P9185_Project1_Report_rw2844

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1 Introduction

MATIK is a newly discovered, highly contagious viral skin disease that causes serious skin rash and infections in patients, and could even be life threatening.

Several scientific labs and drug companies are actively engaged in developing drugs to battle the emerging epidemic. From all the biological and animal studies,three medications, one oral Pill and two skin gels, appeared to be promising. We denote the three medications by Pill A, Gel B and Gel C. Phase I trials have already been conducted to determine their maximum tolerated doses among patients.

Due to urgent need, researchers/clinicians decide to conduct a phase II trial to evaluate the safety and adherence of all the three medications simultaneously.

Based on the information collected from the Phase I trials, and earlier cell line and animal studies. The following doses shown in Table 1 will be used in the trial.

Table 1: Recommended doses/administration schedule

Treatment	Description
Pill A	200 mg, once a day for 4 weeks
Gel B	1% gel concentration; three times a day on affected areas, daily use for 4 weeks
Gel C	2% gel concentration; once a day on affected areas, daily use for 4 weeks

2 Method

2.1 Study Design

2.1.1 Patient population and recruitment

Approximately 180 MATIK patients will be recruited from a variety of health care facilities, including hospitals, primary care clinics, and community-based health services. Recruitment materials will be approved by site Institutional Review Boards/Ethics Committees (IRBs/ECs). Accrual is expected to be completed in approximately 6-9 months per site.

2.1.2 Study Regimen

Study participants will be randomized to one of six regimen sequences (Sequence 1-6, see Table 2). Each sequence will consist of three 4 week periods of study product administration followed by at least a one-week washout period. The duration of product administration including the two washout periods is approximately 15 weeks. Participants will receive study product at the recommended dose, and be administered in the order designated by their randomized sequence (1-6).

Table 2: Study Regimen

Sequence	Period 1	period 2	Period 3
1	Pill A	Gel B	Gel C
2	Gel C	Pill A	Gel B
3	Gel B	Gel C	Pill A
4	Gel B	Pill A	Gel C
5	Pill A	Gel C	Gel B
6	Gel C	Gel B	Pill A

2.2 Study Objectives and Endpoints

2.2.1 Primary Objectives

Since MATIK is a chronic condition, patients will reply on long-term medications to control their viral loads. The primary objective of this trial is to compare the safety and adherence profiles of Pill A, Gel B, and Gel C, i.e. 1) whether the medications are safe for patients, 2) and whether patients could easily adhere to medication schedules so that long term use is feasible.

2.2.2 Secondary Objectives

The secondary objective of the trial is to have preliminary assessment and comparison of systemic and local Pharmacokinetics (PK) of Pill A, Gel B, and Gel C. Additionally, the investigators are interested to: 1) assess the correlation of PK with adherence measures and the occurrence of adverse events and 2) identify demographic factors associated with product adherence and whether they differ by product used (Pill or gel) or regimen (three times a day or once a day).

2.3 Endpoints and their collection schedules

2.3.1 Primary Endpoints

During each week of the 4-week trial periods, participants were followed up every week to record the following measures: 1) Safety: The number of grade 2 or higher adverse events occurred during that week. 2) Adherence: The number of days (out of 7 days) that patients are able to take pills or apply gels as prescribed.

2.3.2 Secondary Endpoints

Pharmacokinetics: The viral loads in the blood plasma and affected skin tissues were measured at the beginning and at the end of each period.

2.3.3 Demographics

Demographic data including age, gender and race of the recruited patients were collected at baseline.

