P9185 Project 1: Protocol of a Phase II MATIK Trial

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I. Introduction

II. Study Design and Material

Notation:

k :subject, $k = 1, ..., 180$
j :sequence, $j = 0, 1, 2$
i :period, $i = 1, 2, 3$
h :week, $h = 1, 2, 3, 4$
π :period effect
τ :treatment effect
α :grouped treatment effects
β :demographic effects
λ :sequence/carryover effect
γ :week effect
b :subject-specific intercepts
μ :fixed-effect intercept
ε :residual error

Table 1: Distributional Summary of Predictor variables in the Study

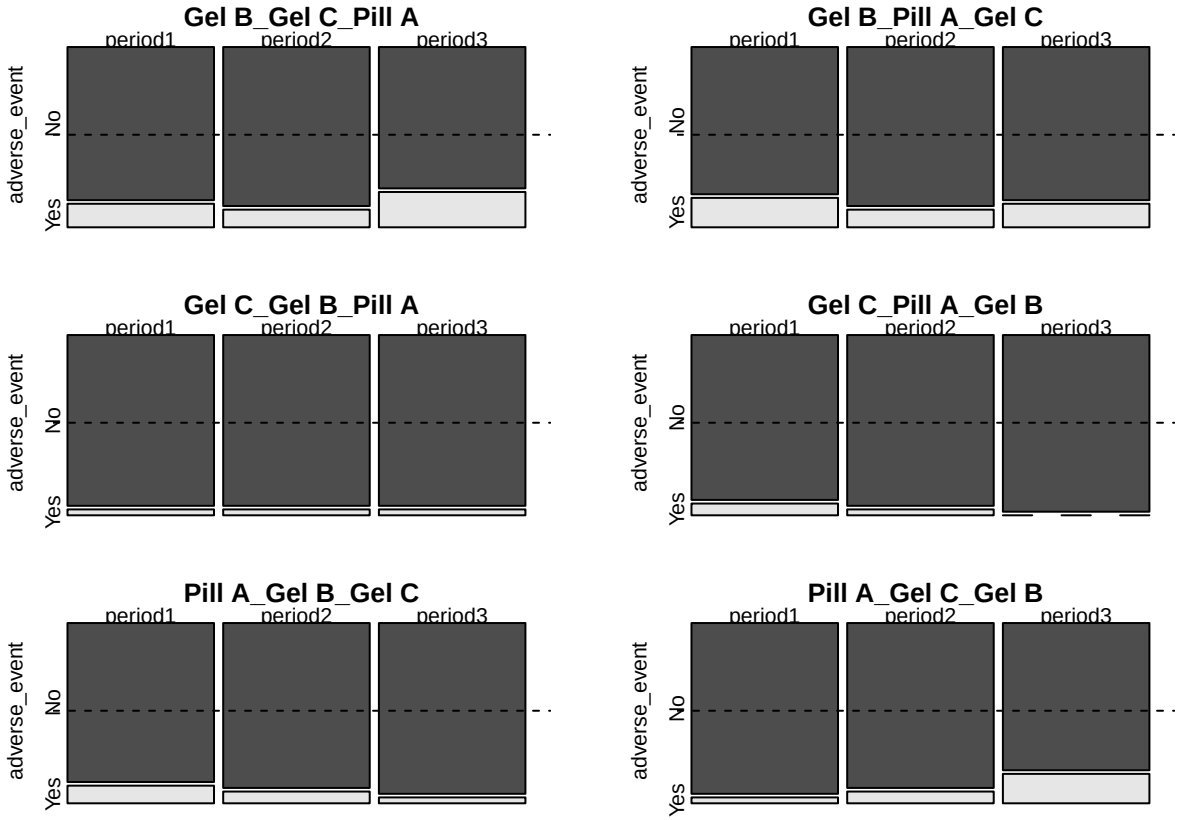
Characteristic	period1			period2		
	No N = 164	**Yes** N = 16	**p-value**	**No** N = 168	**Yes** N = 12	**p-value**
age	31 (25, 37)	42 (40, 44)	<0.001	32 (25, 38)	40 (37, 44)	<0.001

[1] Median (Q1, Q3)

[2] Wilcoxon rank sum test

Primary Objectives: Adverse Event

Proportion of Adverse Events per period



Patient Distribution: 30 people in per treatment sequence Initial Observation: Most patients do not face adverse events over the course of 4 weeks in each of the consecutive periods.

add demographic data

demographic summary

GLMM

Model Selection

Characteristic	OR	95% CI	p-value
(Intercept)	0.00	0.00, 0.00	**<0.001**
Treatment			
Pill A	—	—	
Gel B	1.20	0.55, 2.64	0.6
Gel C	0.84	0.37, 1.92	0.7
Period			
period1	—	—	
period2	0.71	0.31, 1.64	0.4
period3	1.13	0.52, 2.46	0.8
Treatment Sequence			
ABC or BAC	—	—	
CAB or ACB	0.61	0.23, 1.62	0.3
BCA or CBA	0.84	0.35, 2.02	0.7
age	1.19	1.11, 1.27	**<0.001**
gender			
Female	—	—	
Male	0.90	0.43, 1.89	0.8
race			
black	—	—	
others	1.55	0.61, 3.95	0.4
white	1.74	0.65, 4.68	0.3

Abbreviations: CI = Confidence Interval, OR = Odds Ratio

Table 2: LRT Between Model w/ and w/o Interaction Between Tx and Period

term	npar	AIC	BIC	logLik	minus2logL	statistic	df	p.value
glmm2	12	278.67	330.17	-127.34	254.67	NA	NA	NA
glmm1	16	281.34	350.01	-124.67	249.34	5.33	4	0.25

Table 3: LRT Between Model w/ and w/o Race, Gender and Carryover Effect

term	npar	AIC	BIC	logLik	minus2logL	statistic	df	p.value
glmm3	7	271.25	301.29	-128.62	257.25	NA	NA	NA
glmm2	12	278.67	330.17	-127.34	254.67	2.57	5	0.77

Characteristic	OR	95% CI	p-value
(Intercept)	0.00	0.00, 0.00	**<0.001**
Treatment			
Pill A	—	—	
Gel B	1.18	0.54, 2.58	0.7
Gel C	0.85	0.37, 1.94	0.7
Period			
period1	—	—	
period2	0.72	0.31, 1.65	0.4
period3	1.11	0.51, 2.40	0.8
age	1.19	1.12, 1.27	**<0.001**

