Electronic Supplementary Information

Clinical Pharmacokinetics

The influence of patient factors on the population pharmacokinetics of colchicine: implications for safe and effective dosing

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Table S1 Parameter estimates for the published model from Karatze et al [1] used as the initial base model

Parameter	Karatze Model
CL/F (L h^{-1})	31.7
$V1/F$ (L)	202
Q/F (L h^{-1})	44.4
$V2/F$ (L)	609
D_1 (hr)	0.99
$TLAG1$ (hr)	0.12
Between subject variability	
ω_{CL} (variance)	0.059
ω_{V1} (variance)	0.126
ω_{D1} (variance)	0.303
ω_{tlag} (variance)	0.367

[1] Karatza E, IsmailosG, Karalis V. Xenobiotica. 2021;51:643-656, DOI: 10.1080/00498254.2021.1909782

Brief overview of the methodology used to create a virtual population for sampling of covariates (including MATLAB code)

Deidentified patient characteristics from n=309 people with gout recruited for five studies conducted in New Zealand, [1-6] provided the basis for the virtual gout population. The methodology used to create the virtual population has been described elsewhere [7]. In brief, n=10000 virtual individuals were created by expanding the original datafile of n=309 people using a parametric linear regression methodology. The virtual population retained the demographic mix expected for people with gout as well as the correlation between characteristics. The factors simulated in this case were bodyweight, statin use, ACEI use and sex. Weight was restricted to the range of values observed in the original dataset while the frequency of statin use, ACEI use and SEX (male or female) approximated the observed frequency. The distribution of virtual patient characteristics is compared to the observed values in Online resource 1 (Table S2). The MATLAB code used to create the population is reproduced below.

References

1. Stamp LK, Chapman PT, Barclay ML, Horne A, Frampton C, Tan P, et al. A randomised controlled trial of the efficacy and safety of allopurinol dose escalation to achieve target serum urate in people with gout. Ann Rheum Dis. 2017;76:1522–28.
2. Stamp LK, Chapman PT, Barclay ML, Horne A, Frampton C, Tan Pan, et al. Allopurinol dose escalation to achieve serum urate below 6 mg/dL: an open-label extension study. Ann Rheum Dis. 2017; 76(12):2065-70. DOI: 10.1136/annrheumdis-2017-211873.
3. Wright DFB, Duffull SB, Merriman TR, Dalbeth N, Barclay ML, Stamp LK. Predicting allopurinol response in patients with gout. Br J Clin Pharmacol. 2016;81:277-89.
4. Stamp LK, Barclay ML, O'Donnell JL, Zhang M, Drake J, Frampton C, Chapman PT. Relationship between serum urate and plasma oxypurinol in the management of gout: determination of minimum plasma oxypurinol concentration to achieve a target serum urate level. Clin Pharmacol Ther .2011;90:392-8.
5. Stamp LK, Barclay M, O'Donnell JL, Zhang M, Drake J, Frampton C, Chapman PT. Furosemide increases plasma oxypurinol without lowering serum urate—a complex drug interaction: implications for clinical practice. Rheumatology. 2012;51:1670-6.
6. Stamp LK, O'Donnell JL, Frampton C, Drake JM, Zhang M, Chapman PT. Clinically insignificant effect of supplemental vitamin C on serum urate in patients with gout: a pilot randomized controlled trial. Arthritis Rheum. 2013;65:1636-42.
7. Wright DF, Hishe HZ, Stocker SL, Dalbeth N, Horne A, Drake J, Haslett J, Phipps-Green AJ, Merriman TR, Stamp LK. The development and evaluation of dose-prediction tools for allopurinol therapy (Easy-Allo tools). Br J Clin Pharmacol. 2024 May;90(5):1268-79.