2.4 Statistical Analyses

2.4.1 Primary Analysis

2.4.1.1 Analysis on Safety of the Treatments In this trial, patients were assigned to different sequences (see Table 2) of treatment regimens to examine the comparative safety and adherence profiles of the medications for long-term management of MATIK. To investigate the potential for carry-over effects, where the sequence of administered treatments could influence subsequent outcomes, we built the following generalized mixed effects model with logit link to analysis the carry-over effects:

$$\text{logit}\left(\Pr(Y_{ij}=1 \mid \mathbf{X}_{ij}, b_{i0})\right) = \beta_0 + \beta_1 \cdot \text{Period}_{ij} + \beta_2 \cdot \mathbf{I}(\text{Sequence } 2_i = 1) + \beta_3 \cdot \mathbf{I}(\text{Sequence } 2_i = 2) + b_{0i},$$

where Y_{ij} is the indicator of occurrence of any adverse event within the period j for patient i, $i = 1, \ldots, 180$, $j = 1, 2, 3$. We used this summarized outcome for adverse event because the adverse events are rare events. We also used the same outcome for the subsequent analyses on safety of the treatments. Period_{ij} is the j-th period number of patient i. $\mathbf{I}(\text{Sequence } 2_i = k)$ are the dummy variables for the sequence of the treatments the patient i received, where the reference level is Sequence $2_i = 0$, which means the patients received either ABC or BAC, Sequence $2_i = 1$ means the patients received either CAB or ACB, and Sequence $2_i = 2$ means the patients received either BCA or CBA. We did this translation since testing the null hypothesis of no carry-over effects, i.e., $H_0 : \rho_A = \rho_B = \rho_C = 0$, where ρ_k is the carry-over effect of treatment k, is the same as testing the following null hypothesis, $H_0 : \rho_A + \rho_B = \rho_A + \rho_C = \rho_B + \rho_C = 0$. Random intercepts are included to account for the clustered data.

To analyses the treatment effects on the adverse events (after excluding the possibility of

the existence of carry-over effects). We used the following generalized mixed effects model with logit link to analysis the treatment effects:

$$\begin{aligned}\text{logit}(\Pr(Y_{ij}=1 \mid \mathbf{X}_{ij}, b_{i0})) = \beta_0 &+ \beta_1 \cdot \mathbf{I}\left(\text{Treatment}_{ij} = \text{Gel B}\right) + \beta_2 \cdot \mathbf{I}\left(\text{Treatment}_{ij} = \text{Gel C}\right) \\ &+ \beta_3 \cdot \text{Period}_{ij} + \beta_4 \cdot \text{Age}_i \\ &+ \beta_5 \cdot \mathbf{I}(\text{Gender}_i = \text{female}) + \beta_6 \cdot \mathbf{I}(\text{Race}_i = \text{black}) \\ &+ \beta_7 \cdot \mathbf{I}(\text{Race}_i = \text{others}) + b_{i0},\end{aligned}$$

where $\mathbf{I}(A)$ is the indicator of event A, $\mathbf{I}(A) = 0$ is A does not happen, $\mathbf{I}(A) = 1$ is A does happen. Demographic variables are included in the model to reduce variance of the estimates and control for the confounding. Age are centered for better interpretation (average age of this study is 31.933).

2.4.1.2 Analysis on Adherence of Treatments As in the analysis of adverse effects above, we built the following similar generalized mixed effects model with logit link to analysis the carry-over effects on the treatment adherence:

$$\begin{aligned}\text{logit}\left(p_{ijk} \mid \mathbf{X}_{ijk}, b_{0i}\right) = \beta_0 &+ \beta_1 \cdot \text{Period}_{ij} + \beta_2 \cdot \text{Week}_{ijk} \\ &+ \beta_3 \cdot \mathbf{I}(\text{Sequence } 2_i = 1) + \beta_4 \cdot \mathbf{I}(\text{Sequence } 2_i = 2) + b_{0i},\end{aligned}$$

where p_{ijk} is the probability of the i-th patient adhered to the treatment in week k during period j. We assumed the observed outcome Y_{ijk}, which is the number of the number of days (out of 7 days) that patients are able to take pills or apply gels as prescribed, follows a Binomial$(7, p_{ijk})$ distribution. We also used the same outcome for the subsequent analyses on adherence of the treatments. Random intercepts are included to account for the clustered data.