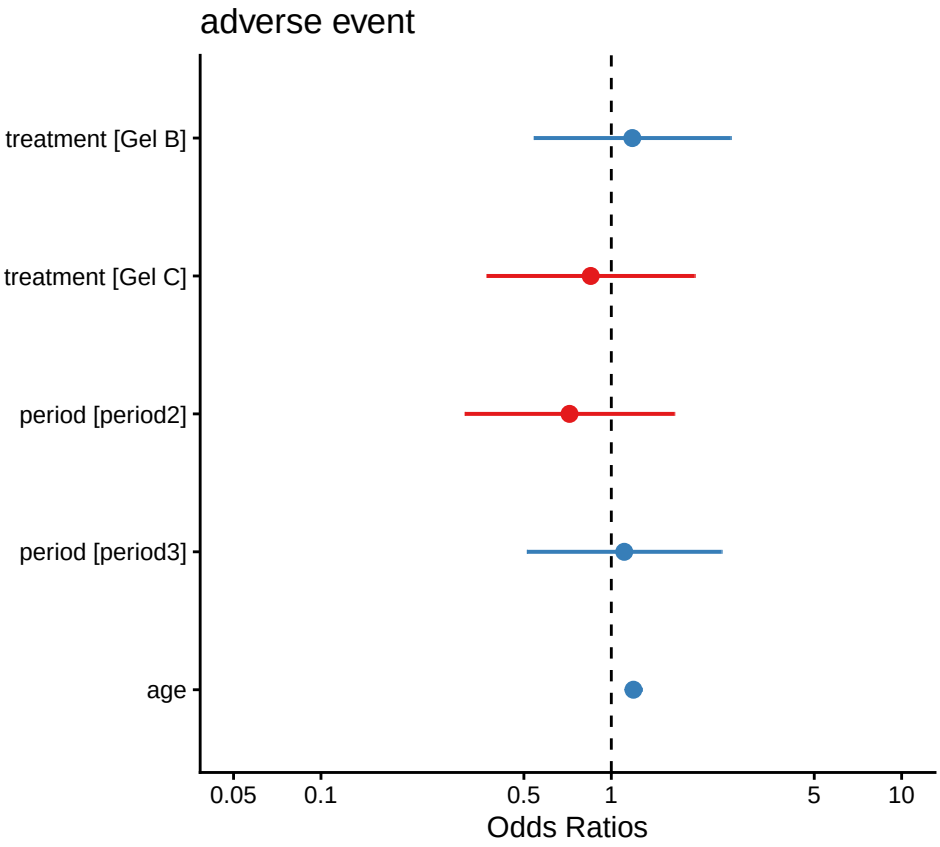
Abbreviations: CI = Confidence Interval, OR = Odds Ratio

Model Result (with Carryover Effect)

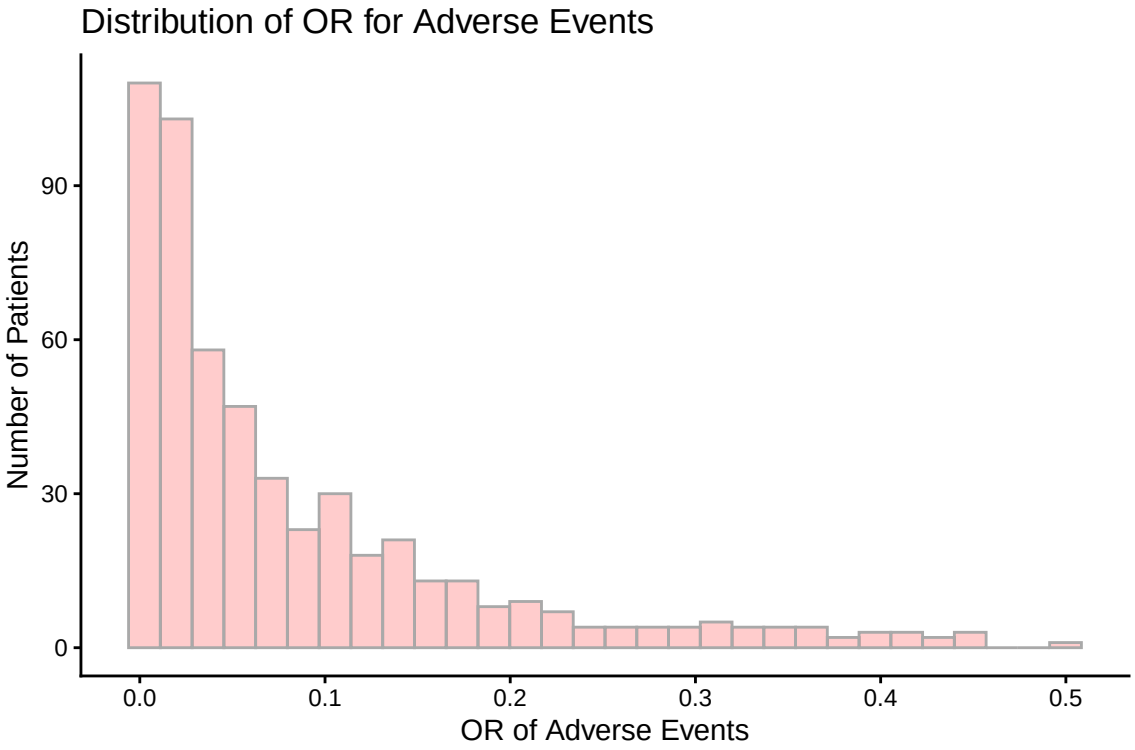
Final Model Result (without Carryover Effect)

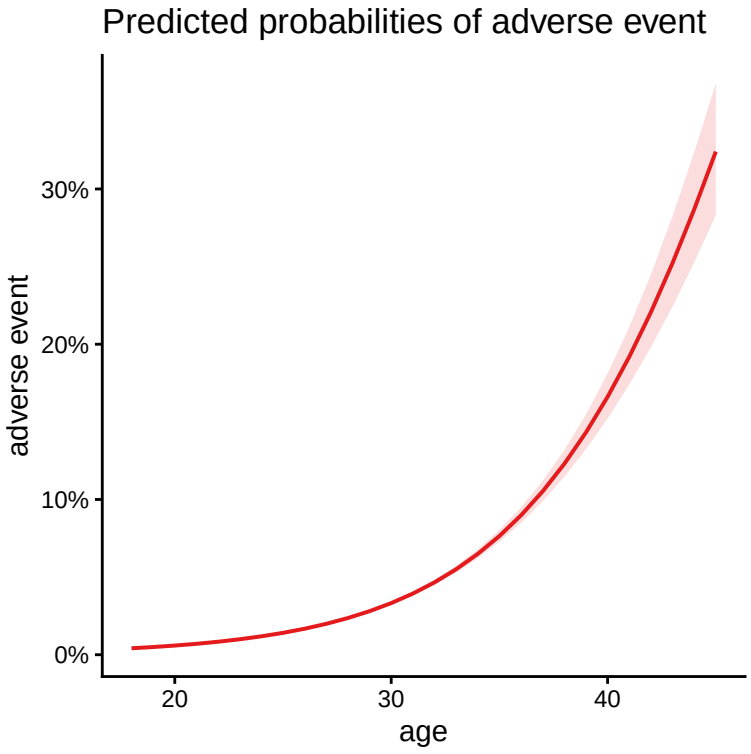
Notation:

$$\widehat{logit}(P(AE_{ijk}=1)) = b_k + \mu + \tau_i + \pi_j + \beta a_k,$$
$$i = 1,2,3,\ j = 1,2,3,\ k = (1,2,\ldots,180),$$
$$b_k \sim N(0, \sigma^2{}_b)$$



