SUPPLEMENTAL MATERIALS

Supplemental Table 1. NONMEM Control Streams

Preliminary and Final Updated Model

```
$SUBROUTINE ADVAN6 TRANS1 TOL=9
 $MODEL
  COMP = (DOSESC1)                    ; 1 DOSE SC PATH 1
  COMP = (CENTRAL,DEFOBS)   ; 2 APL2 CENTRAL
  COMP = (TRANSIT1)                   ; 3 SC TRANSIT1

 $PK
  ;;CATEGORICAL
  COVARIATES;;
  FORM1=0
  IF(FORM.EQ.1) FORM1=1 ;SORBITOL

  FORM2=0
  IF(FORM.EQ.2) FORM2=1 ;DEXTROSE

  FORM3=0
  IF(FORM.EQ.3) FORM3=1 ;MANNITOL

  FORM4=0
  IF(FORM.EQ.4) FORM4=1 ;POWDER

  PNH3=0
  IF(STUD.EQ.302) PNH3=1
  IF(STUD.EQ.308) PNH3=1

  PNH2=0
  IF(STUD.EQ.202)  PNH2=1
  IF(STUD.EQ.204)  PNH2=1
  IF(STUD.EQ.514) PNH2=1
  ;;CATEGORICAL COVARIATES;;

  ;;CONTINUOUS COVARIATES;;
  MWT=70  ;Use  reference  value
  WT=MWT
  IF (BWT.GT.0) WT=BWT
  ;;CONTINUOUS COVARIATES;;
```

```
  ;;TIME-VARYING COVARIATES;;
  MTC3=1 ;MED BASELINE C3
  TC3=MTC3
  IF (C3.GT.0) TC3=C3
  ;;TIME-VARYING COVARIATES;;

 TVCL =
 THETA(1)*(1+PNH*THETA(9))*((WT/MWT)**THETA(10)) TVV2
 = THETA(2)*((WT/MWT)**THETA(11))
 TVKA = THETA(3)

 CL  =  TVCL*EXP(ETA(1))
 V2  =  TVV2*EXP(ETA(2))
 KA = TVKA*EXP(ETA(3))

 F1 = THETA(4)*(1+FORM4*THETA(8))

 S2 = V2                              ; dose = mg, conc = mcg/mL = mg/L

 $DES
 C2 = A(2)/V2  ;mg/L
 DADT(1) = -KA*A(1)
 DADT(2) = KA*A(3) - (CL/V2)*A(2)
 DADT(3) = KA*A(1) - KA*A(3)

 $ERROR (OBSERVATIONS ONLY)
 IF (PNH.EQ.0) W = SQRT(THETA(5)**2)
 IF (PNH2.EQ.1) W = SQRT(THETA(6)**2)
 IF (PNH3.EQ.1) W = SQRT(THETA(7)**2)

IF (F.GT.0) THEN IPRED
 = LOG(F)
 Y         = IPRED + W*ERR(1)
 IRES   =  DV  -  IPRED IWRES
 = IRES/W
 ELSE
 Y = 0
 IPRED = 0
 IRES = 0
  IWRES = 0
 ENDIF
```

```
$THETA
  (0, 0.01)          ;1     TVCL [L/h]
  (0,3.7)            ;2      V2 [L]
  (0.01)             ;3      KA [1/h]
  (0,0.85,1)         ;4      TVF1




  (0,0.3)            ;5     LOG ADD RE HEALTHY
  (0,0.5)            ;6     LOG ADD RE PNH PHASE1&2
  (0,0.2)            ;7     LOG ADD RE PNH PHASE3
  (-1,0.1)           ;8     LYO FORM4 ON F1
  (-1,0.25)          ;9     PNH ON CL
  (0.75)             ;10    WEIGHT ON CL
  (1)                ;11    WEIGHT ON V2

$OMEGA BLOCK(2)
  0.01               ;11 ETA11 - CL
  0.001              ;21 ETA21 - COR V2:CL
  0.01               ;22 ETA22 - V2
$OMEGA
  0.01               ;33 ETA33 - KA

$SIGMA
  1 FIXED

$EST    METHOD=1 INTERACTION PRINT=10 MAXEVAL=9999 NOABORT NSIG=3 SIGL=9
$COV    MATRIX=R COMPRESS PRINT=E

$TABLE ID STUD LINE TIME NTFD ATLD NTLD CMT DOSE DOSEGRP FORM COHORT PNH EVID MDV DV PRED IPRED RES WRES
   CWRES IRES IWRES NPDE NOPRINT NOAPPEND ONEHEADER FILE=fit.tab

$TABLE ID STUD CL V2 KA F1 ETAS(1:LAST)
   FIRSTONLY NOPRINT NOAPPEND ONEHEADER FILE=patab.tab

$TABLE ETAS(1:last) ID DOSE STUD FORM SEXF RACE ETHN PNH BECU
   FIRSTONLY NOPRINT NOAPPEND ONEHEADER FILE=catab.tab

$TABLE ETAS(1:last) ID DOSE AGE BWT BHT BBMI BSA BALB BALT BAST BBILI BSCR BCRCL BEGFR
```

```
   ABEGFR BC3 FIRSTONLY NOPRINT NOAPPEND ONEHEADER FILE=cotab.tab
```