MATLAB code used to generate the virtual gout population

```
clc
clear all
format short g

% read the data file
data=xlsread('Covariates.xlsx');

% column headings (1,2...n);
%STATIN ACEI SEX WTKG FFMKG CLCRCG ULDRUGS ARB CCB BB DIURETIC AGE

nrep=10000;

% extract out the useful columns (statin=1, ACEI=2, SEX=3, Weight=4)
useful_data=data(:,1:4);


% find upp and lower bounds of observed data
Lower_wt=min(useful_data(:,4));
Upper_wt=max(useful_data(:,4));

% simulate the correct proportion of statin, ACEI and SEX
%MALE
a=find(useful_data(:,1)==0 & useful_data(:,2)==0 & useful_data(:,3)==1);  % no statin,
no ACEI, male
prop_M0=round((length(a)/length(useful_data(:,4))),2);

b=find(useful_data(:,1)==1 & useful_data(:,2)==0 & useful_data(:,3)==1);      % statin,
no ACEI, male
prop_MS1=round((length(b)/length(useful_data(:,4))),2);

c=find(useful_data(:,1)==0 & useful_data(:,2)==1 & useful_data(:,3)==1);      % no
statin, ACEI, male
prop_MACE2=round((length(c)/length(useful_data(:,4))),2);

d=find(useful_data(:,1)==1 & useful_data(:,2)==1 & useful_data(:,3)==1);      % statin,
ACEI, male
prop_MSACE3=round((length(d)/length(useful_data(:,4))),2);

%FEMALE
e=find(useful_data(:,1)==0 & useful_data(:,2)==0 & useful_data(:,3)==0);      % no
statin, no ACEI, female
prop_F0=round((length(e)/length(useful_data(:,4))),2);

f=find(useful_data(:,1)==1 & useful_data(:,2)==0 & useful_data(:,3)==0);      % statin,
no ACEI, female
```

```
prop_FS1=round((length(f)/length(useful_data(:,4))),2);

g=find(useful_data(:,1)==0 & useful_data(:,2)==1 & useful_data(:,3)==0);      % no
statin, ACEI, female
prop_FACE2=round((length(g)/length(useful_data(:,4))),2);

h=find(useful_data(:,1)==1 & useful_data(:,2)==1 & useful_data(:,3)==0);      % statin,
ACEI, female
prop_FSACE3=round((length(h)/length(useful_data(:,4))),2);

% stratify dataset by statin, ACEI and SEX

Male=useful_data(find(useful_data(:,1)==0 & useful_data(:,2)==0 &
useful_data(:,3)==1),1:4);       % no statin, no ACEI, male
MaleS=useful_data(find(useful_data(:,1)==1 & useful_data(:,2)==0 &
useful_data(:,3)==1),1:4);      % statin, no ACEI, male
MaleACE=useful_data(find(useful_data(:,1)==0 & useful_data(:,2)==1 &
useful_data(:,3)==1),1:4);     % no statin, ACEI, male
MaleSACE=useful_data(find(useful_data(:,1)==1 & useful_data(:,2)==1 &
useful_data(:,3)==1),1:4);    % statin, ACEI, male

Female=useful_data(find(useful_data(:,1)==0 & useful_data(:,2)==0 &
useful_data(:,3)==0),1:4);       % no statin, no ACEI, female
FemaleS=useful_data(find(useful_data(:,1)==1 & useful_data(:,2)==0 &
useful_data(:,3)==0),1:4);      % statin, no ACEI, female
FemaleACE=useful_data(find(useful_data(:,1)==0 & useful_data(:,2)==1 &
useful_data(:,3)==0),1:4);     % no statin, ACEI, female
FemaleSACE=useful_data(find(useful_data(:,1)==1 & useful_data(:,2)==1 &
useful_data(:,3)==0),1:4);    % statin, ACEI, female

% variance-covariance matrix
vc_Male=cov(Male); % i.e. variance-covariance matrix
vc_MaleS=cov(MaleS); % i.e. variance-covariance matrix
vc_MaleACE=cov(MaleACE); % i.e. variance-covariance matrix
vc_MaleSACE=cov(MaleSACE); % i.e. variance-covariance matrix

vc_Female=cov(Female); % i.e. variance-covariance matrix
vc_FemaleS=cov(FemaleS); % i.e. variance-covariance matrix
vc_FemaleACE=cov(FemaleACE); % i.e. variance-covariance matrix
vc_FemaleSACE=cov(FemaleSACE); % i.e. variance-covariance matrix

% generate multivariate deviates
cov_Male = mvnrnd(mean(Male),vc_Male,round(nrep*prop_M0));
cov_MaleS = mvnrnd(mean(MaleS),vc_MaleS,round(nrep*prop_MS1));
cov_MaleACE = mvnrnd(mean(MaleACE),vc_MaleACE,round(nrep*prop_MACE2));
cov_MaleSACE =
mvnrnd(mean(MaleSACE),vc_MaleSACE,round(nrep*prop_MSACE3));
```

```
cov_Female = mvnrnd(mean(Female),vc_Female,round(nrep*prop_F0));
cov_FemaleS = mvnrnd(mean(FemaleS),vc_FemaleS,round(nrep*prop_FS1));
cov_FemaleACE =
mvnrnd(mean(FemaleACE),vc_FemaleACE,round(nrep*prop_FACE2));
cov_FemaleSACE =
mvnrnd(mean(FemaleSACE),vc_FemaleSACE,round(nrep*prop_FSACE3));

cov_all=[cov_Male; cov_MaleS; cov_MaleACE; cov_MaleSACE; cov_Female;
cov_FemaleS; cov_FemaleACE; cov_FemaleSACE]; % To use as a single dataset which
contains d and nd.

% remove simulates outside the min and max

% [r c] = size(cov_all);
% X = repmat((cov_all(:,4) >= Lower_wt),1,c).*cov_all;
% Y = X(repmat((X(:,1)~=0),1,c));
% [r1 c1] = size(Y);
% cov_all_Lwt = reshape(Y,r1/c,c);

[r c] = size(cov_all);
pw=cov_all(:,4)>=(Lower_wt) & cov_all(:,4)<=(Upper_wt);
yw = repmat(pw,1,c).*cov_all;
cov_FINAL2 = intersect(yw,cov_all,'rows');

% [r_wt c_wt] = size(cov_all_Lwt);
% X_wt = repmat((cov_all_Lwt(:,4) <= Upper_wt),1,c_wt).*cov_all_Lwt;
% Y_wt = X_wt(repmat((X_wt(:,1)~=0),1,c_wt));
% [r1_wt c1_wt] = size(Y_wt);
% cov_FINAL2 = reshape(Y_wt,r1_wt/c_wt,c_wt);

%wt = cov_FINAL2(:,4);
%STATIN=cov_FINAL2(:,1);
%ACEI=(cov_FINAL2(:,2));
%SEX=(cov_FINAL2(:,3));

%T=[STATIN,ACEI,SEX,wt];

xlswrite('Covariates_COLCHICINEsampling', cov_FINAL2);
```

Table S2: Observed patient characteristics compared to the virtual population for the development of the virtual gout population

Patient Characteristics	Observed gout studies (n=309)	Virtual dataset (n=10000)
Weight (kg)	98 (51-172)	101 (51-172)
Taking statins (%)	45	45
Taking ACEI (%)	46	47
Sex (% females)	13	14