To analyses the treatment effects on the treatment adherence (after excluding the possibility of the existence of carry-over effects). We used the following generalized mixed effects model

with logit link to analysis the treatment effects:

$$\begin{aligned}\text{logit}(p_{ijk} \mid \mathbf{X}_{ijk}, b_{0i}) = \beta_0 &+ \beta_1 \cdot \mathbf{I}\left(\text{Treatment}_{ij} = \text{Gel B}\right) + \beta_2 \cdot \mathbf{I}\left(\text{Treatment}_{ij} = \text{Gel C}\right) \\ &+ \beta_3 \cdot \text{Period}_{ij} + \beta_4 \cdot \text{Week}_{ijk} \\ &+ \beta_5 \cdot \text{Age}_i + \beta_6 \cdot \mathbf{I}(\text{Gender}_i = \text{female}) + \beta_7 \cdot \mathbf{I}(\text{Race}_i = \text{black}) \\ &+ \beta_8 \cdot \mathbf{I}(\text{Race}_i = \text{others}) + b_{i0}.\end{aligned}$$

2.4.2 Secondary Analysis

2.4.2.1 Correlation of Pharmacokinetics with Adherence Measures and the Occurrence of Adverse Events To investigate the association between safety, adherence and PK outcomes, we first built the following models to exam the existence of carry-over effect, as we did in the primary analyses:

$$\begin{aligned}\Delta\text{Skin Viral Load}_{ij} = \beta_0 &+ \beta_1 \cdot \text{Period}_{ij} + \beta_2 \cdot \mathbf{I}(\text{Sequence } 2_i = 1) \\ &+ \beta_3 \cdot \mathbf{I}(\text{Sequence } 2_i = 2) + b_{0i},\end{aligned}$$

$$\begin{aligned}\Delta\text{Blood Viral Load}_{ij} = \gamma_0 &+ \gamma_1 \cdot \text{Period}_{ij} + \gamma_3 \cdot \mathbf{I}(\text{Sequence } 2_i = 1) \\ &+ \gamma_3 \cdot \mathbf{I}(\text{Sequence } 2_i = 2) + b_{0i}.\end{aligned}$$

Here ΔSkin Viral Load$_{ij}$ and ΔBlood Viral Load$_{ij}$ are the change in skin/ blood viral load for patient i, calculated by subtracting after period (treatment) viral load from the viral load before each period (baseline viral load for $j = 1$, viral loads after wash out period for $j = 2, 3$), respectively.

To analyses the effects of safety outcomes and adherence outcomes on PK outcomes, together with the treatment effects on systemic and local viral loads, the following linear mixed effects

models are built:

$$\begin{aligned}
\mathrm{E}[\Delta\text{Skin Viral Load}_{ij} \mid \mathbf{X}_{ij}, b_{0i}] = \; & \beta_0 + \beta_1 \cdot \mathbf{I}\left(\text{Treatment}_{ij} = \text{Gel B}\right) \\
& + \beta_2 \cdot \mathbf{I}\left(\text{Treatment}_{ij} = \text{Gel C}\right) \\
& + \beta_3 \cdot \text{Period}_{ij} + \beta_4 \cdot \mathbf{I}\left(\text{Number of adverse event}_{ij} \geq 1\right) \\
& + \beta_5 \cdot \text{Number of days of adherence}_{ij} \\
& + \beta_6 \cdot \text{Age}_i + \beta_7 \cdot \mathbf{I}(\text{Gender}_i = \text{female}) \\
& + \beta_8 \cdot \mathbf{I}(\text{Race}_i = \text{black}) + \beta_9 \cdot \mathbf{I}(\text{Race}_i = \text{others}) + b_{i0},
\end{aligned}$$