Hb Final Updated Model

```
$SIZES PD = -100
$PROB APELLIS APL-2 ER HGB APL2-302 & APL2-308 UPDATE FULL MODEL DEVELOPMENT

$INPUT C STUD USUBJID=DROP STID=DROP NMID=ID TIME ATFD NTFD DAY EVID AMT AMTM CONC=DV
LCONC MCONC LMCONC TYPE CMT MDV CFB PCFB BHGB ADDL II DOSE DOSEGRP FORM VISFLG BLQ AGE
SEXF RACE ETHN PNH BHT BWT BBMI
BSCR BALB BAST BALT BBILI BC3 BC3M BSA BCRCL BEGFR ABEGFR ECU BECU C3 C3M
ADAPEG ADAAPL TFLAG PTBFLAG LOCAL PRBC COHORT PRBCFLG LINE ICL IV2 IKA IF1
IETA1 IETA2 IETA3


$DATA  ../../../../../../DerivedData/ER/HGB/APL2_ER_HGB2_20211019V06.csv IGNORE=@
       IGNORE=(TYPE.EQ.2) ;APL-2 CONC
       IGNORE=(TYPE.EQ.3) ;HGB DOSE
       IGNORE=(LOCAL.EQ.1) ;IGNORE LOCAL LAB
       RESULTS

$SUBROUTINE ADVAN6 TRANS1 TOL=9
$MODEL
COMP = (DOSESC1)                    ; 1 DOSE SC PATH 1
COMP = (CENTRAL,DEFOBS)             ; 2 APL2 CENTRAL
COMP = (TRANSIT1)                   ; 3 SC TRANSIT1
COMP = (HGB)                        ; 4 HGB CONC


$PK
  ;;CATEGORICAL
COVARIATES;;
RASN=0
IF (RACE.EQ.3.OR.RACE.EQ.4) RASN=1 ;ASIAN RACE

JPN=0
IF (RACE.EQ.4) JPN=1 ;JAPANESE ETHNICITY
;;CATEGORICAL COVARIATES;;

;;CONTINUOUS
COVARIATES;;
MAGE=35
AGE2=MAGE
```

```
 IF (AGE.GT.0) AGE2=AGE

 MWT=70 ;Use reference value
 WT=MWT
 IF (BWT.GT.0) WT=BWT

 MBMI=25 ;Use reference value BMI=MBMI

  IF (BBMI.GT.0) BMI=BBMI

  MALB=4.3
  ALB=MALB
  IF (BALB.GT.0) ALB=BALB

  MBILI=1.2 BILI=MBILI
  IF (BBILI.GT.0) BILI=BBILI

 MAST=20
 AST=MAST
 IF (BAST.GT.0) AST=BAST

 MALT=20
 ALT=MALT
 IF (BALT.GT.0) ALT=BALT

 MCRCL=120
 CRCL=MCRCL
 IF (BCRCL.GT.0) CRCL=BCRCL

 MBC3=1 ;MED BASELINE C3
 BASEC3=MBC3
 IF (BC3.GT.0) BASEC3=BC3
 ;;CONTINUOUS COVARIATES;;


;;PK                    MODEL
 PARAMETERS;; CL = ICL
 V2 = IV2 KA
 = IKA  F1  =
 IF1

 S2 = V2; dose = mg, conc = mcg/mL = mg/L
 ;;PK MODEL PARAMETERS;;
```

```
;;ER MODEL
  PARAMETERS;;
  TVBASEHGB = THETA(1)
  TVEMAX = THETA(2)*((CRCL/MCRCL)**THETA(6))
  TVEMAX =
  TVEMAX*(1+THETA(7)*SEXF)*(1+THETA(8)*BECU) TVEC50 =
  THETA(3)
  TVHILL = THETA(4)

  BASEHGB = TVBASEHGB*EXP(ETA(1))
  EMAX = TVEMAX*EXP(ETA(2))
  EC50 = TVEC50*EXP(ETA(3))
  HILL = TVHILL
  ;;ER MODEL PARAMETERS;;


  $DES
  C2 = A(2)/S2  ;mg/L
  DADT(1) = -KA*A(1)
  DADT(2) = KA*A(3) - (CL/V2)*A(2)
  DADT(3) = KA*A(1) - KA*A(3)
  DADT(4) = 0

  $ERROR
  CP = A(2)/S2

  ;;ER MODEL;;
  EDRUG =
  (EMAX*CP**HILL)/(EC50**HILL+CP**HILL) EFF =
  BASEHGB*(1+EDRUG)
  ;;ER MODEL;;

  W = SQRT(THETA(5)**2)

  ;;ERROR MODEL;;
IF (EFF.GT.0) THEN IPRED
  = EFF
  Y          = IPRED + W*ERR(1)
  IRES   =  DV  -  IPRED IWRES
  = IRES/W
  ELSE
```

```
Y = 0
IPRED = 0
IRES = 0
  IWRES = 0
ENDIF
;;ERROR MODEL;;

$THETA
(0,10)                  ;1 BASEHGB
(0.7)                   ;2 EMAX
(0,300)                 ;3 EC50
(0,5)                   ;4 HILL
(0,1)                   ;5 RE HGB ADD
(0.1)                   ;6 CRCL ON EMAX
  (-1, 0.1)             ;7 SEXF ON EMAX
  (0 FIX)                       ;8 BECU ON EMAX

$OMEGA BLOCK(2) CORRELATION
  0.01          ;11 ETA1 - BASEHGB
  -0.5          ;21 ETA21 - EMAX:BASEHGB
  0.35          ;22 ETA2 - EMAX
$OMEGA
  0.25          ;33 ETA3 - EC50
$SIGMA
  1 FIXED


$EST    METHOD=1 INTERACTION PRINT=10 MAXEVAL=9999 NOABORT NSIG=2 SIGL=6
$COV    MATRIX=R COMPRESS PRINT=E

$TABLE ID STUD LINE TIME ATFD NTFD CMT CP DOSE DOSEGRP FORM COHORT PNH EVID MDV DV BECU PRED IPRED RES WRES
    CWRES IRES IWRES NPDE NOPRINT NOAPPEND ONEHEADER FILE=fit.tab

$TABLE ID STUD CL V2 KA IETA1 IETA2 IETA3 CP BASEHGB EMAX EC50 HILL
    ETAS(1:LAST) FIRSTONLY NOPRINT NOAPPEND ONEHEADER FILE=patab.tab

$TABLE ETAS(1:last) ID DOSE STUD FORM SEXF RACE ETHN PNH
    BECU FIRSTONLY NOPRINT NOAPPEND ONEHEADER FILE=catab.tab

$TABLE ETAS(1:last) ID DOSE AGE BWT BHT BBMI BSA BALB BALT BAST BBILI BSCR BCRCL BEGFR ABEGFR
    BC3 BHGB FIRSTONLY NOPRINT NOAPPEND ONEHEADER FILE=cotab.tab
```