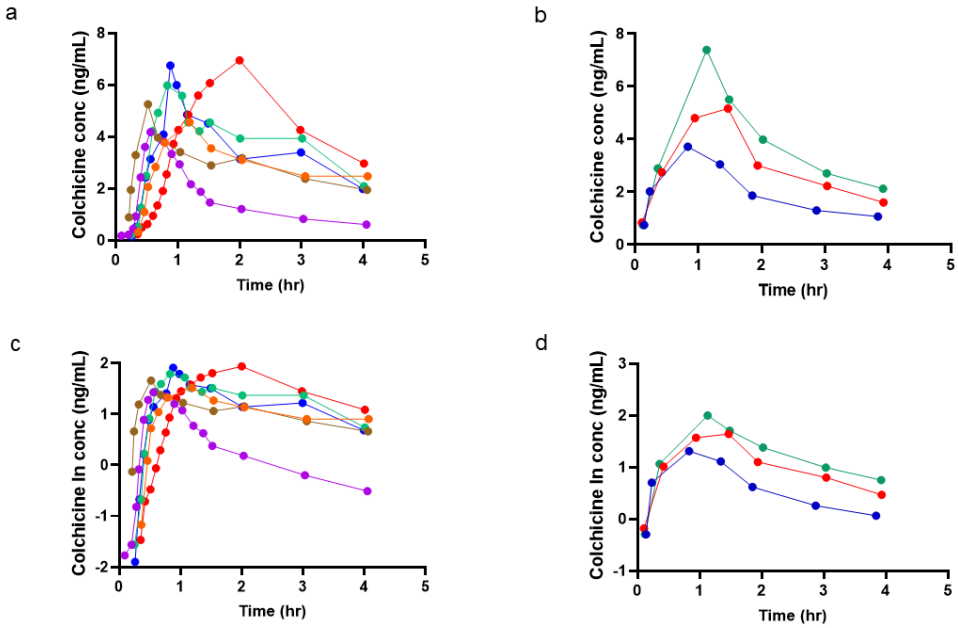

Fig S1. Plots of extracted data from Ferron et al [7] (a) and Thomas et al [5] (b) showing the first 4 hours after the dose and highlighting an apparent zero order absorption. Plots (c) and (d) present the natural log (ln) of the data from Ferron et al [7] (c) and Thomas et al [5] (d) (note that the Y axes is linear but the data is the natural log).

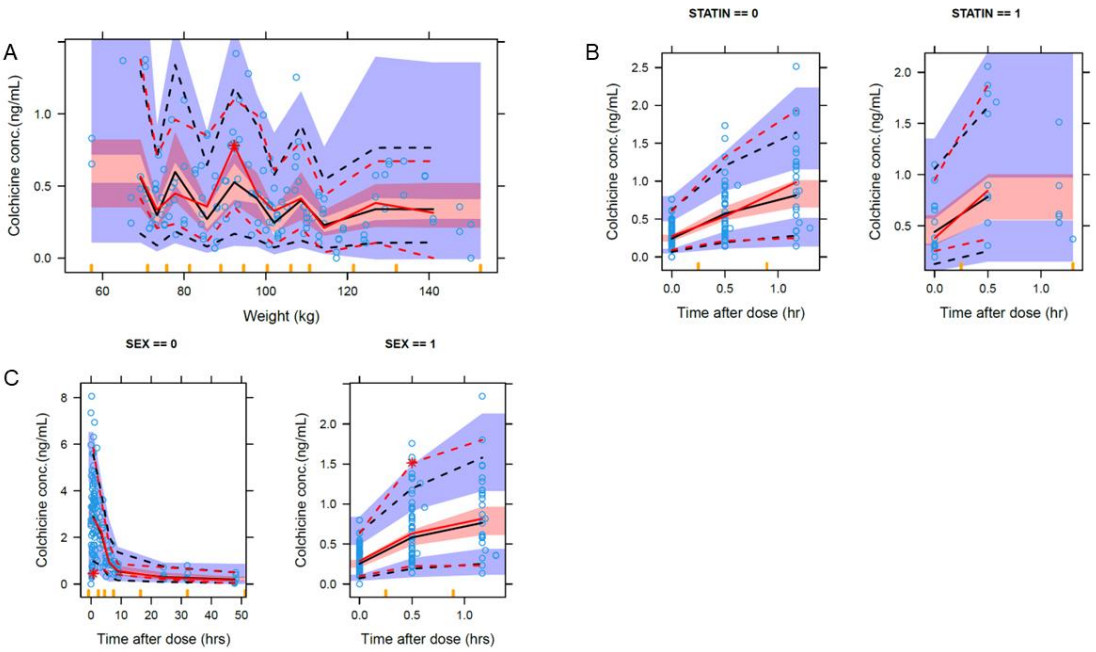

Fig S2 Prediction-corrected visual predictive checks (pcVPCs) for the final colchicine model stratified by significant covariates; (a) total body weight, (b) statin use, (c) sex. The X axis shows the time after the dose in hours for plots b-d and body weight for a. The median (solid black line), the 5 th and 95 th percentiles (dashed black line) of the of the model-predicted data is shown against the same percentiles of the observed data (red solid and dashed lines). The shaded area represented the 95% confidence interval around the percentiles.

