

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

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1 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 cyclosporine 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.

2 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.

3 Methods

3.1 Data Preparation

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 (LLOQ) of 1.0 mg/L.

Below-limit-of-quantification (BLQ) observations were handled using the M7+ method during the model development. M7+ method is a censoring method that replaces all BLQ values with **zero**, and adds the LLOQ to the additive error. Missing covariate data were filled using simple imputation with the function `fill(c(covariate), .direction = "downup")` from **tidyverse** package. Parameter estimates for the model development followed an iterative approach comprising at least three iterations, until the difference between estimates no longer surpassed one percent. This approach was executed for both the base and the covariate model development.

3.2 Model Development and Validation

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 stepwise 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. From there, the final model was generated (see Appendix A1). Model robustness and parameter precision were assessed through sampling importance resampling (SIR); 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.

3.3 Exposure-Response Analysis

After establishing and validating the popPK model, an exposure-response model was set up for colectomy at week 12. A quantile-quantile (QQ) plot for area under the curve from zero to last point ($AUC_{0-tlast}$) and colectomy was generated using ggplot2 package.

```
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
```

4 Results

4.1 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_V1 <- 31.84

cs <- PMXForest::getCovStats(
  data,
  covariates = "ALB",
  minLevels = 10,
  probs = c(0.05, 0.95),
  idVar = "ID",
  missVal = -99,
  nsig = 3
)

dfCovs <- PMXForest::createInputForestData(list(
  ADA = c(0, 1),
  ALB = c(cs$ALB["5%"], cs$ALB["95%"])
))

covnames <- c(
  "ADA negative", "ADA positive",
  "ALB 27 g/L", "ALB 35 g/L"
)

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

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

# ---- Helpers (copy as-is) ----
.once_log <- local({ .done <- FALSE; function(expr) { if (!.done) { .done <- TRUE; force(.done) } } })
.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-Z]", "", nm)
names(thetas) <- nm
thetas
}
.get_theta <- function(thetas, k) {
  nm <- names(thetas)
  candidates <- c(paste0("THETA", k), paste0("THETA(", k, ")"), paste0("THETA.", k), paste0("THETA..", k))
  for (c in candidates) { idx <- match(c, nm, nomatch = 0); if (idx > 0) return(unname(the
  if (length(thetas) >= k) return(unname(thetas[[k]])))
  stop(sprintf("Theta %d not found in 'thetas'. Available names: %s", k, paste(nm, collapse =
}

# ---- 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"]]
  TH5 <- .get_theta(thetas, 5)
  CLADA <- if (ADA == 0) 1 else (1 + TH5)
  CLADA
}

f_V1 <- function(thetas, df, ...) {
  thetas <- .normalize_thetas(thetas)
  .once_log(message("f_V1: thetas names = ", paste(names(thetas), collapse = ", ")))
  ALB <- df[["ALB"]]
  TH6 <- .get_theta(thetas, 6)
  V1ALB <- 1 + TH6 * (ALB - ALB_REF_V1)
  V1ALB
}

# ---- Data & parameters ----
extFile <- "run12.ext"
covFile <- "run12.cov"

dfSamplesCOV <- getSamples(covFile, extFile, n = 1000)