LDH Final Updated Model

```
$SIZES PD = -100
$PROB APELLIS APL-2 ER LDH APL2-302 & APL2-308 UPDATE

$INPUT C STUD USUBJID=DROP STID=DROP NMID=ID TIME ATFD NTFD DAY EVID AMT AMTM CONC
LCONC=DV MCONC LMCONC TYPE CMT MDV CFB PCFB BLDH ADDL II DOSE DOSEGRP FORM VISFLG BLQ AGE
SEXF RACE ETHN PNH BHT BWT BBMI
BSCR BALB BAST BALT BBILI BC3 BC3M BSA BCRCL BEGFR ABEGFR ECU BECU C3 C3M
ADAPEG ADAAPL TFLAG PTBFLAG LOCAL PRBC COHORT PRBCFLG LINE ICL IV2 IKA IF1
IETA1 IETA2 IETA3


$DATA  ../../../../../../DerivedData/ER/LDH/APL2_ER_LDH2_20211012V07.csv IGNORE=@
            IGNORE=(TYPE.EQ.2) ;APL-2 CONC
            IGNORE=(LOCAL.EQ.1) ;IGNORE LOCAL LAB
            RESULTS

$SUBROUTINE ADVAN6 TRANS1 TOL=6
$MODEL
  COMP = (DOSESC1)                    ; 1 DOSE SC PATH 1
  COMP = (CENTRAL,DEFOBS)   ; 2 APL2 CENTRAL
  COMP = (TRANSIT1)                   ; 3 SC TRANSIT1
  COMP = (LDH)                        ; 4 LDH CONC


$PK
  ;; CATEGORICAL COVARIATES;;


;;PK                    MODEL
  PARAMETERS;; CL = ICL
  V2   =   IV2
  KA  =  IKA
  F1 = IF1

  S2 = V2                             ; dose = mg, conc = mcg/mL = mg/L
;;PK MODEL PARAMETERS;;

;;ER MODEL
  PARAMETERS;;
  TVBLDH = THETA(1)
```

```
  IF(BECU.EQ.1) TVBLDH = THETA(2)

  TVEMAX = THETA(3)
  IF (BECU.EQ.1) TVEMAX = THETA(4) + THETA(8)*ECU
  TVEC50 = THETA(5)

  TVHILL = THETA(6)

  BASELDH = EXP(TVBLDH + ETA(1))
  EMAX =
  EXP(TVEMAX+ETA(2))/(EXP(TVEMAX+ETA(2))+1) EC50
  = EXP(TVEC50 + ETA(3))
  HILL = TVHILL
;;ER MODEL PARAMETERS;;


$DES
C2 = A(2)/S2  ;mg/L
DADT(1) = -KA*A(1)
DADT(2) = KA*A(3) - (CL/V2)*A(2)
DADT(3) = KA*A(1) - KA*A(3)
DADT(4) = 0

$ERROR
CP = A(2)/S2

;;ER MODEL;;
EDRUG =
(EMAX*CP**HILL)/(EC50**HILL+CP**HILL) EFF =
BASELDH*(1-EDRUG)
;;ER MODEL;;

W = SQRT(THETA(7)**2)

;;ERROR MODEL;;
IF (EFF.GT.0) THEN IPRED
 = LOG(EFF)
 Y        = IPRED + W*ERR(1)
 IRES   =  DV  -  IPRED IWRES
 = IRES/W
 ELSE
 Y = 0
```

```
IPRED = 0
IRES = 0
 IWRES = 0
ENDIF
;;ERROR MODEL;;

$THETA
(7.5)                   ;1 LOG BASELDH
(5.4)                   ;2 LOG BASELDH BECU
 (2)                    ;3 LOGIT EMAX
 (-1.5)                 ;4 LOGIT EMAX BECU
 (2.2)                  ;5 LOG EC50
 (2.9)                  ;6 HILL
 (0,0.3)                ;7 RE LDH LOG ADD
 (0.5)                  ;8 ECU ON EMAX

$OMEGA BLOCK(3)
 0.2             ;11 ETA1 - BASELDH
 -0.02           ;21 ETA21 - EMAX:BASELDH
 0.2             ;22 ETA2 - EMAX
 0                       ;31 ETA31 - EC50:BASELDH
 0.02            ;32 ETA32 - EC50:EMAX
 0.2             ;33 ETA3 - EC50

$SIGMA
 1 FIXED


$EST    METHOD=1 INTERACTION PRINT=10 MAXEVAL=9999 NOABORT NSIG=2 SIGL=6
$COV    MATRIX=R COMPRESS PRINT=E

$TABLE ID STUD LINE TIME ATFD NTFD CMT CONC CP DOSE DOSEGRP FORM COHORT PNH LOCAL EVID MDV DV BECU PRED IPRED RES WRES CWRES IRES IWRES
NPDE
   NOPRINT NOAPPEND ONEHEADER FILE=fit.tab

$TABLE ID STUD CL V2 KA IETA1 IETA2 IETA3 CP BASELDH EMAX EC50 HILL ETAS(1:LAST) FIRSTONLY
   NOPRINT NOAPPEND ONEHEADER FILE=patab.tab

$TABLE ETAS(1:last) ID DOSE STUD FORM SEXF RACE ETHN PNH BECU FIRSTONLY
   NOPRINT NOAPPEND ONEHEADER FILE=catab.tab

$TABLE ETAS(1:last) ID DOSE AGE BWT BHT BBMI BSA BALB BALT BAST BBILI BSCR BCRCL BEGFR ABEGFR BC3 BLDH FIRSTONLY NOPRINT
   NOAPPEND ONEHEADER FILE=cotab.tab
```

Hb, hemoglobin; LDH, lactate dehydrogenase; PK, pharmacokinetic

Supplemental Table 2. Summary of categorical and continuous covariates by study

Covariate	CP0713-1 N=24	CP1014 N=16	101 N=36	102 N=16	401 N=16	AIRIS N=16	PHAROAH (NCT02264639) N=9	PADDOCK (NCT02588833) N=22	PALOMINO (NCT03593200) N=4	PEGASUS (NCT03500549) N=80	PRINCE (NCT04085601) N=45	Total N=284
Patient status, n (%)												
Healthy	24 (100)	16 (100)	36 (100)	16 (100)	16 (100)	16 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	124 (44)
PNH patient	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	9 (100)	22 (100)	4 (100)	80 (100)	45 (100)	160 (56)
Race												
White	22 (91.7)	15 (93.8)	27 (75.0)	0 (0)	11 (68.8)	15 (93.8)	8 (88.9)	3 (13.6)	4 (100)	49 (61.3)	0 (0)	154 (54.2)
Black	0 (0)	0 (0)	2 (5.60)	0 (0)	0 (0)	0 (0)	1 (11.1)	0 (0)	0 (0)	2 (2.50)	2 (4.40)	7 (2.50)
Asian	2 (8.30)	1 (6.20)	5 (13.9)	16 (100)	2 (12.5)	0 (0)	0 (0)	15 (68.2)	0 (0)	12 (15.0)	32 (71.1)	85 (29.9)
Other	0 (0)	0 (0)	2 (5.60)	0 (0)	3 (18.8)	1 (6.20)	0 (0)	4 (18.2)	0 (0)	1 (1.20)	11 (24.4)	22 (7.70)
Missing	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	16 (20.0)	0 (0)	16 (5.60)
Sex												
Male	17 (70.8)	14 (87.5)	28 (77.8)	13 (81.2)	7 (43.8)	10 (62.5)	1 (11.1)	13 (59.1)	1 (25.0)	31 (38.8)	23 (51.1)	158 (55.6)
Female	7 (29.2)	2 (12.5)	8 (22.2)	3 (18.8)	9 (56.2)	6 (37.5)	8 (88.9)	9 (40.9)	3 (75.0)	49 (61.3)	22 (48.9)	126 (44.4)
Age (years), median (range)	27.0 (21.0, 55.0)	28.0 (23.0, 38.0)	29.0 (19.0, 47.0)	38.0 (29.0, 50.0)	25.5 (22.0, 49.0)	65.0 (25.0, 72.0)	48.0 (24.0, 72.0)	38.0 (22.0, 67.0)	27.0 (22.0, 47.0)	50.5 (19.0, 81.0)	41.0 (22.0, 74.0)	36.0 (19.0, 81.0)
Weight (kg), median (range)	71.1 (61.5, 79.2)	68.2 (60.8, 78.9)	72.6 (52.8, 88.4)	68.7 (54.4, 84.2)	68.9 (56.7, 88.6)	80.0 (52.8, 93.0)	78.1 (57.0, 148)	63.4 (42.3, 102)	80.1 (65.0, 87.0)	72.4 (51.0, 156)	61.8 (41.0, 95.0)	70.0 (41.0, 156)
Baseline C3 (g/L), median (range)[a]	1.07 (0.750, 1.51)	1.07 (0.760, 1.40)	1.00 (0.640, 1.51)	1.15 (0.780, 1.59)	1.15 (0.855, 1.59)	1.00 (0.850, 1.23)	1.17 (0.820, 1.400)	0.905 (0.630, 1.25)	1.15 (0.900, 1.20)	0.875 (0.470, 1.64)	0.920 (0.600, 1.44)	1.00 (0.470, 1.64)