NONMEM code for the final colchicine pharmacokinetic model

```
Author: Dan Wright
$PROBLEM 66_FINAL_colchicine
$INPUT   ID STUDY DAT1=DROP TIME TAD AMT II ADDL RATE CMT DVID DV MDV ROUTE
LAGFLAG AGE SEX HTCM WTKG FFMKG SCR CLCRCG EGFR URATE DIURETIC
DIURCLASS=DROP DIURDOSE ARB ACEI AB BB CCB STATIN ADH HAQ11 VAS EQ5D HSS
HGB PLATE WCC NEUTS LYMPH EOS ALP GGT ALT CK AELASTVISIT FLARESLM ETHNICTY
$DATA   colchNMfile_v4_0_ADVAN3_ALL2.csv
  IGNORE=#  IGNORE(ROUTE.EQ.2)

$SUBR ADVAN3 TRANS4
$PK

  IF (WTKG.GT.0) THEN
;     FATKG=WTKG-FFMKG
;     NFMCL=FFMKG + FFATCL*FATKG
;     NFMV=FFMKG + FFATV*FATKG
     SIZEV=WTKG/70
     SIZECL=(WTKG/70)**0.75
  ELSE
     SIZEV=1
     SIZECL=1
  ENDIF

  IF(SEX.EQ.0) THEN
    FSEX=THETA(13)  ; The fractional effect of female sex
  ELSE
    FSEX=1
  ENDIF

   IF (STATIN.EQ.1) THEN
     STATINCL=THETA(12) ; The fractional effect of statin use
   ELSE
     STATINCL=1
   ENDIF

IF(STUDY.EQ.1) FORM=1          ; NZ Gout study
IF(STUDY.GT.1) FORM=1+THETA(11)   ; formulation difference for extracted data

  ; COVARIATE MODEL
  TVCL=THETA(1)*STATINCL*SIZECL
  TVV1=THETA(2)*SIZEV*FSEX
  TVQ=THETA(3)*SIZECL
  TVV2=THETA(4)*SIZEV*FSEX
  TVD1=THETA(5)
  IF(LAGFLAG.EQ.1) THEN
     TVLAG=THETA(8)
```

```
  ELSE
    TVLAG=THETA(10)
  ENDIF
  TVF1=THETA(9)*FORM

  ; MODEL FOR RANDOM BETWEEN SUBJECT VARIABILITY
  CL=TVCL*EXP(ETA(1))
  V1=TVV1*EXP(ETA(2))
  Q=TVQ  ;*EXP(ETA(3))
  V2=TVV2*EXP(ETA(3))
  D1 = TVD1  ;*EXP(ETA(5))
  TLAG = TVLAG   ;*EXP(ETA(6))
  F1 = TVF1    ;*EXP(ETA(6))

  ; SCALE CONCENTRATIONS
  S1=V1
  ALAG1=TLAG

$ERROR
  IPRED=F
  W=SQRT(THETA(6)**2+THETA(7)**2*F*F)
  W=W
  IRES = DV-IPRED
  IWRES = IRES/W
  Y = IPRED+W*EPS(1)

$THETA
   (1,5)                          ; 1. CL
   (1,202)                ; 2. V1
   (1,44)                         ; 3. Q
   (1,609)                ; 4. V2
   (0,0.99)                       ; 5. D1
   0.006          FIX             ; 6. RUV_ADD
   (0,0.1)                ; 7. RUV_PROP
   1.3             FIX             8. TLAG1
   0.469    FIX                   ; 9. F1_oral
   0                FIX           ; 10. TLAG2
   (-5,-0.1,5)                    ; 11. FORM (Formulation effect)
   (0,0.75)                       ; 12. STATINCL
   (0,0.75)                       ; 13. FSEX

$OMEGA
   0.1               ; PPV_CL
   0.126    FIX             ; PPV_V1
   0.284    FIX       ; PPV_V2

$SIGMA
```

```
  1 FIX             ; EPS1
$EST NOABORT MAXEVAL=9999 NSIG=3 SIGL=9 PRINT=1
METHOD=COND INTERACTION

$COV
$TABLE ID TIME TAD IPRED IWRES DVID CWRES MDV
      NOPRINT ONEHEADER FILE=sdtab_66
$TABLE ID SEX AGE
      NOPRINT ONEHEADER FILE=catab_66
$TABLE ID WTKG FFMKG SCR CLCRCG STATIN ADH ETHNICTY
      NOPRINT ONEHEADER FILE=cotab_66
$TABLE ID STUDY TAD CL V1 Q V2 D1 ETA(1) ETA(2) ETA(3) DV MDV IPRED PRED TIME
      NOPRINT ONEHEADER FILE=patab_66
```

Table S3 Simulated colchicine plasma concentrations and the probability of achieving concentrations within the nominal therapeutic range of 0.5-3 ng/mL for colchicine 0.5 mg daily under different covariates.