AE Prediction

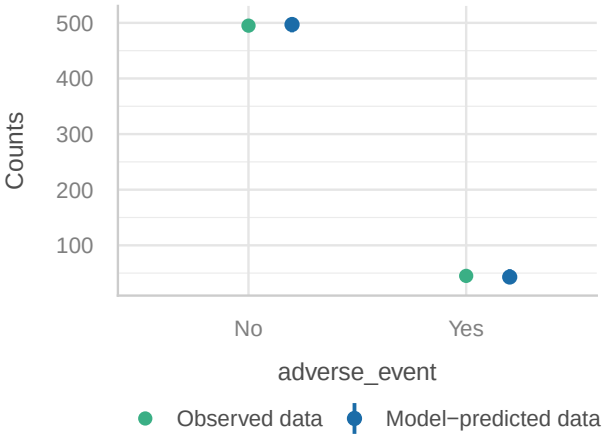




Model Diagnostics

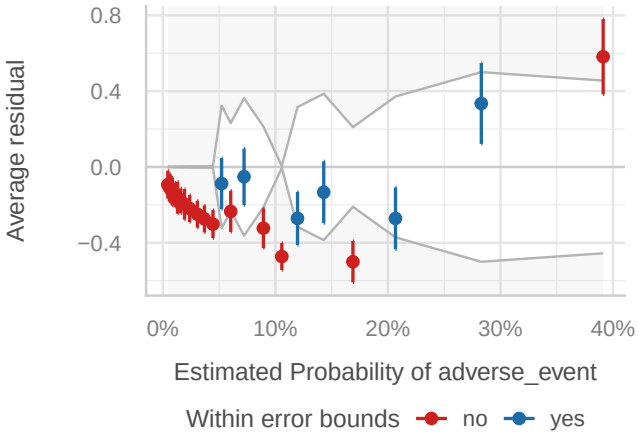
Posterior Predictive Check

Model−predicted intervals should include observed data points



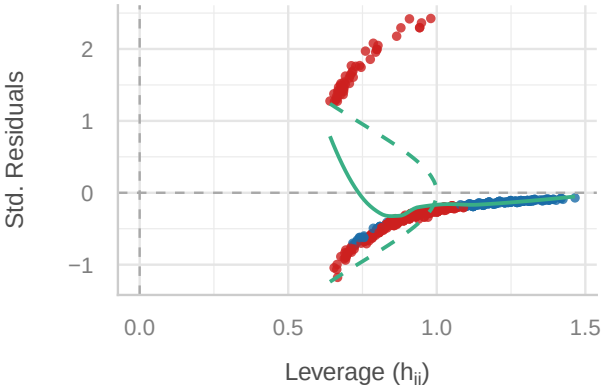
Binned Residuals

Points should be within error bounds



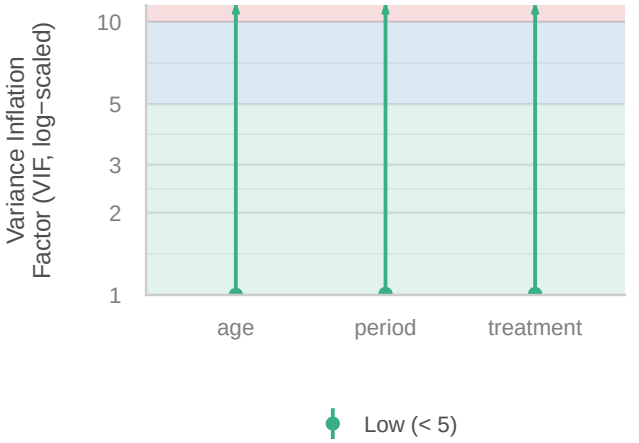
Influential Observations

Points should be inside the contour lines



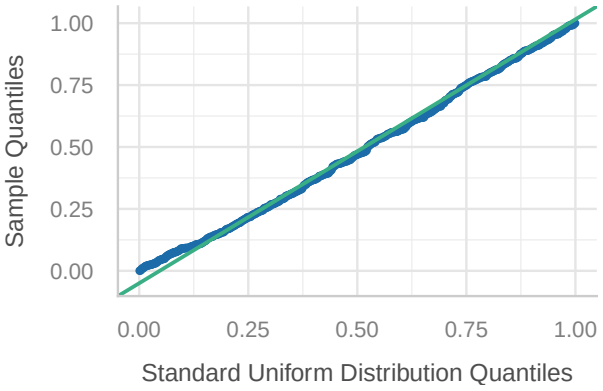
Collinearity

High collinearity (VIF) may inflate parameter uncertainty



Distribution of Quantile Residuals

Dots should fall along the line



Normality of Random Effects (ptid)

Dots should be plotted along the line

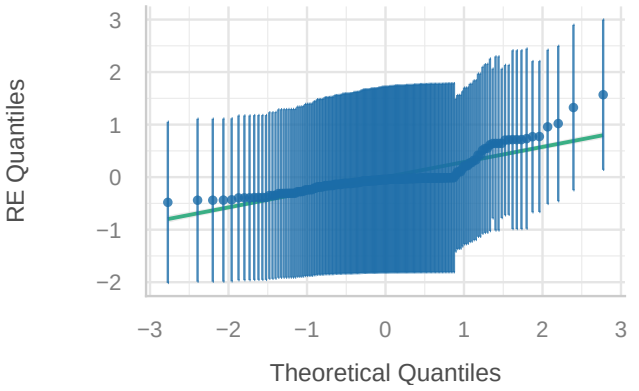


Table 4: **Table 1. Baseline Characteristics**

Characteristic	**Overall** N = 180[1]	**ABC** N = 30[1]	**ACB** N = 30[1]	**BAC** N = 30[1]	**BCA** N = 30
Age (years)	32 (8) [18, 45]	33 (8) [19, 44]	31 (7) [18, 42]	31 (7) [20, 44]	33 (8) [19, 45]
Race					
Black	64 (36%)	12 (40%)	13 (43%)	12 (40%)	10 (33%)
White	52 (29%)	8 (27%)	9 (30%)	7 (23%)	7 (23%)
Other	64 (36%)	10 (33%)	8 (27%)	11 (37%)	13 (43%)
Female	81 (45%)	13 (43%)	11 (37%)	16 (53%)	14 (47%)