[a]There were data for patients missing from PEGASUS (n=16 missing) and PRINCE (n=2 missing).

Supplemental Table 3. Parameter Estimates for the PK Model

Theta/Parameter (Units)	Estimate	ASE	% RSE	95% CI
1 TVCL (L/h)	0.0117	0.000577	4.94	0.0106–0.0128
2 TVV2 (L)	3.96	0.196	4.96	3.57–4.34
3 TVKA (h^{-1})	0.0370	0.00138	3.73	0.0343–0.0397
4 F1	0.758	0.0389	5.13	0.681–0.834
8 Lyophilized formulation on F1	0.220	0.0385	17.5	0.145–0.296
9 PNH on CL	0.257	0.0302	11.8	0.197–0.316
10 WT on CL	0.646	0.0666	10.3	0.515–0.776
11 WT on V2	0.809	0.0847	10.5	0.643–0.975
Residual variability (%)				
5 RE healthy subjects	20.0			19.4–20.6
6 RE PNH Phase 1 and 2	32.6			30.7–34.6
7 RE PNH Phase 3	16.3			15.7–16.9
IIV (CV%)				
ETA1 – CL	20.9			18.8–22.9
ρ (ETA1-CL, ETA2-V2)	0.571			-
ETA2 – V2	21.4			18.6–23.8
ETA3 – KA	52.5			46.0–58.5
OFV	–8708.818			
CN	90			

ASE, asymptotic standard error; CI, confidence interval; CL, clearance; CN, condition number; CV, coefficient of variation; ETA, interindividual random effect parameter sampled from N(0, ω2); F1, subcutaneous bioavailability; IIV, interindividual variability; KA, first-order absorption rate constant; OFV, objective function value; PK, pharmacokinetics; PNH, patients with paroxysmal nocturnal hemoglobinuria; RE, proportional residual error; RSE, relative standard error; TVCL, typical value of clearance; TVKA, typical value of first-order absorption rate constant; TVV2, typical value of volume of the central compartment; V2, volume of the central compartment; WT, body weight.

Supplemental Table 4. Parameter Estimates for the Hb PK/PD Model

Theta/Parameter (Units)	Estimate (Transformed Estimate[a])	ASE	% RSE	95% CI (Transformed 95% CI[a])
1 BaseHb (g/dL)	8.74	0.0950	1.09	8.55–8.93
2 E_{max}	0.510	0.0402	7.88	0.431–0.589
3 EC50 (µg/mL)	337	17.9	5.30	302–372
4 Hill	4.66	0.435	9.33	3.81–5.52
6 CrCl on E_{max}	0.641	0.106	16.6	0.433–0.850
7 Female sex on E_{max}	–0.337	0.0609	18.0	–0.457 to –0.218
Residual Variability				
5 RE Additive (g/dL)	0.913			0.888–0.938
IIV				
$\omega_{1,1}^2$ BaseHb	0.0162 (12.8 CV%)			0.0119–0.0204 (10.9–14.4 CV%)
$\omega_{2,1}$ E_{max}:BaseHb	–0.0437 (ρ = –0.580)			–0.062 to –0.026
$\omega_{2,2}^2$ E_{max}	0.351 (64.8 CV%)			0.239–0.463 (52.0–76.7 CV%)
$\omega_{3,3}^2$ EC50	0.291 (58.1 CV%)			0.201–0.381 (47.2–68.1 CV%)
CN	16.1			

ASE, asymptotic standard error; BaseHb, population estimate of baseline hemoglobin level; CI, confidence interval; CN, condition number; CrCl, creatinine clearance calculated using the Cockcroft-Gault equation; CV, coefficient of variation; EC50, pegcetacoplan concentration eliciting 50% of maximal effect; E_{max}, maximum proportional drug effect; ETA, interindividual random effect parameter sampled from N(0, ω2); Hb, hemoglobin; Hill, sigmoidicity coefficient; IIV, interindividual variability; PK, pharmacokinetic; RE, residual error; RSE, relative standard error.

[a]Transformations are calculated as the exponentiation of the estimate for log-transformed parameters, the anti-logit of the estimate for logit transformed parameters, CV% calculated as $(\sqrt{\exp(\omega^2)} - 1) \cdot 100\%$ for log-normal IIV parameters, and the correlation coefficient for off-diagonal IIV parameters. η-shrinkage: 5.4% ($\eta_1^{BaseLDH}$), 17.5% ($\eta 2^{Emax}$), 30.3% ($\eta 3^{EC50}$).