Colchicine dose	$C_{min,ss}$ (ng/mL)	$Cp_{max,ss}$ (ng/mL)	$Cp_{av,ss}$ (ng/mL)
0.5 mg daily			
Weight quartile 1 (50.0-79.9kg)			
Median [5-95th percentiles]	0.50 [0.19-1.17]	1.79 [1.05-3.03]	0.77 [0.41-1.44]
P>0.5 ng/mL	50	100	87
P<3.0 ng/mL	100	94	100
Weight quartile 2 (80.0-96.9kg)			
Median [5-95th percentiles]	0.41 [0.16-0.96]	1.39 [0.86-2.23]	0.62 [0.34-1.19]
P>0.5 ng/mL	37	100	72
P<3.0 ng/mL	100	100	100
Weight quartile 3 (97-109.9kg)			
Median [5-95th percentiles]	0.36 [0.15-0.79]	1.22 [0.77-1.86]	0.54 [0.32-0.99]
P>0.5 ng/mL	27	100	61
P<3.0 ng/mL	100	100	100
Weight quartile 4 (>110kg)			
Median [5-95th percentiles]	0.30 [0.13-0.69]	1.00 [0.67-1.65]	0.45 [0.26-0.88]
P>0.5 ng/mL	17	100	42
P<3.0 ng/mL	100	100	100
Not taking a statin			
Median [5-95th percentiles]	0.33 [0.14-0.70]	1.18 [0.72-2.20]	0.52 [0.30-0.90]
P>0.5 ng/mL	19	100	64
P<3.0 ng/mL	100	100	100
Taking a statin			
Median [5-95th percentiles]	0.60 [0.29-1.29]	1.60 [1.01-2.86]	0.84 [0.47-1.57]
P>0.5 ng/mL	67	100	93
P<3.0 ng/mL	100	97	100
Male			
Median [5-95th percentiles]	0.38 [0.15-0.93]	1.27 [0.72-2.25]	0.57 [0.30-1.16]
P>0.5 ng/mL	32	100	63
P<3.0 ng/mL	100	100	99
Female			
Median [5-95th percentiles]	0.36 [0.12-0.99]	2.07 [1.08-3.40]	0.64 [0.31-1.33]
P>0.5 ng/mL	290.	100	70
P<3.0 ng/mL	100	88	100

P<0.5 ng/mL = the percentage of the simulated concentrations less than 0.5 ng/mL. P>3 ng/mL = the percentage of the simulated concentrations above 3 ng/mL.

Table S4 Simulated colchicine plasma concentrations and the probability of achieving concentrations within the nominal therapeutic range of 0.5-3 ng/mL for colchicine 1 mg daily under different covariates.

Colchicine dose	**$C_{min,ss}$ (ng/mL)**	**$Cp_{max,ss}$ (ng/mL)**	**$Cp_{av,ss}$ (ng/mL)**
1 mg daily			
Weight quartile 1 (50.0-79.9kg)			
Median [5-95th percentiles]	1.02 [0.36-2.49]	3.61 [2.19-3.61]	1.57 [0.78-3.05]
P>0.5 ng/mL	88	100	100
P<3.0 ng/mL	97	28	95
Weight quartile 2 (80.0-96.9kg)			
Median [5-95th percentiles]	0.88 [0.33-2.04]	2.83 [1.69-4.76]	1.29 [0.69-2.48]
P>0.5 ng/mL	84	100	100
P<3.0 ng/mL	100	56	98
Weight quartile 3 (97-109.9kg)			
Median [5-95th percentiles]	0.73 [0.32-1.68]	2.35 [1.57-3.78]	1.10 [0.63-2.05]
P>0.5 ng/mL	74	80	100
P<3.0 ng/mL	100	100	99
Weight quartile 4 (>110kg)			
Median [5-95th percentiles]	0.59 [0.27-1.38]	2.03[1.29-3.28]	0.90 [0.53-1.69]
P>0.5 ng/mL	62	100	97
P<3.0 ng/mL	100	93	100
Not taking a statin			
Median [5-95th percentiles]	0.64 [0.25-1.41]	2.35 [1.46-4.41]	1.02 [0.55-1.90]
P>0.5 ng/mL	68	100	99
P<3.0 ng/mL	100	74	100
Taking a statin			
Median [5-95th percentiles]	1.22 [0.48-2.38]	3.21 [1.97-5.33]	1.64 [0.88-2.91]
P>0.5 ng/mL	95	100	100
P<3.0 ng/mL	99	42	96
Male			
Median [5-95th percentiles]	0.76 [0.29-1.97]	2.50 [1.50-4.37]	1.15 [0.60-2.40]
P>0.5 ng/mL	78	100	99
P<3.0 ng/mL	99	70	99
Female			
Median [5-95th percentiles]	0.69 [0.24-1.81]	4.12 [2.24-6.97]	1.24 [0.61-2.52]
P>0.5 ng/mL	69	100	98
P<3.0 ng/mL	100	18	98

P<0.5 ng/mL = the percentage of the simulated concentrations less than 0.5 ng/mL. P>3 ng/mL = the percentage of the simulated concentrations above 3 ng/mL.

Table S5 Simulated colchicine plasma concentrations and the probability of achieving concentrations within the nominal therapeutic range of 0.5-3 ng/mL for colchicine 1.5 mg daily under different covariates.