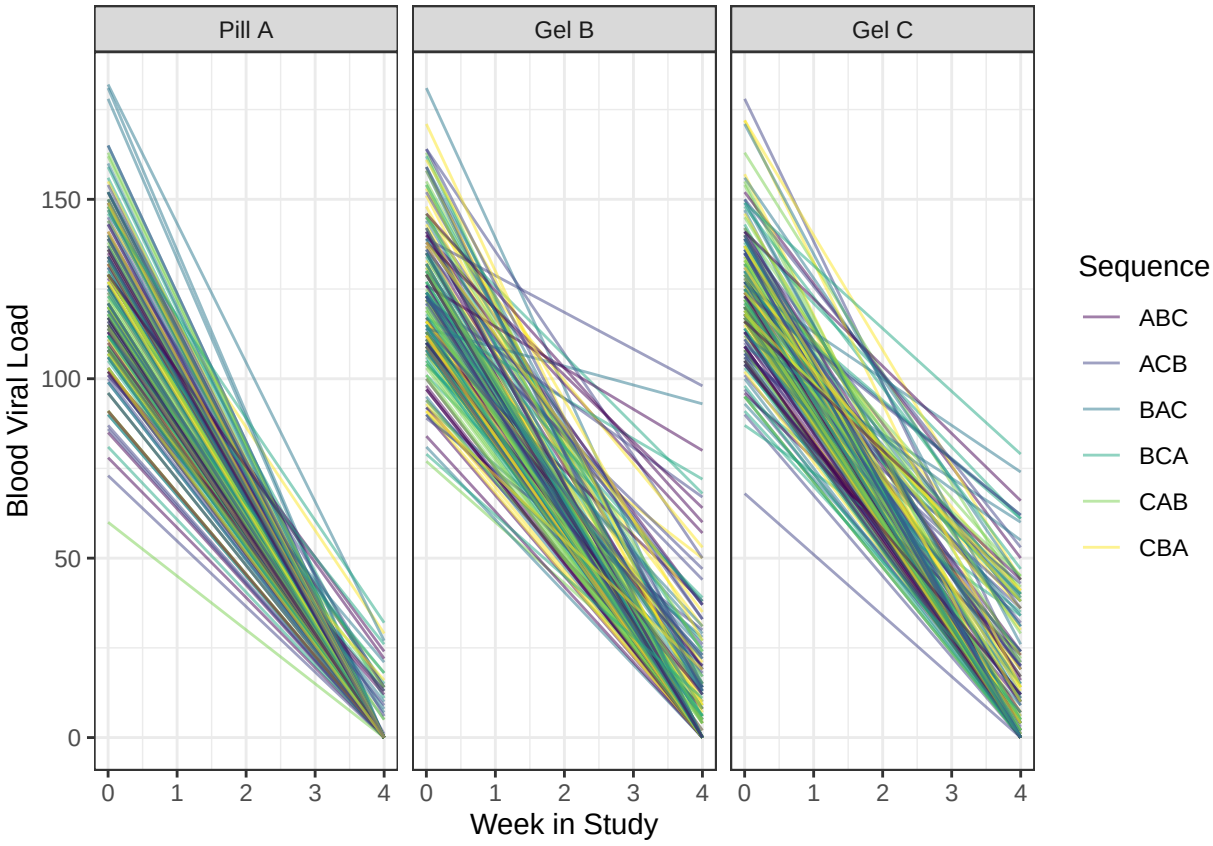
[1]Mean (SD) [Min, Max]; n (%)
[2]Kruskal-Wallis rank sum test; Pearson's Chi-squared test

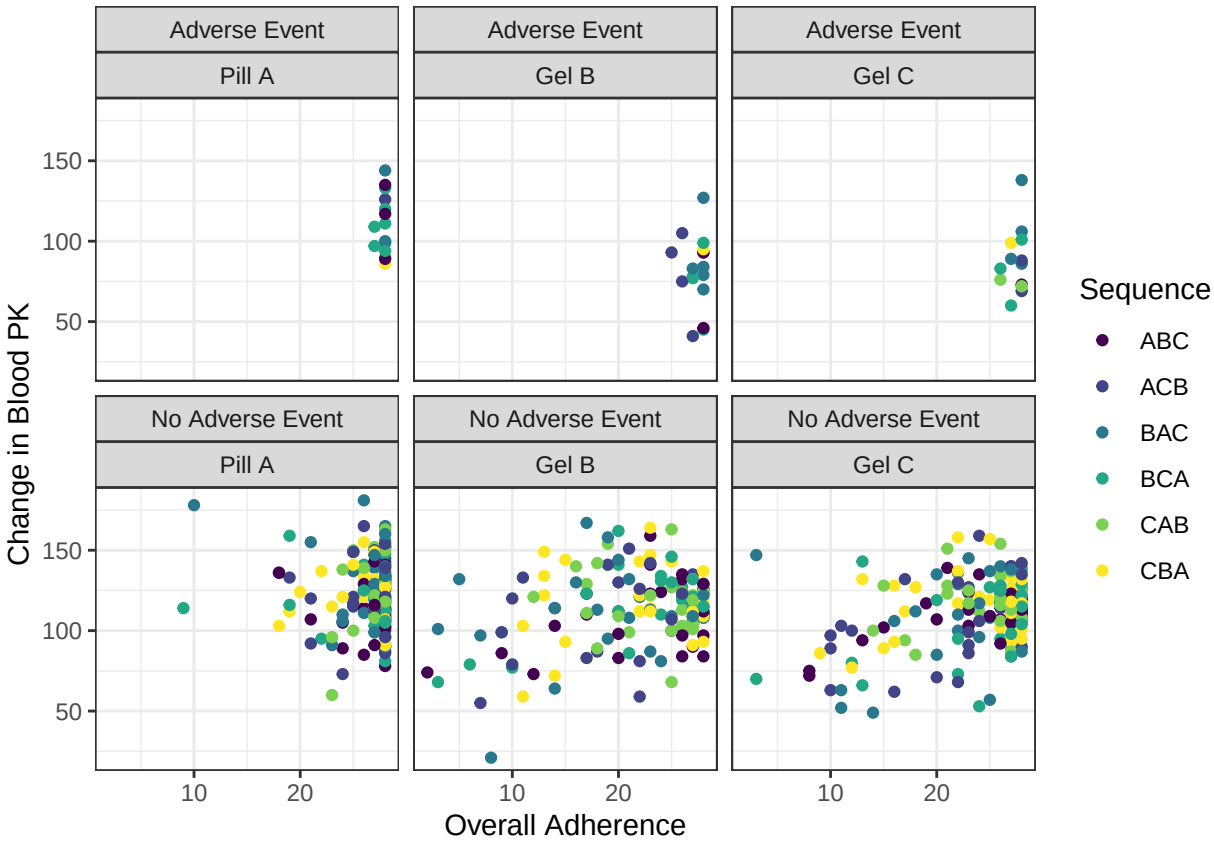
Secondary Objectives

preliminary assessment and comparison of systemic and local Pharmacokinetics (PK) of Pill A, Gel B, and Gel C and the correlation of PK with adherence measures and the occurrence of adverse events