and

$$\begin{aligned}
\mathrm{E}[\Delta\text{Blood Viral Load}_{ij} \mid \mathbf{X}_{ij}, b_{0i}] = \; & \gamma_0 + \gamma_1 \cdot \mathbf{I}\left(\text{Treatment}_{ij} = \text{Gel B}\right) \\
& + \gamma_2 \cdot \mathbf{I}\left(\text{Treatment}_{ij} = \text{Gel C}\right) \\
& + \gamma_3 \cdot \text{Period}_{ij} + \gamma_4 \cdot \mathbf{I}\left(\text{Number of adverse event}_{ij} \geq 1\right) \\
& + \gamma_5 \cdot \text{Number of days of adherence}_{ij} \\
& + \gamma_6 \cdot \text{Age}_i + \gamma_7 \cdot \mathbf{I}(\text{Gender}_i = \text{female}) \\
& + \gamma_8 \cdot \mathbf{I}(\text{Race}_i = \text{black}) + \gamma_9 \cdot \mathbf{I}(\text{Race}_i = \text{others}) + b_{i0},
\end{aligned}$$

where the number of days of adherence in the period is centered at the mean adherence day of that period.

2.4.2.2 Identify Demographic Factors associated with Product Adherence In order to identify demographic factors associated with product adherence and whether they differ by product used (Pill or Gel) or regimen (three times a day or once a day), we built the following marginal models including product/regimen and their interactions with demo-

graphic variables in the models:

$$\begin{aligned}
\text{logit}\left(p_{ijk} \mid \mathbf{X}_{ijk}\right) = {} & \beta_0 + \beta_1 \cdot \text{Period}_{ij} + \beta_2 \cdot \text{Week}_{ijk} \\
& + \beta_3 \cdot \text{Age}_i + \beta_4 \cdot \mathbf{I}(\text{Gender}_i = \text{female}) + \beta_5 \cdot \mathbf{I}(\text{Race}_i = \text{black}) \\
& + \beta_6 \cdot \mathbf{I}(\text{Race}_i = \text{others}) \\
& + \beta_7 \cdot \mathbf{I}(\text{Product Type}_{ij} = \text{Gel}) + \beta_8 \cdot \text{Age}_i \cdot \mathbf{I}(\text{Product Type}_{ij} = \text{Gel}) \\
& + \beta_9 \cdot \mathbf{I}(\text{Gender}_i = \text{female}) \cdot \mathbf{I}(\text{Product Type}_{ij} = \text{Gel}) \\
& + \beta_{10} \cdot \mathbf{I}(\text{Race}_i = \text{black}) \cdot \mathbf{I}(\text{Product Type}_{ij} = \text{Gel}) \\
& + \beta_{11} \cdot \mathbf{I}(\text{Race}_i = \text{others}) \cdot \mathbf{I}(\text{Product Type}_{ij} = \text{Gel}),
\end{aligned}$$

and

$$\begin{aligned}
\text{logit}\left(p_{ijk} \mid \mathbf{X}_{ijk}\right) = {} & \gamma_0 + \gamma_1 \cdot \text{Period}_{ij} + \gamma_2 \cdot \text{Week}_{ijk} \\
& + \gamma_3 \cdot \text{Age}_i + \gamma_4 \cdot \mathbf{I}(\text{Gender}_i = \text{female}) + \gamma_5 \cdot \mathbf{I}(\text{Race}_i = \text{black}) \\
& + \gamma_6 \cdot \mathbf{I}(\text{Race}_i = \text{others}) \\
& + \gamma_7 \cdot \mathbf{I}(\text{Regimen}_{ij} = \text{Three times a day}) \\
& + \gamma_8 \cdot \text{Age}_i \cdot \mathbf{I}(\text{Regimen}_{ij} = \text{Three times a day}) \\
& + \gamma_9 \cdot \mathbf{I}(\text{Gender}_i = \text{female}) \cdot \mathbf{I}(\text{Regimen}_{ij} = \text{Three times a day}) \\
& + \gamma_{10} \cdot \mathbf{I}(\text{Race}_i = \text{black}) \cdot \mathbf{I}(\text{Regimen}_{ij} = \text{Three times a day}) \\
& + \gamma_{11} \cdot \mathbf{I}(\text{Race}_i = \text{others}) \cdot \mathbf{I}(\text{Regimen}_{ij} = \text{Three times a day}),
\end{aligned}$$

where age are centered in both models above.