Colchicine dose	$C_{min,ss}$ (ng/mL)	$Cp_{max,ss}$ (ng/mL)	$Cp_{av,ss}$ (ng/mL)
1.5 mg daily			
Weight quartile 1 (50.0-79.9kg)			
Median [5-95th percentiles]	1.41 [0.52-3.60]	5.51 [3.23-8.83]	2.23 [1.17-4.41]
P>0.5 ng/mL	96	100	100
P<3.0 ng/mL	91	3	76
Weight quartile 2 (80.0-96.9kg)			
Median [5-95th percentiles]	1.30 [0.50-2.82]	4.24 [2.56-6.83]	1.94 [1.05-3.49]
P>0.5 ng/mL	95	100	100
P<3.0 ng/mL	96	11	88
Weight quartile 3 (97-109.9kg)			
Median [5-95th percentiles]	1.12 [0.43-2.48]	3.62 [2.31-5.73]	1.66 [0.91-3.10]
P>0.5 ng/mL	91	100	100
P<3.0 ng/mL	98	24	95
Weight quartile 4 (>110kg)			
Median [5-95th percentiles]	0.85 [0.36-2.05]	3.00 [1.97-4.89]	1.31 [0.77-2.60]
P>0.5 ng/mL	86	100	100
P<3.0 ng/mL	100	50	98
Not taking a statin			
Median [5-95th percentiles]	0.99 [0.38-2.23]	3.70 [2.23-7.12]	1.57 [0.83-2.97]
P>0.5 ng/mL	88	100	100
P<3.0 ng/mL	99	26	95
Taking a statin			
Median [5-95th percentiles]	1.86 [0.88-4.08]	4.91 [2.86-8.14]	2.52 [1.46-4.71]
P>0.5 ng/mL	100	100	100
P<3.0 ng/mL	86	7	68
Male			
Median [5-95th percentiles]	1.12 [0.38-2.84]	3.77 [2.14-6.72]	1.70 [0.83-3.61]
P>0.5 ng/mL	90	100	100
P<3.0 ng/mL	96	27	89
Female			
Median [5-95th percentiles]	1.08 [0.35-2.72]	6.15 [3.17-10.21]	1.88 [0.89-3.78]
P>0.5 ng/mL	87	100	100
P<3.0 ng/mL	96	4	87

P<0.5 ng/mL = the percentage of the simulated concentrations less than 0.5 ng/mL. P>3 ng/mL = the percentage of the simulated concentrations above 3 ng/mL.

Table S6 Simulated colchicine plasma concentrations and the probability of achieving concentrations within the nominal therapeutic range of 0.5-3 ng/mL for colchicine 0.5 mg twice daily under different covariates.

Colchicine dose	$C_{min,ss}$ (ng/mL)	$Cp_{max,ss}$ (ng/mL)	$Cp_{av,ss}$ (ng/mL)
0.5 mg twice daily			
Weight quartile 1 (50.0-79.9kg)			
Median [5-95th percentiles]	1.19 [0.45-2.71]	2.43 [1.53-4.16]	1.49 [0.79-2.92]
P>0.5 ng/mL	93	100	100
P<3.0 ng/mL	97	71	96
Weight quartile 2 (80.0-96.9kg)			
Median [5-95th percentiles]	1.04 [0.44-2.14]	1.97 [1.24-3.33]	1.28 [0.68-2.32]
P>0.5 ng/mL	91	100	100
P<3.0 ng/mL	100	90	99
Weight quartile 3 (97-109.9kg)			
Median [5-95th percentiles]	0.87 [0.36-1.84]	1.65 [1.08-2.71]	1.06 [0.59-1.92]
P>0.5 ng/mL	85	100	98
P<3.0 ng/mL	100	97	100
Weight quartile 4 (>110kg)			
Median [5-95th percentiles]	0.71 [0.29-1.49]	1.40 [0.88-2.24]	0.88 [0.47-1.66]
P>0.5 ng/mL	80	100	93
P<3.0 ng/mL	100	99	100
Not taking a statin			
Median [5-95th percentiles]	0.79 [0.34-1.57]	1.62 [0.99-2.86]	1.02 [0.58-1.82]
P>0.5 ng/mL	83	100	97
P<3.0 ng/mL	100	96	100
Taking a statin			
Median [5-95th percentiles]	1.38 [0.65-2.71]	2.23 [1.49-3.83]	1.60 [0.91-2.87]
P>0.5 ng/mL	99	100	100
P<3.0 ng/mL	97	79	96
Male			
Median [5-95th percentiles]	0.90 [0.40-2.03]	1.78 [1.06-3.09]	1.12 [0.60-2.21]
P>0.5 ng/mL	88	100	99
P<3.0 ng/mL	100	94	99
Female			
Median [5-95th percentiles]	0.82 [0.33-2.04]	2.62 [1.44-4.34]	1.21 [0.62-2.45]
P>0.5 ng/mL	83	100	99
P<3.0 ng/mL	99	68	99

P<0.5 ng/mL = the percentage of the simulated concentrations less than 0.5 ng/mL. P>3 ng/mL = the percentage of the simulated concentrations above 3 ng/mL.

Table S7 Simulated colchicine plasma concentrations and the probability of achieving concentrations within the nominal therapeutic range of 0.5-3 ng/mL for colchicine 1 mg twice daily under different covariates settings.

Colchicine dose	$C_{min,ss}$ (ng/mL)	$Cp_{max,ss}$ (ng/mL)	$Cp_{av,ss}$ (ng/mL)
1 mg twice daily			
Weight quartile 1 (50.0-79.9kg)			
Median [5-95th percentiles]	2.36 [0.99-5.13]	4.93 [3.05-8.08]	3.01 [1.60-5.46]
P>0.5 ng/mL	100	100	100
P<3.0 ng/mL	71	4	49
Weight quartile 2 (80.0-96.9kg)			
Median [5-95th percentiles]	1.98 [0.80-4.36]	3.87 [2.44-6.53]	2.48 [1.32-4.64]
P>0.5 ng/mL	100	100	100
P<3.0 ng/mL	82	20	70
Weight quartile 3 (97-109.9kg)			
Median [5-95th percentiles]	1.62 [0.73-3.55]	3.29 [2.15-5.54]	2.05 [1.16-3.87]
P>0.5 ng/mL	99	100	100
P<3.0 ng/mL	88	37	82
Weight quartile 4 (>110kg)			
Median [5-95th percentiles]	1.46 [0.56-3.32]	2.81 [1.73-4.74]	1.78 [0.96-3.56]
P>0.5 ng/mL	98	100	100
P<3.0 ng/mL	93	58	90
Not taking a statin			
Median [5-95th percentiles]	1.51 [0.65-3.12]	3.28 [1.94-5.98]	1.98 [1.04-3.60]
P>0.5 ng/mL	98	100	100
P<3.0 ng/mL	94	40	86
Taking a statin			
Median [5-95th percentiles]	2.74 [1.28-5.48]	4.72 [2.85-7.94]	3.19 [1.78-5.88]
P>0.5 ng/mL	100	100	100
P<3.0 ng/mL	57	8	43
Male			
Median [5-95th percentiles]	1.79 [0.68-4.39]	3.56 [1.98-6.81]	2.24 [1.09-4.91]
P>0.5 ng/mL	99	100	100
P<3.0 ng/mL	85	32	74
Female			
Median [5-95th percentiles]	1.66 [0.66-4.26]	5.08 [2.80-8.74]	2.43 [1.25-4.88]
P>0.5 ng/mL	98	100	100
P<3.0 ng/mL	84	7	68