Blood PK

$$Y_{ik} = \mu + b_k + \pi_i + \tau_i + \lambda_i + \alpha_{ik} + \beta_{ik} + \varepsilon_{ik}, \quad b_k \sim N(0, \sigma_b^2), \quad \varepsilon_{ik} \sim N(0, \sigma^2)$$






```
## Linear mixed model fit by REML. t-tests use Satterthwaite's method [
## lmerModLmerTest]
## Formula: bloodVL_change ~ treatment + overall_adhere + overall_safety +
##     period + (1 | ptid)
##    Data: merged
##
## REML criterion at convergence: 4827.4
##
## Scaled residuals:
##     Min      1Q  Median      3Q     Max
## -3.5936 -0.5795  0.0153  0.6127  3.0873
##
## Random effects:
##  Groups   Name        Variance Std.Dev.
##  ptid     (Intercept)  23.09    4.805
##  Residual             445.60   21.109
## Number of obs: 540, groups:  ptid, 180
##
## Fixed effects:
##                                Estimate Std. Error       df t value
## (Intercept)                     73.4552     6.7058 419.7422  10.954
## treatmentGel B                  -6.7916     2.3555 417.1354  -2.883
## treatmentGel C                  -9.0880     2.2967 391.5595  -3.957
## overall_adhere                   0.9365     0.1882 269.4894   4.975
## overall_safetyNo Adverse Event  26.4624     3.4675 521.9424   7.632
## periodperiod2                   -2.3295     2.2271 356.0129  -1.046
## periodperiod3                   -1.5433     2.2252 355.4545  -0.694
```

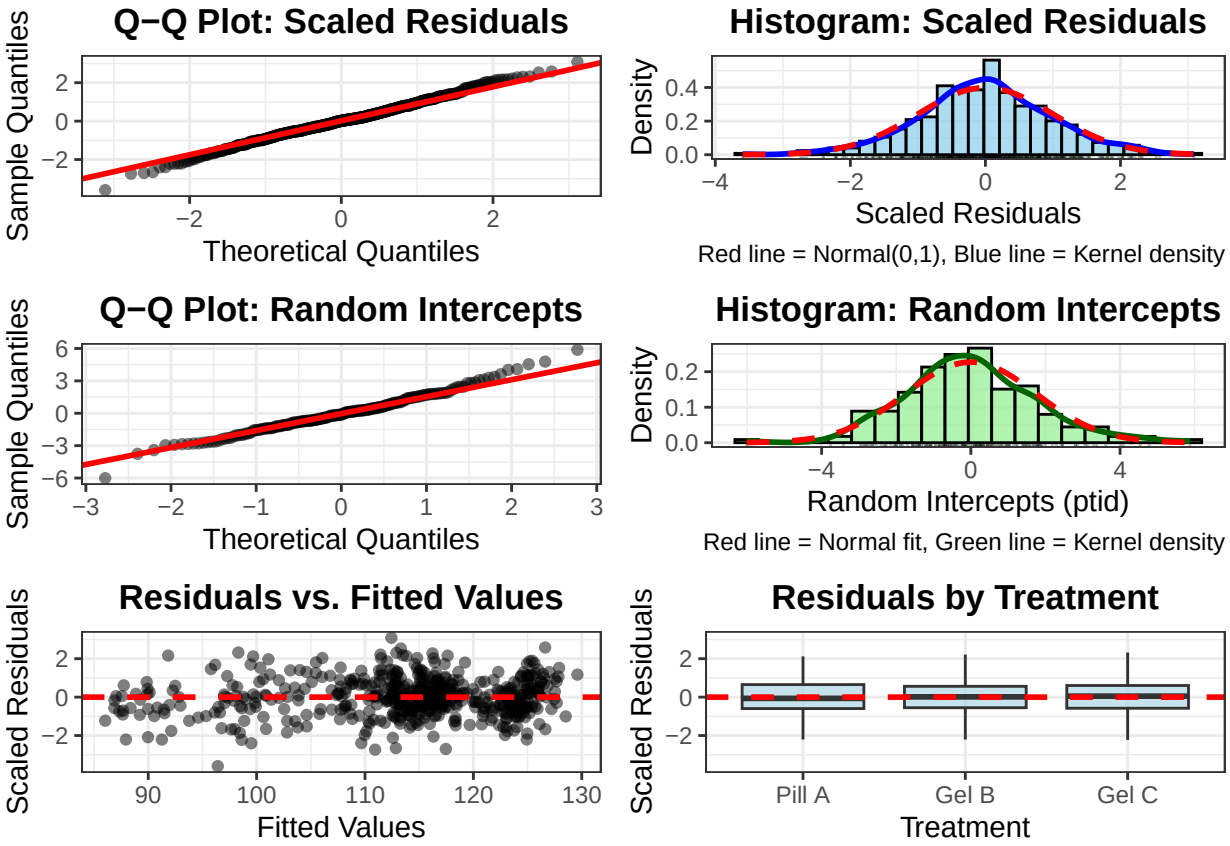
Comparison	Beta	95% CI	p-value
Intercept (Pill A, Period 1, Sequence 0, No Adherence or AE)	73.5	60.3, 86.6	**<0.001**
Treatment			
Gel B vs Pill A	-6.8	-11.4, -2.2	**0.004**
Gel C vs Pill A	-9.1	-13.6, -4.6	**<0.001**
Additional Day of Adherence	0.9	0.6, 1.3	**<0.001**
Adverse Event			
No Adverse Event	26.5	19.7, 33.3	**<0.001**
Period			
Period 2 vs Period 1	-2.3	-6.7, 2.1	0.3
Period 3 vs Period 1	-1.5	-5.9, 2.8	0.5

Abbreviation: CI = Confidence Interval

```
##                                          Pr(>|t|)
## (Intercept)                    < 0.0000000000000002 ***
## treatmentGel B                              0.00414 **
## treatmentGel C                 0.000090106833765 ***
## overall_adhere                 0.000001161748202 ***
## overall_safetyNo Adverse Event 0.000000000000111 ***
## periodperiod2                               0.29629
## periodperiod3                               0.48842
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##             (Intr) trtmGB trtmGC ovrll_ ov_NAE prdpr2
## treatmntGlB -0.437
## treatmntGlC -0.359  0.538
## overall_dhr -0.832  0.328  0.247
## ovrll_sfNAE -0.616  0.080  0.032  0.196
## periodperd2 -0.129 -0.009 -0.006 -0.026 -0.038
## periodperd3 -0.173  0.001  0.001  0.004  0.009  0.499
```