# 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]", "", nm)
names(dfSamplesCOV) <- nm

# ---- Compute ----
dfresCOV <- getForestDFSCM(

```

```

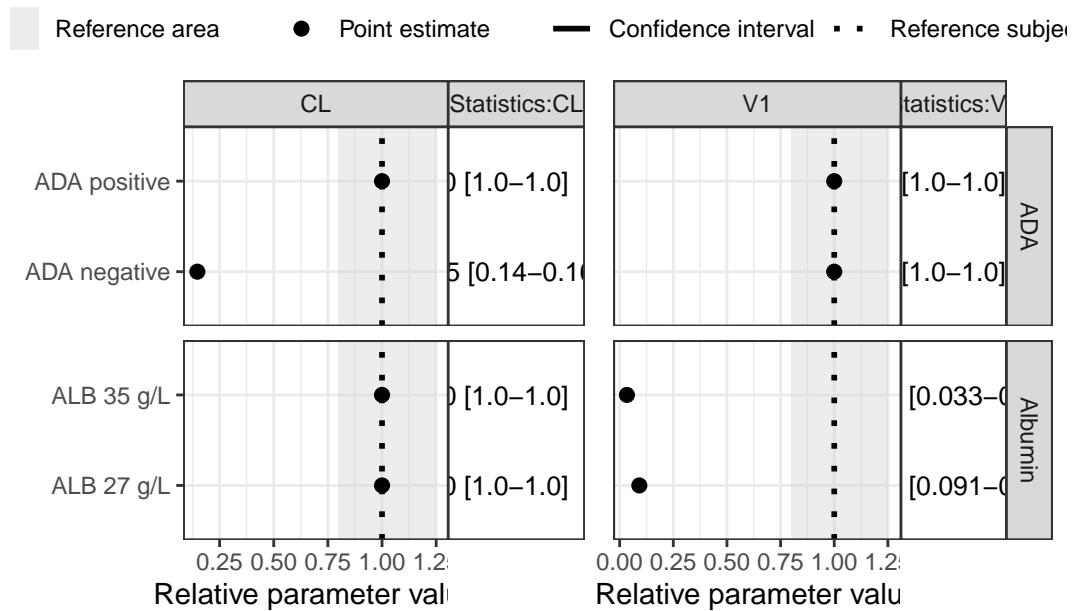
dfCovs      = dfCovs,
cdfCovsNames = covnames,
functionList = list(f_CL, f_V1),
functionListName = functionListName,
noBaseThetas = 6,
dfParameters = dfSamplesCOV,
iMiss       = -99
)

```

```

forestPlot(dfresCOV, parameters= c("CL", "V1"),
            groupNameLabels = covariateGroupNames,
            referenceInfo    = "Reference: (CL) ADA = 0 (negative), ALB = 31.88 g/L; (V1)",
            noVar             = 4,
            size = theme_get()$text$size * 0.92,
            tabTextSize = 10)

```



Reference: (CL) ADA = 0 (negative), ALB = 31.88 g/L; (V1) ALB = 31.85 g/L, BW = 1.03 mg/L

```
ggsave("PMXForestSCMPlus.png", width = 11, height = 7, units = "in")
```

5 Discussion

6 Conclusion

Acknowledgements

References

Appendix

A1. Final Model

```
; ; 1. Based on: run09
;; 2. Description: PMX001 2CMT LINEAR M7+
;; Joshua I., Ali K.
;; 2026-01-07

$PROBLEM PMX001 Two Compartment Model with Linear Elimination (M7+ Censoring)

$INPUT DUMMY=DROP ID TIME WEEK DOSE=AMT RATE CONC=DROP ADA BW ALB SEX AGE
CREAT COL EVID BLQ CONC_M7=DV

$DATA dataset_clean.csv IGNORE=@

$ABBR DERIV2=NO

$SUBROUTINES
ADVAN13 ; general nonlinear model
TOL=5 ; tolerance for $DES, higher TOL: more accurate, but slower to compute

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

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

; fixed effects
TVCL = THETA(1)
TVV1 = THETA(2)
TVV2 = THETA(3)
TVQ = THETA(4)

; covariate effects
IF (ADA.EQ.0) CLADA = 1 ; most common
IF (ADA.EQ.1) CLADA = (1 + THETA(5))
V1ALB = ( 1 + THETA(6)*(ALB - 31.84))

; individual values with random effects (ETAs)
```

```

CL = TVCL * EXP(ETA(1)) * CLADA
V1 = TVV1 * EXP(ETA(2)) * V1ALB
V2 = TVV2
Q = TVQ

K10 = CL/V1
K12 = Q/V1
K21 = Q/V2

; scaling factor: DOSE (mg) and DV (mg/L)
S1 = V1/1
S2 = V2/1

$THETA ; values are determined in 3 iterations
(0.001, 1.41, 3) ; CL (L/d) [1]
(0.001, 4.73, 7) ; V1 (L) [2,3]
(0.01, 0.231, 0.8) ; V2 (L)
(0.001, 2.15, 5) ; Q (L/d)
(0.001, 5.78, 8) ; CLADA
(-0.140,-0.127,-0.001) ; V1ALB

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

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

PROP_SD = SIGMA(1)
ADD_SD = SIGMA(2)

IF (BLQ.EQ.1) ADD_SD = ADD_SD + LLOQ ; BLQ inflation
W = SQRT(ADD_SD**2+PROP_SD**2) ; final residual error
IF (W.LE.0.000001) W=0.000001 ; protective code

IRES = DV - IPRED
IWRES = IRES / W
Y = IPRED * (1 + EPS(1)) + EPS(2)