P<0.5 ng/mL = the percentage of the simulated concentrations less than 0.5 ng/mL. P>3 ng/mL = the percentage of the simulated concentrations above 3 ng/mL.

Table S8 Simulated colchicine plasma concentrations and the probability of achieving concentrations within the nominal therapeutic range of 0.5-3 ng/mL for colchicine 1.5 mg twice daily under different covariates settings.

Colchicine dose	$C_{min,ss}$ (ng/mL)	$Cp_{max,ss}$ (ng/mL)	$Cp_{av,ss}$ (ng/mL)
1.5 mg twice daily			
Weight quartile 1 (50.0-79.9kg)			
Median [5-95th percentiles]	3.46 [1.46-7.67]	7.33 [4.63-12.64]	4.41 [2.43-8.41]
P>0.5 ng/mL	100	100	100
P<3.0 ng/mL	39	0	16
Weight quartile 2 (80.0-96.9kg)			
Median [5-95th percentiles]	2.86 [1.28-6.56]	5.72 [3.60-9.58]	3.59 [2.05-6.91]
P>0.5 ng/mL	100	100	100
P<3.0 ng/mL	55	1	32
Weight quartile 3 (97-109.9kg)			
Median [5-95th percentiles]	2.45 [1.00-5.90]	4.97 [3.20-8.40]	3.07 [1.70-6.25]
P>0.5 ng/mL	100	100	100
P<3.0 ng/mL	68	3	48
Weight quartile 4 (>110kg)			
Median [5-95th percentiles]	2.09 [0.89-4.33]	4.20 [2.72-7.11]	2.62 [1.44-4.86]
P>0.5 ng/mL	99	100	100
P<3.0 ng/mL	77	11	63
Not taking a statin			
Median [5-95th percentiles]	2.26 [1.00-4.91]	4.83 [3.01-8.85]	2.95 [1.60-5.69]
P>0.5 ng/mL	100	100	100
P<3.0 ng/mL	73	5	51
Taking a statin			
Median [5-95th percentiles]	3.94 [1.77-8.12]	6.91 [4.14-11.63]	4.68 [2.53-8.56]
P>0.5 ng/mL	100	100	100
P<3.0 ng/mL	26	0	12
Male			
Median [5-95th percentiles]	2.63 [1.06-6.12]	5.24 [2.90-9.28]	3.33 [1.66-6.64]
P>0.5 ng/mL	100	100	100
P<3.0 ng/mL	60	6	40
Female			
Median [5-95th percentiles]	2.53 [1.03-5.85]	7.82 [4.39-13.27]	3.70 [1.94-7.31]
P>0.5 ng/mL	100	100	100
P<3.0 ng/mL	63	0	30

P<0.5 ng/mL = the percentage of the simulated concentrations less than 0.5 ng/mL. P>3 ng/mL = the percentage of the simulated concentrations above 3 ng/mL.

MATLAB code for the model simulations

FILE: Go_PK_Colchcine_STO_sampling

```
% set number of simulations
num_ptt=10;
% dosing
dot=40;                 Days of therapy
di=24;                  Dosing interval
dn=(24/di)*dot;             Dose number
d=0.5*1000;                 Converts to mcg

hld=dot*24;                 Hour of last dose

% covariate simulations
WT_level=[0 74.99];         Set upper and lower limit of WT bands
STATIN_USE=0;               0=no statin, 1=taking statin
SEX=1;                  0=female, 1=male

% PK Parameters
F1=0.469;
POP_CL=19.7;                        L/hr
POP_V1=249;                 L
POP_V2=817;                 L
POP_Q=30.1;                         L/hr
POP_D1=0.99;                Duration of zero order input (hr)
POP_TLAG=0;                 hr

% simulate patients and data
for mn=1:num_ptt
   initial
   para_COL
   get_covariates5_sto
   get_patient
   k20=CL/V1;
   k23=Q/V1;
   k32=Q/V2;
   PKSim
   colchicine_sim(mn,:)=COLCH_sim;
   CP_tau(mn,:)=colchicine_sim(mn,hld-di:hld)';
   CP_auc(mn,:) = trapz(CP_tau(mn,:));
   CPssave(mn,:)= CP_auc(mn,:)./di;
   %CPssave(mn,:)=d/(CL*di);
   Col_peakFIND(mn,:)=max(colchicine_sim(mn,(dn-1)*di:dn*di));
   Col_minFIND(mn,:)=min(colchicine_sim(mn,(dn-1)*di:dn*di));
   Colchicine_peak(mn,:)=Col_peakFIND(mn,:);
   Colchicine_trough(mn,:)=Col_minFIND(mn,:);
end

Cpssave_min_range=min(CPssave);
```

```
Cpssave_max_range=max(CPssave);
Colchicine_peakMIN_range=min(Colchicine_peak);
Colchicine_peakMAX_range=max(Colchicine_peak);
Colchicine_troughMIN_range=min(Colchicine_trough);
Colchicine_troughMAX_range=max(Colchicine_trough);
Cpmin_range = prctile(Colchicine_trough,[5 95],"all")
Cpmax_range = prctile(Colchicine_peak,[5 95],"all")
AUC_range = prctile(CP_auc,[5 95],"all")
CPssave_range = prctile(CPssave,[5 95],"all")

a=find(Colchicine_peak > 3);
Prob_tox_peak=(length(a)/length(Colchicine_peak))*100

aa=find(Colchicine_peak < 0.5);
Prob_below_peak=(length(aa)/length(Colchicine_peak))*100

b=find(Colchicine_trough > 3);
Prob_tox_trough=(length(b)/length(Colchicine_trough))*100

bb=find(Colchicine_trough < 0.5);
Prob_below_trough=(length(bb)/length(Colchicine_trough))*100
```