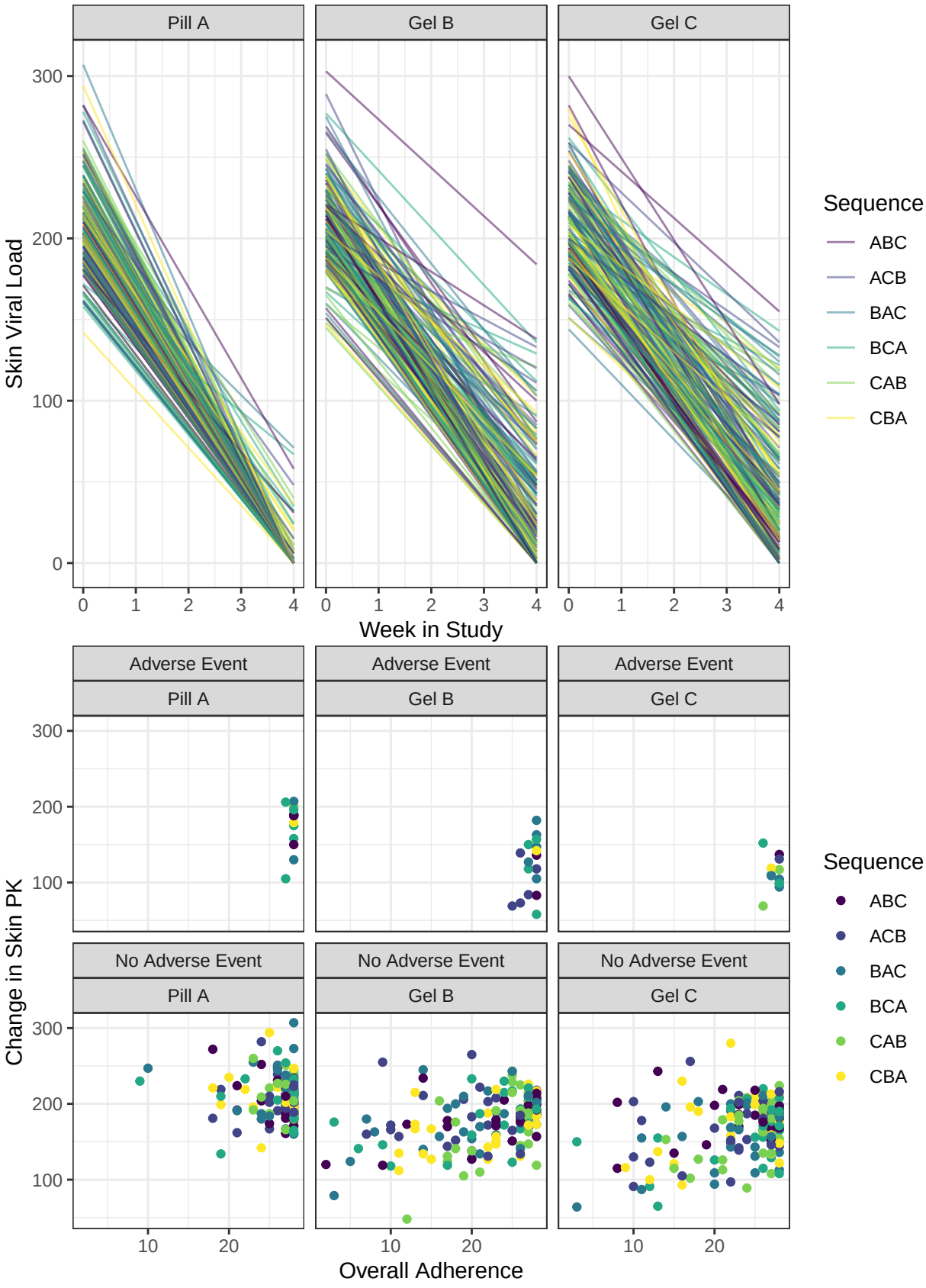
```
##  contrast       estimate   SE  df t.ratio p.value
##  Pill A - Gel B     6.79 2.36 417   2.882  0.0115
##  Pill A - Gel C     9.09 2.30 391   3.956  0.0003
##  Gel B - Gel C      2.30 2.24 359   1.027  0.5602
##
## Results are averaged over the levels of: overall_safety, period
## Degrees-of-freedom method: kenward-roger
## P value adjustment: tukey method for comparing a family of 3 estimates
```

```
##  contrast          estimate   SE  df t.ratio p.value
##  period1 - period2    2.330 2.23 355   1.046  0.5484
##  period1 - period3    1.543 2.23 355   0.694  0.7674
##  period2 - period3   -0.786 2.23 356  -0.353  0.9337
##
## Results are averaged over the levels of: treatment, overall_safety
## Degrees-of-freedom method: kenward-roger
## P value adjustment: tukey method for comparing a family of 3 estimates
```



Skin PK

Linear Model


Pill A
Gel B
Gel C
Skin Viral Load
Week in Study
Sequence
ABC
ACB
BAC
BCA
CAB
CBA
Adverse Event
No Adverse Event
Change in Skin PK
Overall Adherence

##

Comparison	Beta	95% CI	p-value
Intercept (Pill A, Period 1, Sequence 0, No Adherence or AE)	105.6	86.0, 125.2	**<0.001**
Treatment			
Gel B vs Pill A	-24.4	-31.5, -17.3	**<0.001**
Gel C vs Pill A	-37.0	-44.0, -30.0	**<0.001**
Additional Day of Adherence	1.8	1.3, 2.4	**<0.001**
Adverse Event			
No Adverse Event	55.8	45.5, 66.0	**<0.001**
Period			
Period 2 vs Period 1	0.9	-5.9, 7.6	0.8
Period 3 vs Period 1	1.6	-5.2, 8.4	0.6