Supplemental Table 5. PK/PD Parameter Estimates for the LDH PK/PD Model

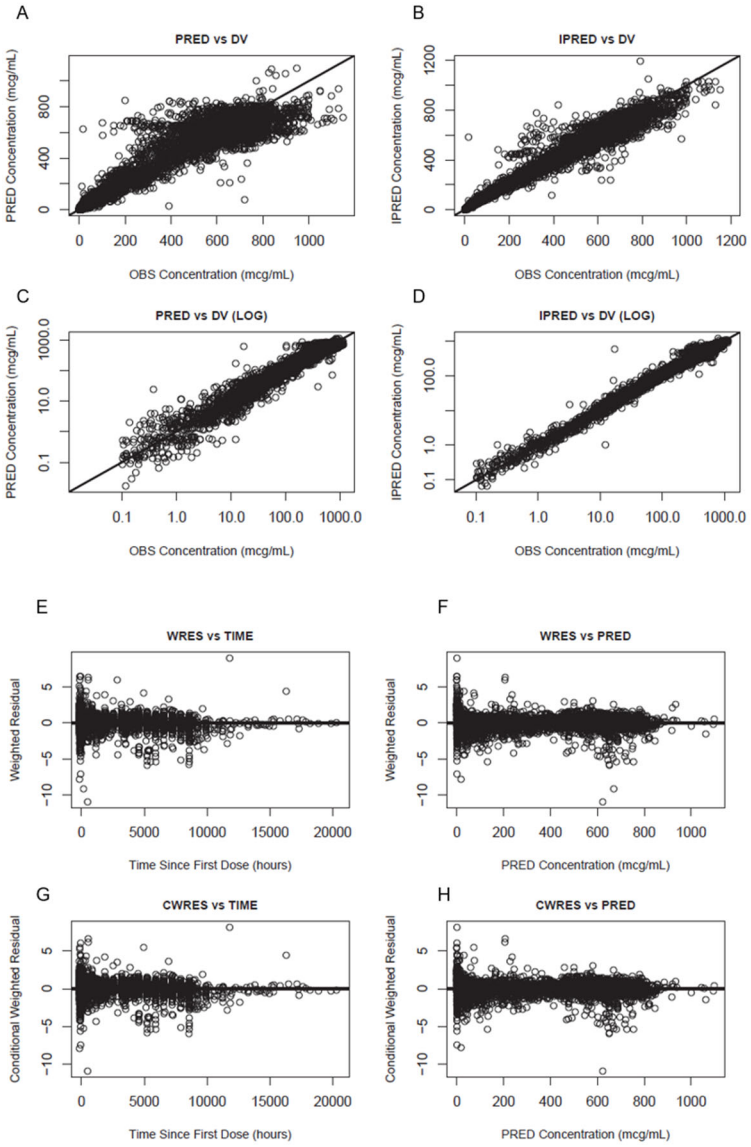
Theta/Parameter (Units)	Estimate	ASE	% RSE	95% CI	Transformed Estimate[a]	Transformed 95% CI[a]
1 Log BaseLDH (U/L)	7.56	0.0539	0.712	7.46–7.67	1920	1740–2140
2 Log BaseLDH BECU (U/L)	5.52	0.0477	0.865	5.42–5.61	249	226–273
3 Logit E_{max}	2.40	0.117	4.85	2.17–2.63	0.917	0.898–0.933
4 Logit E_{max} BECU	–1.39	0.135	9.70	–1.65 to –1.12	0.200	0.161–0.246
5 Log EC50 (μg/mL)	5.23	0.0614	1.17	5.11–5.35	187	166–211
6 Hill	3.42	0.296	8.65	2.84–4.00	--	--
8 Eculizumab Co-treatment on Logit E_{max}	0.783	0.0907	11.6	0.605–0.961	--	--
Residual Variability						
7 Log additive	0.305	0.00406	1.33	0.297–0.313	30.5%	29.7–31.3%
IIV						
$\omega_{1,1}^2$ BaseLDH	0.182			0.138–0.226	44.7 CV%	38.5–50.4 CV%
$\omega_{2,1}$ E_{max}:BaseLDH	0.265			0.185–0.344	0.719	--
$\omega_{2,2}^2$ E_{max}	0.745			0.506–0.983	--	--
$\omega_{3,2}$ EC50:E_{max}	0.167			0.0903–0.244	0.556	--
$\omega_{3,3}^2$ EC50	0.121			0.0616–0.181	35.9 CV%	25.2–44.5 CV%
CN	196					

ASE, asymptotic standard error; CI, confidence interval; CN, condition number; CV, approximate coefficient of variation; BaseLDH, population estimate of baseline lactate dehydrogenase level; BECU, baseline eculizumab; EC50, pegcetacoplan concentration eliciting 50% of maximal effect; E_{max}, maximum proportional drug effect; Hill, sigmoidicity coefficient; IIV, interindividual variability; PD, pharmacodynamic, PK, pharmacokinetic; RE, residual error; RSE, relative standard error.

[a]Transformations are calculated as the exponentiation of the estimate for log-transformed parameters, the anti-logit of the estimate for logit transformed parameters, CV% calculated as $(\sqrt{\exp(\omega^2)} - 1) \cdot 100\%$ for log-normal IIV parameters, and the correlation coefficient for off-diagonal IIV parameters. η-shrinkage: 5.4% ($\eta_1^{BaseLDH}$), 17.5% ($\eta 2^{Emax}$), 30.3% ($\eta 3^{EC50}$).

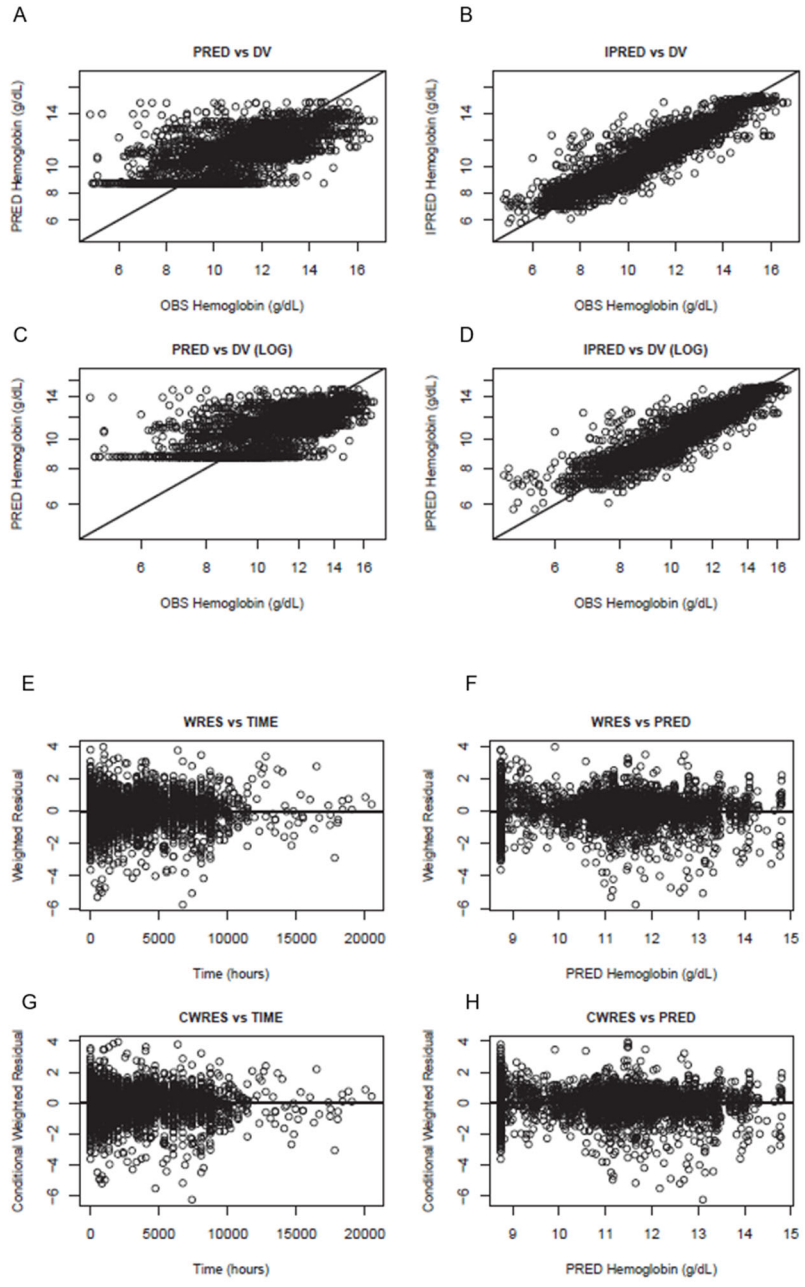
Covariate effects were evaluated using centered additive parameterizations for continuous covariates and additive parameterizations for categorical covariates on the transformed scale.