FILE: initial

This files helps in estimating the new dose time

```
for ijk=1:dn % 1:30
   new_dose_time(1,ijk)=di*ijk;
end
```

FILE: para_COL

Simulates PK parameters

```
MU=[POP_CL POP_V1 POP_V2 POP_Q POP_D1 POP_TLAG];
logMU=log(MU);
PPV = [0.101   0       0       0      0      0
       0      0.126    0       0      0      0
       0      0       0.284    0      0      0
       0      0       0       0      0      0
       0      0       0       0      0.3    0
       0      0       0       0      0      0.367];
```

FILE: get_covariates5_sto

Covariate sampling
% read covariate file

```
covariates_sim=xlsread('Covariates_COLCHICINEsampling.xlsx');
[rc cz] = size(covariates_sim);
```

% columns: STATIN SEX WT

```
% sample WT
pw=covariates_sim(:,3)<=(WT_level(2)) & covariates_sim(:,4)>(WT_level(1));
yw = repmat(pw,1,cz).*covariates_sim;
covariates_sim2 = intersect(yw,covariates_sim,'rows');

% STATIN
pd=covariates_sim2(:,1)==STATIN_USE; % 0=no statin, 1=taking statin
yd = repmat(pd,1,cz).*covariates_sim2;
covariates_sim3 = intersect(yd,covariates_sim2,'rows');

% SEX
ps=covariates_sim3(:,2)==SEX; % 0=female, 1=male
ys = repmat(ps,1,cz).*covariates_sim3;
covariates_sim4 = intersect(ys,covariates_sim3,'rows');

% creates random sample
rx = randi(length(covariates_sim4(:,1)),1,1);

STATIN=covariates_sim4(rx,1);
ACEI=covariates_sim4(rx,2);
SEX=covariates_sim4(rx,3);
WT=covariates_sim4(rx,4);

SIZECL=(WT/70)^0.75;
SIZEV=(WT/70);
if SEX==1
   FSEX=1;        male
else
   FSEX=0.53;
end
if STATIN==1
   FSTATIN=0.70;  taking statin
else
   FSTATIN=1;     NOT taking statin
end
```

FILE: get_patient

```
THETA=exp(mvnrnd(logMU, PPV));
CL=THETA(1)*FSTATIN*SIZECL;
V1=THETA(2)*SIZEV*FSEX;
V2=THETA(3)*SIZEV*FSEX;
Q=THETA(4)*SIZECL;
D1=THETA(5);
rx = randi(100);
if rx > 20
   TLAG=THETA(6);
else
   TLAG=1.3;
end
```

FILE: PKSim

```
options = odeset('RelTol',1e-8); %ignore this line
   A0=[d 0 0];
   TIME_rows=0;
   dn_r=(1:1:dn);       generates a vector of 1:dn (e.g. 1 2 3 4 5...dn)
   rr_r=length(dn_r);
   for ij=1:dn
      if ij > 1
         tmax=new_dose_time(ij)-new_dose_time(ij-1);
         t_diff=new_dose_time(ij-1);
      else
         tmax=new_dose_time(ij);
         t_diff=0;
      end
      new_dose_time1=[0 new_dose_time];
      time=[0:1:tmax]; % tmax
      sol=ode45(@ode_colchicine,[0 tmax],[A0],options,TLAG,D1,k23,k32,k20);
      A1=deval(sol, time, 1)';
      A2=deval(sol, time, 2)';
      COLCH=A2./V1;
      A3=deval(sol, time, 3)';
      [r c]=size(COLCH);
      A0=[d A2(r,:) A3(r,:)];
      r_new=[r-1];
      time_new=[time(1):time(di)];
      COLCH1=[COLCH(1:r-1,:)];
      T(TIME_rows+1:TIME_rows+r_new,1)=time_new'+t_diff;
      COLCH_sim(TIME_rows+1:TIME_rows+r_new,1)=COLCH1;
      TIME_rows=TIME_rows+r_new;
   end
```

FILE: ode_colchicine

```
function dAdt = ode_colchicine(t,A,TLAG,K0,k23,k32,k20)

Ratein=A(1)/K0;
if t<TLAG
   A(1)=0;
End

if t<K0
   Ratein=Ratein;
else
   Ratein=0;
End

dAdt=[-Ratein
      Ratein-k23*A(2)+k32*A(3)-k20*A(2)
      k23*A(2)-k32*A(3)];
```