$OMEGA
0.608 ; IIV CL
0.375 ; IIV V1

$SIGMA ; residual variability
0.289 ; EPS(1), proportional

```

```

1E-13 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 for standard outcomes
ID TIME TAD DV EVID PRED IPRED WRES IWRES RES IRES CWRES CL V1 V2 Q K10 K12
K21 ADA SEX COL BW ALB AGE CREAT NOPRINT ONEHEADER FILE=run12_table

;; 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

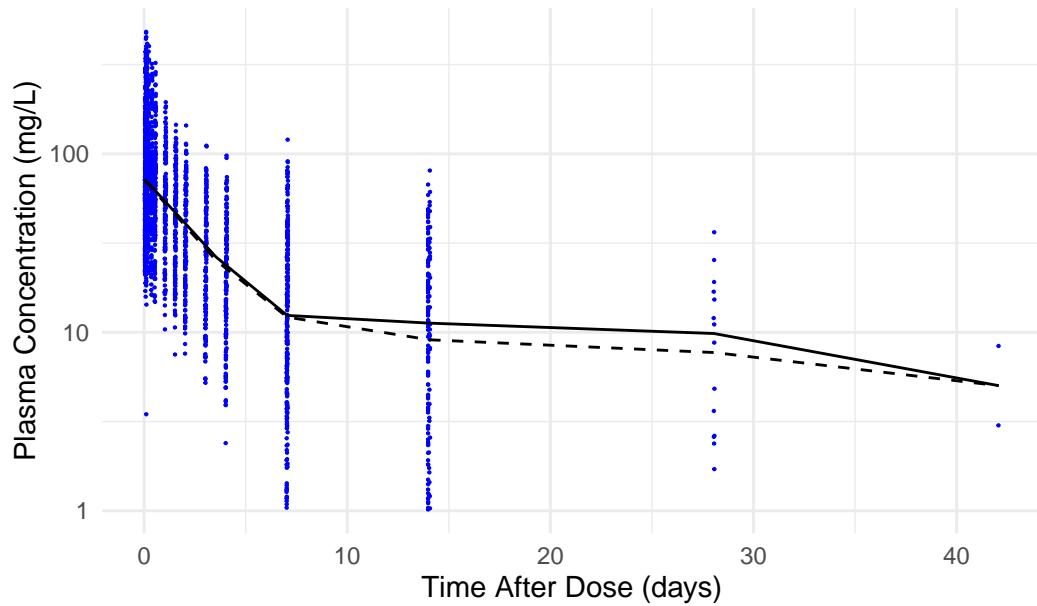
```

A2. Exploratory Data Analysis

```
data <- data %>%
  arrange(ID, TIME) %>%
  group_by(ID) %>%
  mutate(
    last_dose_time = cummax(if_else(EVID == 1, TIME, -Inf)),
    last_dose_time = if_else(is.finite(last_dose_time),
                             last_dose_time, NA_real_),
    TAD = TIME - last_dose_time
  ) %>%
  ungroup()

ggplot(data %>% filter(CONC_M7!=0),
       aes(y = CONC_M7,
           x = TAD)) +
  geom_point(color = "blue", size = 0.1) +
  stat_summary_bin(bins = 13,
                   fun.y = mean,
                   geom = "line",
                   linetype = "dashed") +
  stat_summary_bin(bins = 13,
                   fun.y = median,
                   geom = "line") +
  scale_y_log10() +
  labs(x = "Time After Dose (days)",
       y = "Plasma Concentration (mg/L)",
       title = "Concentration-Time Profile of PMX001") +
  theme_minimal()
```

Concentration–Time Profile of PMX001



```
h1 <- ggplot(data, aes(x = AGE)) +
  geom_histogram(color = "black", fill = "white", binwidth = 3) +
  theme_minimal()
h2 <- ggplot(data, aes(x = ALB)) +
  geom_histogram(color = "black", fill = "white", binwidth = 1.8) +
  theme_minimal()
h3 <- ggplot(data, aes(x = BW)) +
  geom_histogram(color = "black", fill = "white", binwidth = 3) +
  theme_minimal()
h4 <- ggplot(data, aes(x = CREAT)) +
  geom_histogram(color = "black", fill = "white", binwidth = 0.12) +
  theme_minimal()
h1 + h2 + h3 + h4 + plot_annotation(title = "Histograms of Continuous Covariates")
```

Histograms of Continuous Covariates