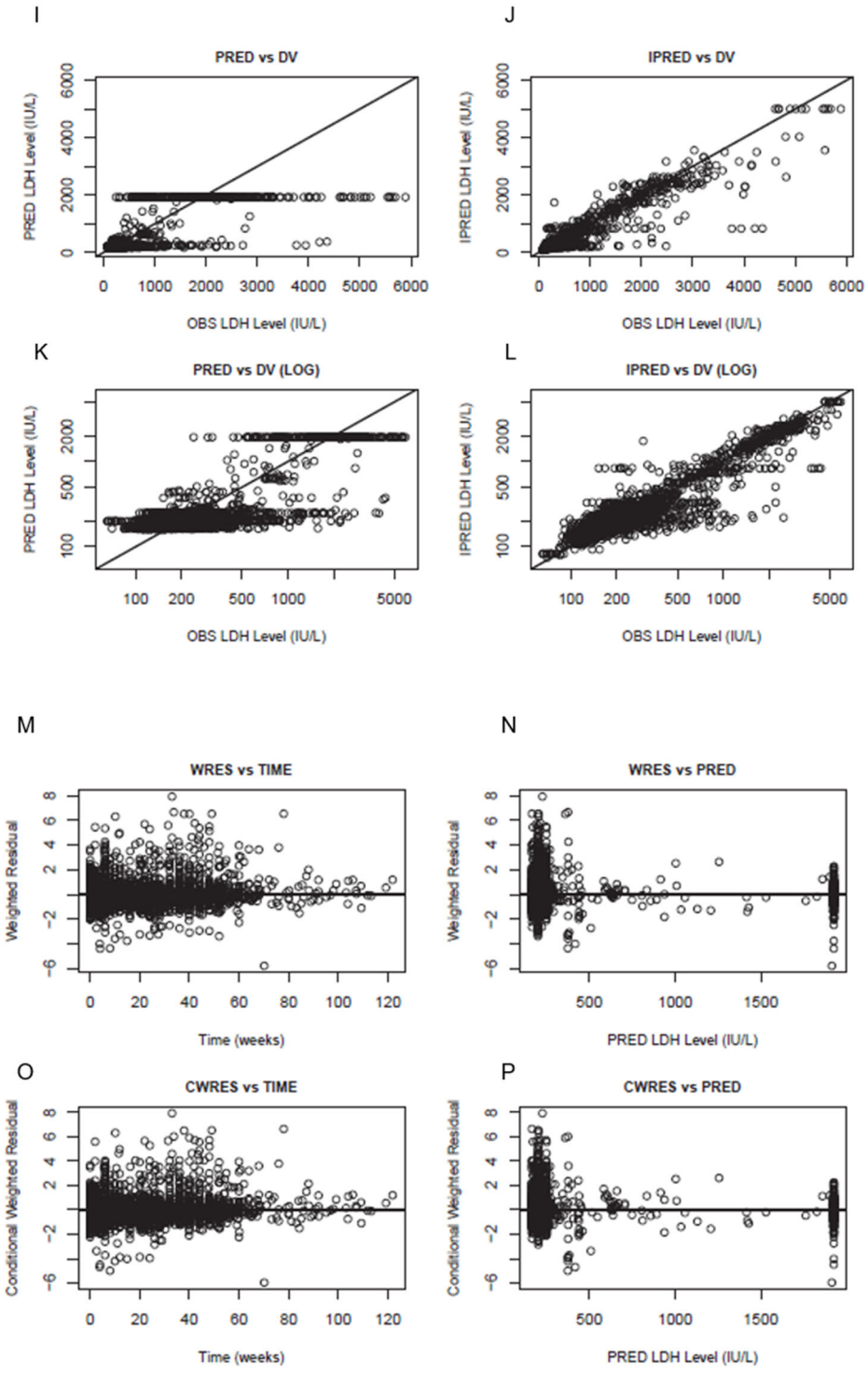
Supplemental Figure 1. Goodness-of-fit Plots for the PK model



CWRES, conditional weighted residuals; DV, observations; IPRED, individual predictions; OBS, observed; PRED, predicted; WRES, weighted residuals

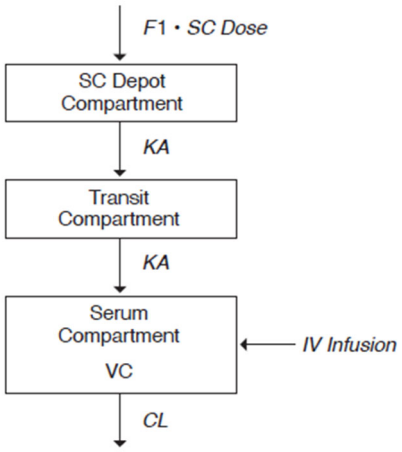
Supplemental Figure 2 Goodness-of-fit Plots for the PK/PD model for Hb (A-G) and LDH (I-P)