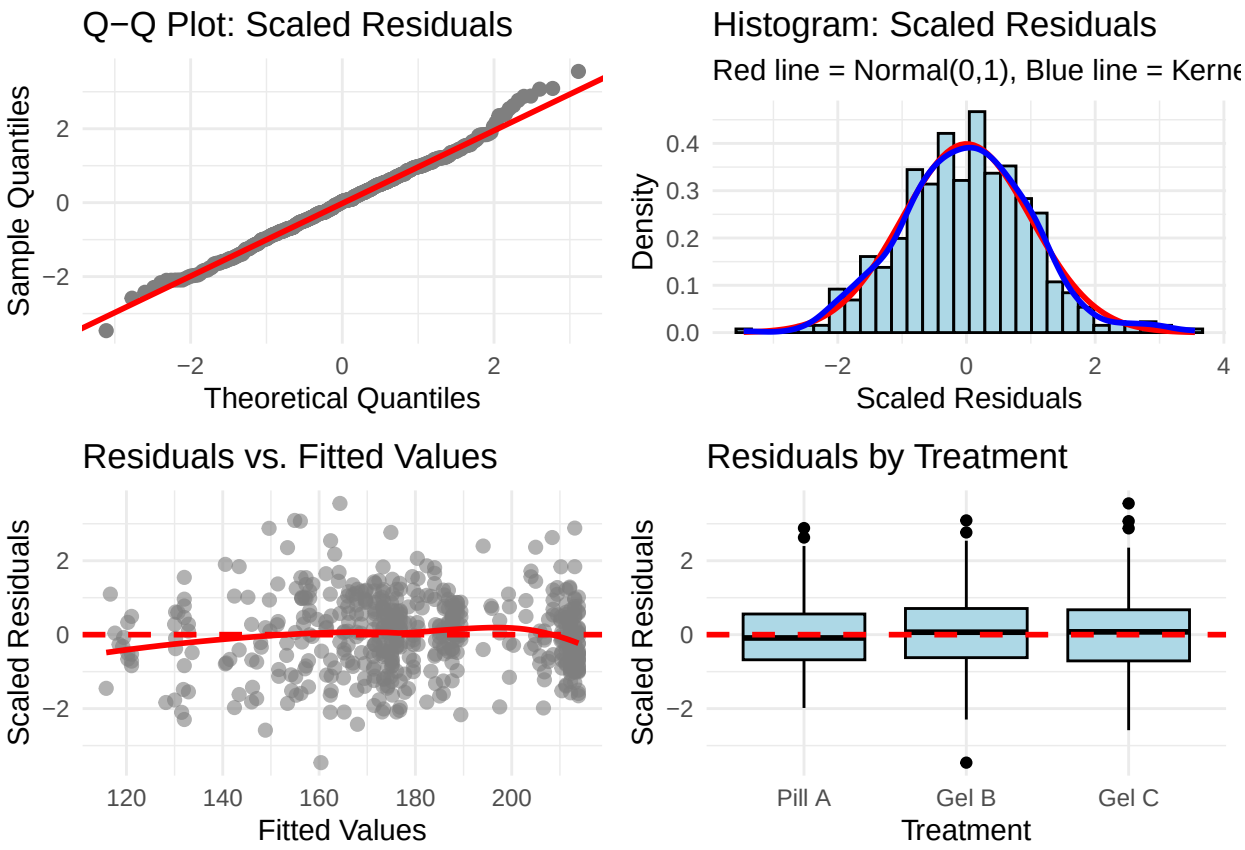
Abbreviation: CI = Confidence Interval

```
## Call:
## lm(formula = skinVL_change ~ treatment + overall_adhere + overall_safety +
##     period, data = merged)
##
## Residuals:
##      Min       1Q   Median       3Q      Max
## -112.388  -22.128    1.035   20.921  115.662
##
## Coefficients:
##                                Estimate Std. Error t value             Pr(>|t|)
## (Intercept)                    105.6003     9.9680  10.594 < 0.0000000000000002
## treatmentGel B                 -24.4131     3.6314  -6.723       0.000000000046
## treatmentGel C                 -36.9951     3.5493 -10.423 < 0.0000000000000002
## overall_adhere                   1.8154     0.2753   6.594       0.000000000103
## overall_safetyNo Adverse Event  55.7940     5.2166  10.696 < 0.0000000000000002
## periodperiod2                    0.8567     3.4535   0.248                0.804
## periodperiod3                    1.6225     3.4507   0.470                0.638
##
## (Intercept)                    ***
## treatmentGel B                 ***
## treatmentGel C                 ***
## overall_adhere                 ***
## overall_safetyNo Adverse Event ***
## periodperiod2
## periodperiod3
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Residual standard error: 32.74 on 533 degrees of freedom
## Multiple R-squared:  0.3581, Adjusted R-squared:  0.3508
## F-statistic: 49.55 on 6 and 533 DF,  p-value: < 0.00000000000000022
```

```
##  contrast       estimate   SE  df t.ratio p.value
##  Pill A - Gel B     24.4 3.63 533   6.723 <0.0001
##  Pill A - Gel C     37.0 3.55 533  10.423 <0.0001
##  Gel B - Gel C      12.6 3.47 533   3.631  0.0009
##
```

```
## Results are averaged over the levels of: overall_safety, period
## P value adjustment: tukey method for comparing a family of 3 estimates
```

```
##  contrast          estimate   SE  df t.ratio p.value
##  period1 - period2   -0.857 3.45 533  -0.248  0.9666
##  period1 - period3   -1.623 3.45 533  -0.470  0.8853
##  period2 - period3   -0.766 3.45 533  -0.222  0.9733
##
## Results are averaged over the levels of: treatment, overall_safety
## P value adjustment: tukey method for comparing a family of 3 estimates
```



Linear Mixed Model

```
## Linear mixed model fit by REML. t-tests use Satterthwaite's method [
## lmerModLmerTest]
## Formula: skinVL_change ~ treatment + overall_adhere + overall_safety +
##     period + (1 | ptid)
##    Data: merged
##
## REML criterion at convergence: 5269.4
##
## Scaled residuals:
##     Min      1Q  Median      3Q     Max
## -3.4333 -0.6760  0.0316  0.6391  3.5333
##
## Random effects:
##  Groups   Name        Variance Std.Dev.
##  ptid     (Intercept)    0      0.00
##  Residual             1072     32.74
```

Comparison	Beta	95% CI	p-value
Intercept (Pill A, Period 1, Sequence 0, No Adherence or AE)	105.6	86.0, 125.2	**<0.001**
Treatment			
Gel B vs Pill A	-24.4	-31.5, -17.3	**<0.001**
Gel C vs Pill A	-37.0	-44.0, -30.0	**<0.001**
Additional Day of Adherence	1.8	1.3, 2.4	**<0.001**
Adverse Event			
No Adverse Event	55.8	45.5, 66.0	**<0.001**
Period			
Period 2 vs Period 1	0.9	-5.9, 7.6	0.8
Period 3 vs Period 1	1.6	-5.2, 8.4	0.6

