal product PMX001 was collected for **75 adult patients** with acute severe ulcerative colitis over the course of **17 weeks**. In this study, patients received four times one dose of 3, 6 or 9 mg/kg per two weeks. This data was processed in R (version 4.5.2). Plasma concentrations (in mg/L) were measured using enzyme-linked immuno-sorbent assay (ELISA), which had a lower limit of quantification of 1.0 mg/L.

Below-limit-of-quantification (BLQ) observations were handled using the M7+ method during the model development. The M3 method was investigated for the final PopPK model. Parameter estimates for the model development followed an iterative approach comprising at least three iterations. This approach was executed for both the base and the covariate model development.

Population pharmacokinetic (PopPK) modeling was conducted using NONMEM, with model execution and workflow management supported by Pirana and Perl-speaks-NONMEM (PsN). Based on the censored dataset, a two-compartment base model with linear elimination was constructed.

Covariate selection was performed using the enhanced stepswise covariate model (in short, SCM+) algorithm integrated in PsN. The covariates in the dataset were as follows: antidrug antibody (= immunogenicity, `ADA`), age, serum albumin concentration (`ALB`), body weight (`BW`), serum creatinine concentration (`CREAT`), and sex. Covariates that were significantly correlated with the PK parameters, were assessed for clinical relevance using a forest plot, generated from the R package `PMXForest`. 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 1000 simulated datasets.

Running Code

```
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
```

```
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
```

```
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
```