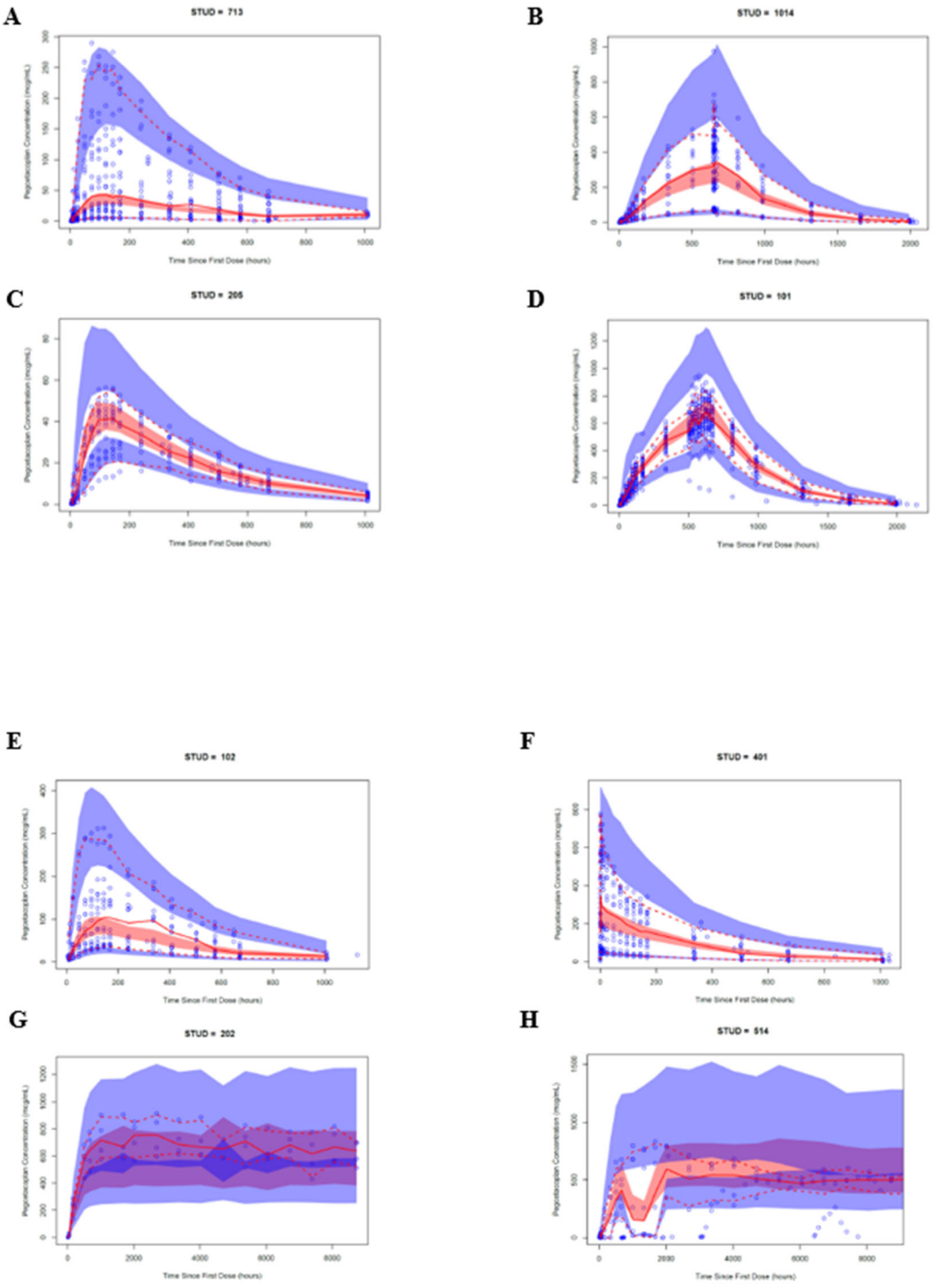
CWRES, conditional weighted residuals; DV, observations; IPRED, individual predictions; LDH, lactate dehydrogenase; OBS, observed; PRED, predicted; WRES, weighted residuals

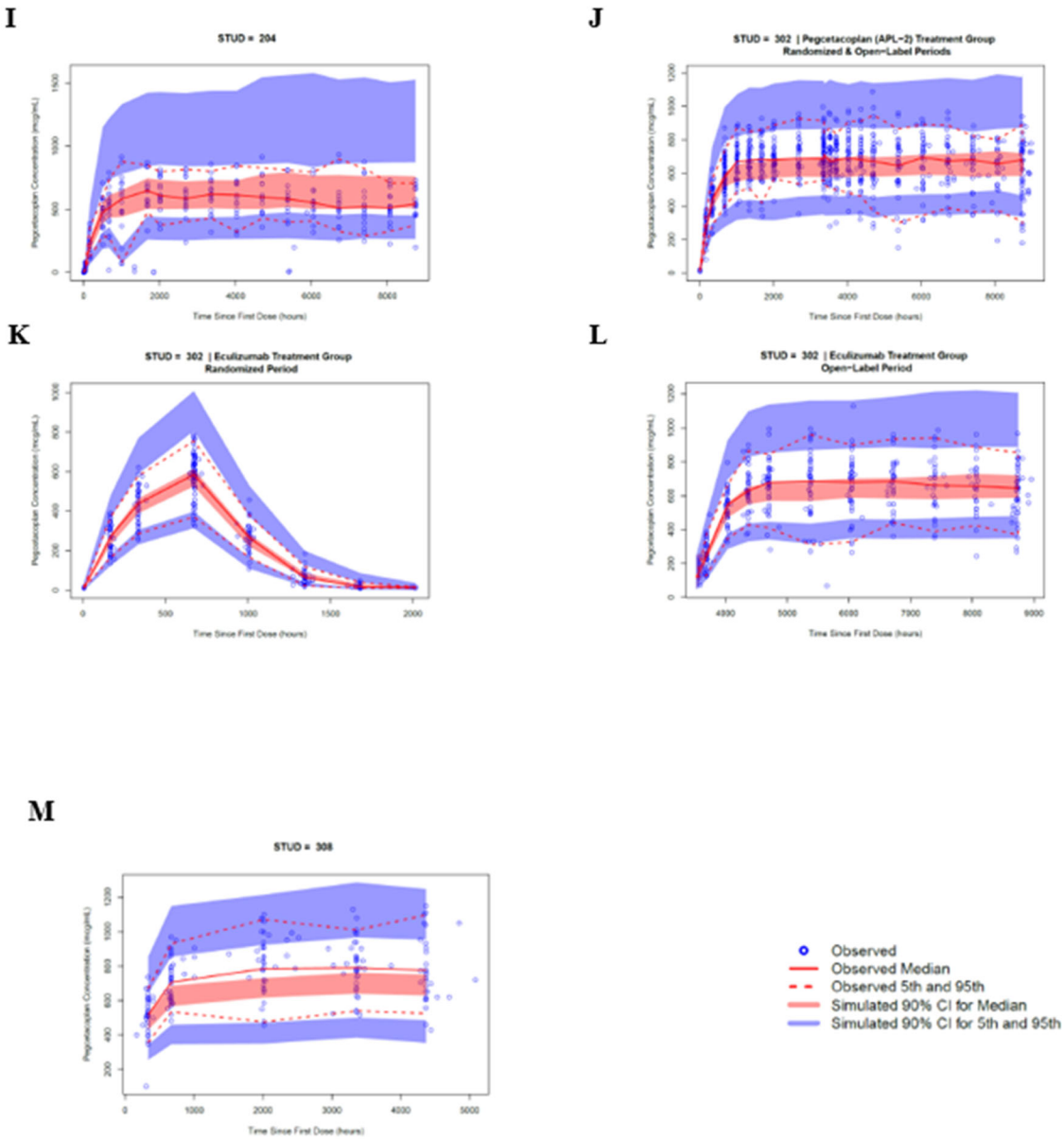
Supplemental Figure 3. Model Structure for Population PK analysis



CL, clearance; F1, subcutaneous bioavailability; KA, first-order absorption rate constant; IV, intravenous; PK, pharmacokinetics; SC, subcutaneous; VC, volume of distribution in the central compartment.