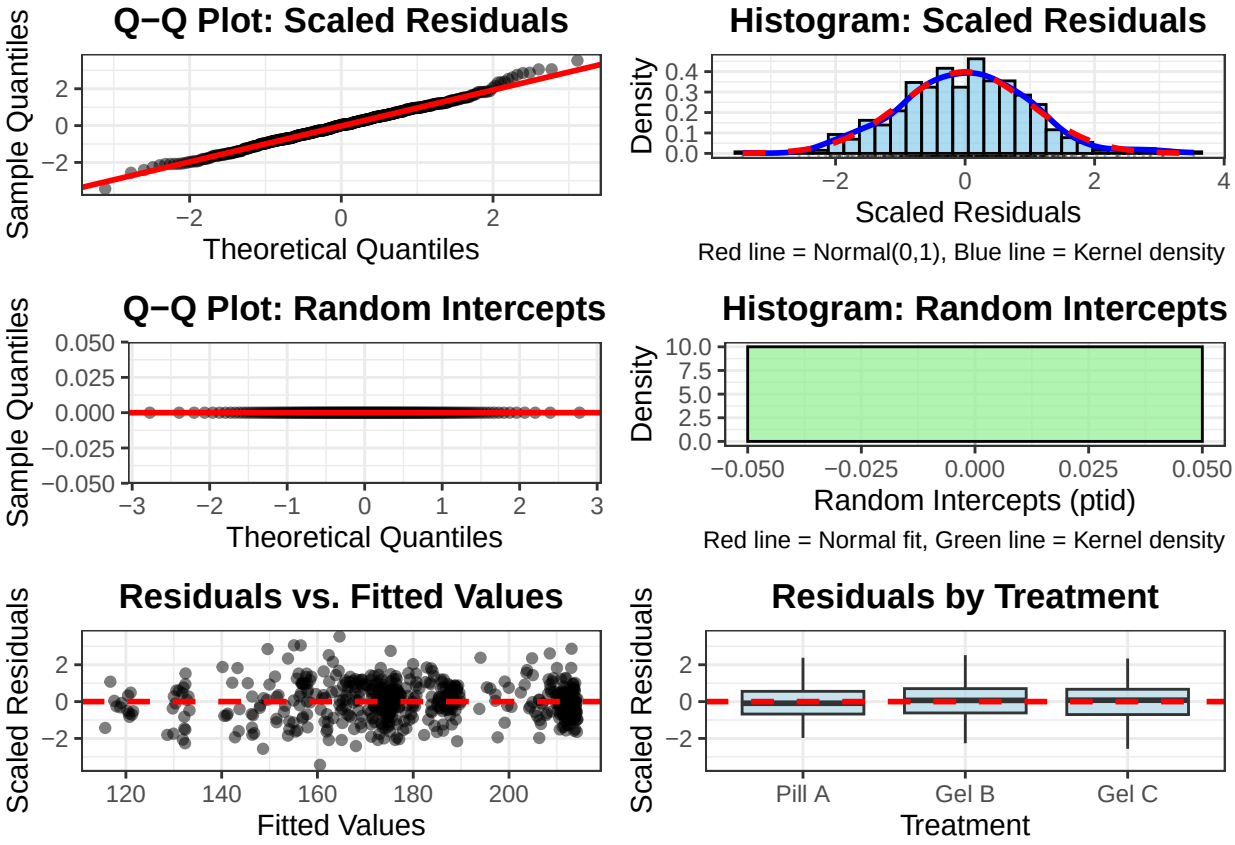
Abbreviation: CI = Confidence Interval

```
## Number of obs: 540, groups:  ptid, 180
##
## Fixed effects:
##                                Estimate Std. Error       df t value
## (Intercept)                    105.6003     9.9680 533.0000  10.594
## treatmentGel B                 -24.4131     3.6314 533.0000  -6.723
## treatmentGel C                 -36.9951     3.5493 533.0000 -10.423
## overall_adhere                   1.8154     0.2753 533.0000   6.594
## overall_safetyNo Adverse Event  55.7940     5.2166 533.0000  10.696
## periodperiod2                    0.8567     3.4535 533.0000   0.248
## periodperiod3                    1.6225     3.4507 533.0000   0.470
##                                          Pr(>|t|)
## (Intercept)                    < 0.0000000000000002 ***
## treatmentGel B                      0.000000000046 ***
## treatmentGel C                 < 0.0000000000000002 ***
## overall_adhere                      0.000000000103 ***
## overall_safetyNo Adverse Event < 0.0000000000000002 ***
## periodperiod2                                 0.804
## periodperiod3                                 0.638
## ---
## Signif. codes:  0 '***' 0.001 '**' 0.01 '*' 0.05 '.' 0.1 ' ' 1
##
## Correlation of Fixed Effects:
##             (Intr) trtmGB trtmGC ovrll_ ov_NAE prdpr2
## treatmntGlB -0.429
## treatmntGlC -0.354  0.534
## overall_dhr -0.826  0.311  0.234
## ovrll_sfNAE -0.627  0.079  0.033  0.206
## periodperd2 -0.137 -0.008 -0.005 -0.025 -0.037
## periodperd3 -0.180  0.001  0.001  0.004  0.009  0.499
## optimizer (nloptwrap) convergence code: 0 (OK)
## boundary (singular) fit: see help('isSingular')
```

```
##  contrast       estimate   SE  df t.ratio p.value
##  Pill A - Gel B     24.4 3.63 412   6.721 <0.0001
##  Pill A - Gel C     37.0 3.55 388  10.422 <0.0001
##  Gel B - Gel C      12.6 3.47 359   3.631  0.0009
```

```
##
## Results are averaged over the levels of: overall_safety, period
## Degrees-of-freedom method: kenward-roger
## P value adjustment: tukey method for comparing a family of 3 estimates
```

```
##  contrast          estimate   SE  df t.ratio p.value
##  period1 - period2   -0.857 3.45 356  -0.248  0.9666
##  period1 - period3   -1.623 3.45 355  -0.470  0.8853
##  period2 - period3   -0.766 3.45 356  -0.222  0.9733
##
## Results are averaged over the levels of: treatment, overall_safety
## Degrees-of-freedom method: kenward-roger
## P value adjustment: tukey method for comparing a family of 3 estimates
```



Combined Table

	Blood Viral Load			Skin	
Comparison	**Beta**	**95% CI**	**p-value**	**Beta**	**95**
Intercept (Pill A, Period 1, Sequence 0, No Adherence or AE)	73.5	60.3, 86.6	**<0.001**	105.6	86.
Treatment					
Gel B vs Pill A	-6.8	-11.4, -2.2	**0.004**	-24.4	-31
Gel C vs Pill A	-9.1	-13.6, -4.6	**<0.001**	-37.0	-44
Additional Day of Adherence	0.9	0.6, 1.3	**<0.001**	1.8	1
Adverse Event					
No Adverse Event	26.5	19.7, 33.3	**<0.001**	55.8	45
Period					
Period 2 vs Period 1	-2.3	-6.7, 2.1	0.3	0.9	-5
Period 3 vs Period 1	-1.5	-5.9, 2.8	0.5	1.6	-5

Abbreviation: CI = Confidence Interval