Covariate Relevance: Forest Plot

This section adds a forest plot to assess the relevance of key covariates (CREAT, SEX, ALB, BW, ADA, AGE) on exposure in the cleaned dataset.

```
library(PMXForest)
library(ggplot2)

theme_set(theme_bw())

ALB_REF_CL <- 31.88
ALB_REF_V1 <- 31.85
BW_REF_V1  <- 65.93
```

```r
dfCovs <- PMXForest::createInputForestData(list(
  ADA = c(0, 1),
  ALB = c(25, 45),
  BW  = c(50, 90)
))

covnames <- c(
  "ADA negative","ADA positive",
  "ALB 25 g/L","ALB 45 g/L",
  "BW 50 kg","BW 90 kg"
)

covariateGroupNames <- c("ADA","Albumin","Body weight")

functionListName <- c("CL","V1")

# ---- Helpers (copy as-is) ----
.once_log <- local({ .done <- FALSE; function(expr) { if (!.done) { .done <<- TRUE; force(ex
.normalize_thetas <- function(thetas) {
  if (is.data.frame(thetas)) thetas <- unlist(thetas, use.names = TRUE)
  if (is.matrix(thetas))     thetas <- as.vector(thetas)
  nm <- names(thetas)
  if (is.null(nm) || any(is.na(nm)) || all(nm == "")) nm <- paste0("THETA", seq_along(thetas)
  nm <- toupper(nm); nm <- gsub("\\s+", "", nm); nm <- gsub("[()]", "", nm); nm <- gsub("[^A-
  names(thetas) <- nm
  thetas
}
.get_theta <- function(thetas, k) {
  nm <- names(thetas)
  candidates <- c(paste0("THETA", k), paste0("THETA(", k, ")"), paste0("THETA.", k), paste0("
  for (c in candidates) { idx <- match(c, nm, nomatch = 0); if (idx > 0) return(unname(theta
  if (length(thetas) >= k) return(unname(thetas[[k]]))
  stop(sprintf("Theta %d not found in 'thetas'. Available names: %s", k, paste(nm, collapse =
}
```

```r
# ---- Your covariate functions (robust) ----
f_CL <- function(thetas, df, ...) {
  thetas <- .normalize_thetas(thetas)
  .once_log(message("f_CL: thetas names = ", paste(names(thetas), collapse = ", ")))
  ADA <- df[["ADA"]]; ALB <- df[["ALB"]]
  TH6 <- .get_theta(thetas, 6)
  TH7 <- .get_theta(thetas, 7)
```

```
  TH5 <- .get_theta(thetas, 5)
  CLALB <- if (ALB <= ALB_REF_CL) 1 + TH6 * (ALB - ALB_REF_CL) else 1 + TH7 * (ALB - ALB_REF
  CLADA <- if (ADA == 0) 1 else (1 + TH5)
  CLALB * CLADA
}

f_V1 <- function(thetas, df, ...) {
  thetas <- .normalize_thetas(thetas)
  .once_log(message("f_V1: thetas names = ", paste(names(thetas), collapse = ", ")))
  ALB <- df[["ALB"]]; BW <- df[["BW"]]
  TH8 <- .get_theta(thetas, 8)
  TH9 <- .get_theta(thetas, 9)
  TH10 <- .get_theta(thetas, 10)
  TH11 <- .get_theta(thetas, 11)
  V1ALB <- if (ALB <= ALB_REF_V1) 1 + TH8 * (ALB - ALB_REF_V1) else 1 + TH9 * (ALB - ALB_REF
  V1BW  <- if (BW  <= BW_REF_V1) 1 + TH10 * (BW - BW_REF_V1) else 1 + TH11 * (BW - BW_REF_V1)
  V1ALB * V1BW
}

# ---- Data & parameters ----
extFile <- "final_backward.ext"
covFile <- "final_backward.cov"

dfSamplesCOV <- getSamples(covFile, extFile, n = 175)

# Optional but recommended: normalize column names at the source
nm <- names(dfSamplesCOV)
nm <- toupper(nm); nm <- gsub("\\s+", "", nm); nm <- gsub("[()]", "", nm); nm <- gsub("[^A-Z
names(dfSamplesCOV) <- nm

# If your model truly has 11 THETAs, this should be TRUE:
stopifnot(sum(grepl("^THETA[0-9]+$", names(dfSamplesCOV))) >= 11)

# ---- Compute ----
dfresCOV <- getForestDFSCM(
  dfCovs           = dfCovs,
  cdfCovsNames     = covnames,
  functionList     = list(f_CL, f_V1),
  functionListName = functionListName,
  noBaseThetas     = 11,
  dfParameters     = dfSamplesCOV,
  iMiss            = -99
```

```
)

print(dfresCOV)
```

```
   ADA ALB  BW GROUP GROUPNAME COVNUM      COVNAME PARAMETER   REFFUNC
1    0 -99 -99     1       ADA      1 ADA negative        CL 66.649929
2    0 -99 -99     1       ADA      1 ADA negative        V1 -7.805334
21   1 -99 -99     1       ADA      2 ADA positive        CL 66.649929
22   1 -99 -99     1       ADA      2 ADA positive        V1 -7.805334
3  -99  25 -99     2       ALB      3   ALB 25 g/L        CL 66.649929
31 -99  25 -99     2       ALB      3   ALB 25 g/L        V1 -7.805334
4  -99  45 -99     2       ALB      4   ALB 45 g/L        CL 66.649929
41 -99  45 -99     2       ALB      4   ALB 45 g/L        V1 -7.805334
5  -99 -99  50     3        BW      5     BW 50 kg        CL 66.649929
51 -99 -99  50     3        BW      5     BW 50 kg        V1 -7.805334
6  -99 -99  90     3        BW      6     BW 90 kg        CL 66.649929
61 -99 -99  90     3        BW      6     BW 90 kg        V1 -7.805334
    REFFINAL     POINT POINT_NOVAR_REL_REFFUNC POINT_REL_REFFUNC
1  66.283007 11.569405               0.1731479         0.1735847
2  -9.517972 -7.805334               1.0000000         1.0000000
21 66.283007 66.649929               1.0000000         1.0000000
22 -9.517972 -7.805334               1.0000000         1.0000000
3  66.283007  8.974944               0.1344598         0.1346580
31 -9.517972 -2.407273               0.2142993         0.3084138
4  66.283007 20.790843               0.3150472         0.3119410
41 -9.517972  1.324508              -0.1077517        -0.1696927
5  66.283007 66.649929               1.0000000         1.0000000
51 -9.517972  3.494247              -0.3209507        -0.4476742
6  66.283007 66.649929               1.0000000         1.0000000
61 -9.517972 -1.360140               0.1435822         0.1742577
   POINT_REL_REFFINAL COVEFF          Q1 Q1_REL_REFFUNC Q1_REL_REFFINAL
1           0.1745456   TRUE   4.0914854     0.06138769      0.06172752
2           0.8200627  FALSE -28.3314260     3.62975200      2.97662415
21          1.0055357  FALSE  23.6149167     0.35431270      0.35627407
22          0.8200627  FALSE -28.3314260     3.62975200      2.97662415
3           0.1354034   TRUE   6.7446849     0.10119568      0.10175587
31          0.2529186   TRUE  -4.6283702     0.59297531      0.48627692
4           0.3136678   TRUE  17.0375538     0.25562749      0.25704256
41         -0.1391587   TRUE   0.1349830    -0.01729369     -0.01418191
5           1.0055357  FALSE  23.6149167     0.35431270      0.35627407
51         -0.3671209   TRUE  -0.8307102     0.10642853      0.08727806
6           1.0055357  FALSE  23.6149167     0.35431270      0.35627407
```

```
61          0.1429022   TRUE  -3.6535852     0.46808827      0.38386172
           Q2 Q2_REL_REFFUNC Q2_REL_REFFINAL Q1_NOVAR_REL_REFFUNC
1   17.766566     0.26656542      0.26804104           0.16123358
2    1.950321    -0.24987024     -0.20490926           1.00000000
21 104.817567     1.57265835      1.58136409           1.00000000
22   1.950321    -0.24987024     -0.20490926           1.00000000
3   11.029092     0.16547793      0.16639397           0.10589538
31  -0.267811     0.03431129      0.02813740          -0.34939699
4   23.221146     0.34840466      0.35033332           0.20135095
41   2.376338    -0.30445048     -0.24966848          -0.86395610
5  104.817567     1.57265835      1.58136409           1.00000000
51   7.541765    -0.96623226     -0.79237101          -1.38647671
6  104.817567     1.57265835      1.58136409           1.00000000
61   0.313666    -0.04018610     -0.03295512           0.07661551
   Q2_NOVAR_REL_REFFUNC REFROW
1             0.1858378     NO
2             1.0000000     NO
21            1.0000000     NO
22            1.0000000     NO
3             0.2843007     NO
31            1.4690620     NO
4             0.8599133     NO
41            0.2581927     NO
5             1.0000000     NO
51           -0.1257661     NO
6             1.0000000     NO
61            0.5962417     NO
```

```r
F1 <- forestPlot(dfresCOV,parameters= c("CL", "V1"),
           groupNameLabels    = covariateGroupNames,
           referenceInfo      = "Reference: (CL) ADA = 0 (negative), ALB = 31.88 g/L; (V1) AL
           noVar              = 4,
           size = theme_get()$text$size * 0.92,
           tabTextSize = 10)
ggsave("PMXForestSCMPlus.png", plot = F1, width = 9.4, height = 5, units = "in")
```