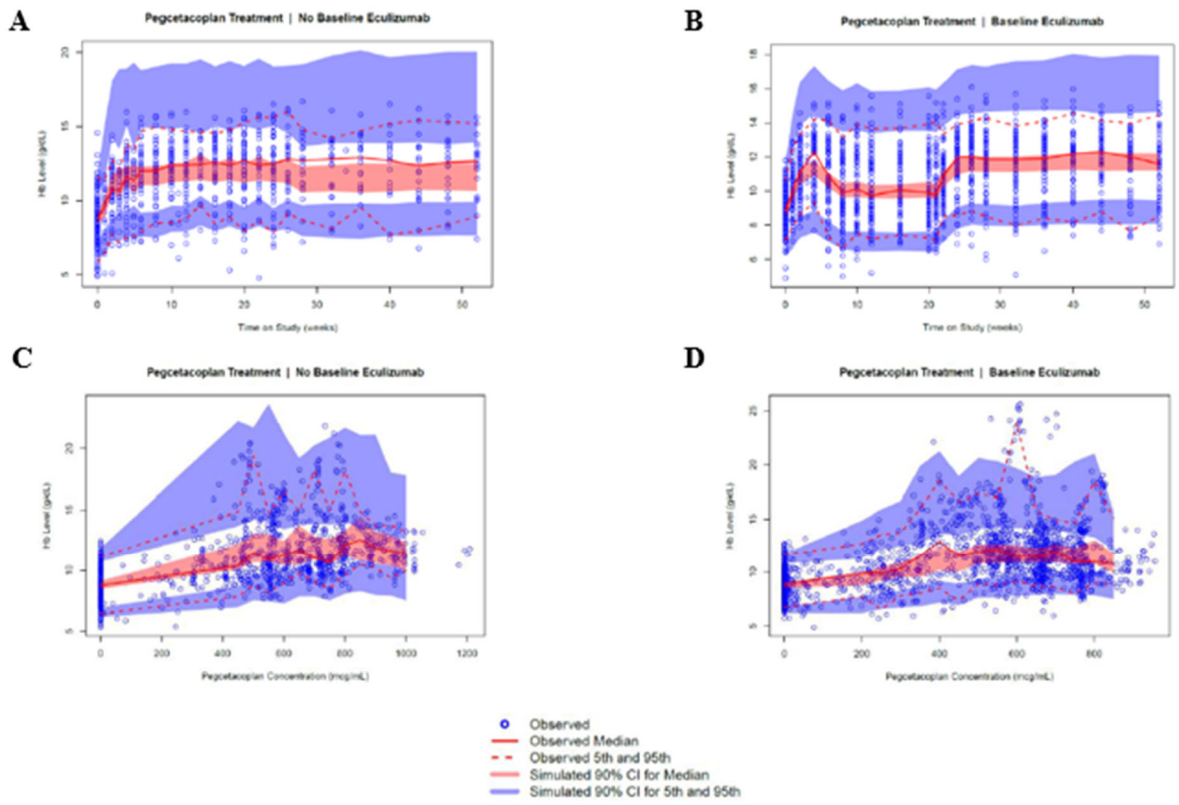
Supplemental Figure 4. Visual Predictive Check Plots by Study for PK Model





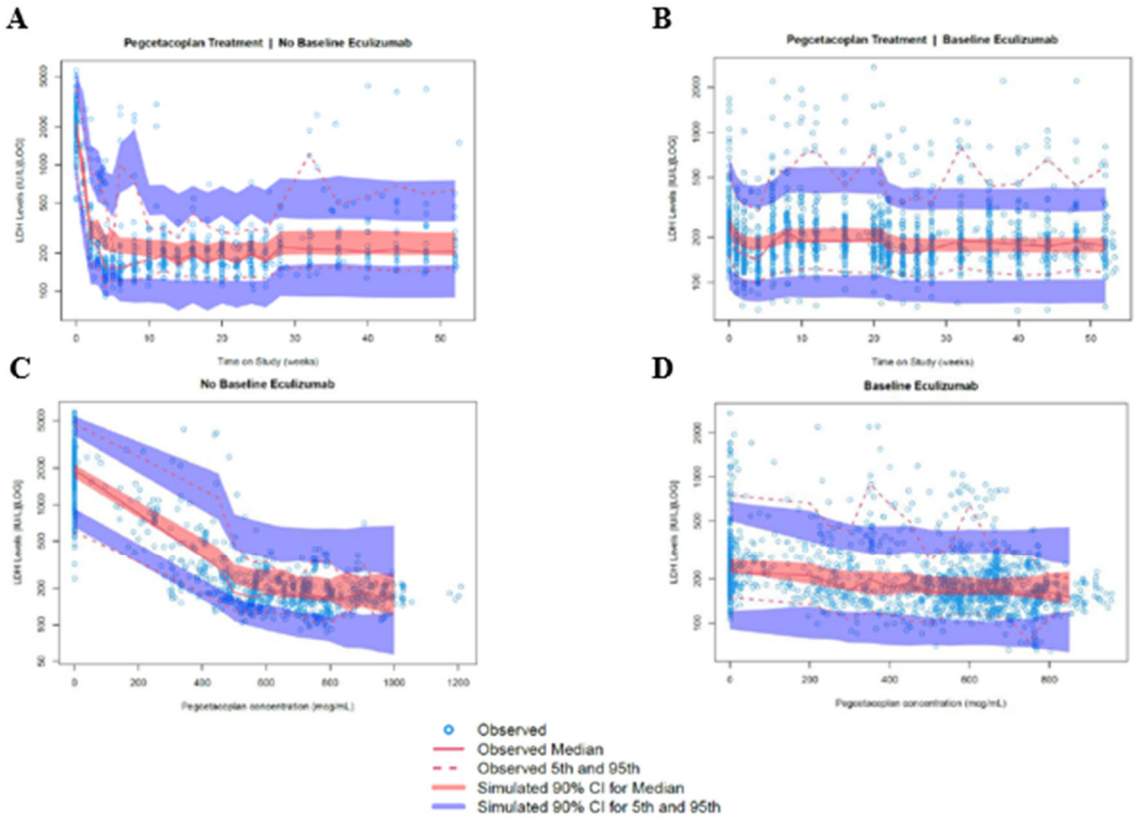
PK, pharmacokinetics.

Supplemental Figure 5. Visual Predictive Check Plots for the Hb PK/PD Model – Stratified by Baseline Eculizumab Treatment Status



Hb, hemoglobin; PD, pharmacodynamics; PK, pharmacokinetics.

Supplemental Figure 6. Visual Predictive Check Plots for the LDH PK/PD Model – Stratified by Baseline Eculizumab Treatment Status



CI, confidence interval; LDH, lactate dehydrogenase; PD, pharmacodynamics; PK, pharmacokinetics.