3 Result

3.1 Baseline Characteristics of the Study Population

Table 3 shows the distributions of the baseline covariates, including demographic variables and baseline viral loads. The similarities in these baseline measures suggest that the randomization process was successful in distributing known potential confounders evenly across

groups. Such balance is indicative of the effectiveness of the randomization procedure, enhancing the internal validity of the study by reducing the likelihood that observed differences in outcomes can be attributed to pre-existing differences among treatment groups. This equitable distribution of baseline characteristics establishes a solid foundation for subsequent analyses of the treatments.

Table 3: Descriptive statistics of baseline characteristics of the 180 subjects by treatment sequences.

	ABC	ACB	BAC	BCA	CAB	CBA	Overall
	(N=30)	(N=30)	(N=30)	(N=30)	(N=30)	(N=30)	(N=180)
Age							
Mean (SD)	33.4 (8.29)	31.0 (7.14)	30.9 (7.23)	32.9 (8.44)	32.3 (6.82)	31.0 (7.39)	31.9 (7.54)
Median [Min, Max]	34.0 [19.0, 44.0]	29.0 [18.0, 42.0]	31.5 [20.0, 44.0]	32.0 [19.0, 45.0]	33.0 [21.0, 44.0]	31.5 [20.0, 44.0]	32.0 [18.0, 45.0]
Gender							
Male	17 (56.7%)	19 (63.3%)	14 (46.7%)	16 (53.3%)	18 (60.0%)	15 (50.0%)	99 (55.0%)
Female	13 (43.3%)	11 (36.7%)	16 (53.3%)	14 (46.7%)	12 (40.0%)	15 (50.0%)	81 (45.0%)
Race							
White	8 (26.7%)	9 (30.0%)	7 (23.3%)	7 (23.3%)	12 (40.0%)	9 (30.0%)	52 (28.9%)
Black	12 (40.0%)	13 (43.3%)	12 (40.0%)	10 (33.3%)	8 (26.7%)	9 (30.0%)	64 (35.6%)
Others	10 (33.3%)	8 (26.7%)	11 (36.7%)	13 (43.3%)	10 (33.3%)	12 (40.0%)	64 (35.6%)
Baseline blood viral load							
Mean (SD)	120 (18.3)	123 (22.5)	119 (21.0)	123 (17.0)	128 (14.3)	127 (17.3)	123 (18.6)
Median [Min, Max]	122 [78.0, 152]	121 [73.0, 165]	114 [81.0, 181]	124 [79.0, 162]	125 [105, 163]	124 [95.0, 172]	122 [73.0, 181]
Baseline skin viral load							
Mean (SD)	207 (29.0)	203 (24.3)	212 (30.1)	205 (23.3)	207 (23.6)	209 (29.9)	207 (26.7)
Median [Min, Max]	202 [161, 282]	203 [161, 282]	205 [154, 275]	199 [167, 277]	207 [160, 245]	204 [151, 280]	203 [151, 282]

3.2 Longitudinal Outcomes of the Patients

Figure 1 shows the change of primary outcomes, the safety outcome and the adherence, across the 4 weeks in one treatment period. Since adverse events are rare, we summarized the number of patients who ever experienced adverse events during a week. From the upper panel we can see that there is a increasing trend of experiencing adverse event towards the end of the period for all treatments. From the lower panel, we see a the lines are trend downwards, which means that the odds of adherence are decreasing over time.

To identify potential demographic factors that affect the treatments adherence, and their interaction with product type and regimen, figure 2 shows the adherence rate versus age stratified by product type and regimen, as well as gender and race. Overall, we found a higher adherence rate among patients who were using pill than who were using gel. We also found that patients who were prescribed a lower frequency of using pill/gel daily has a higher

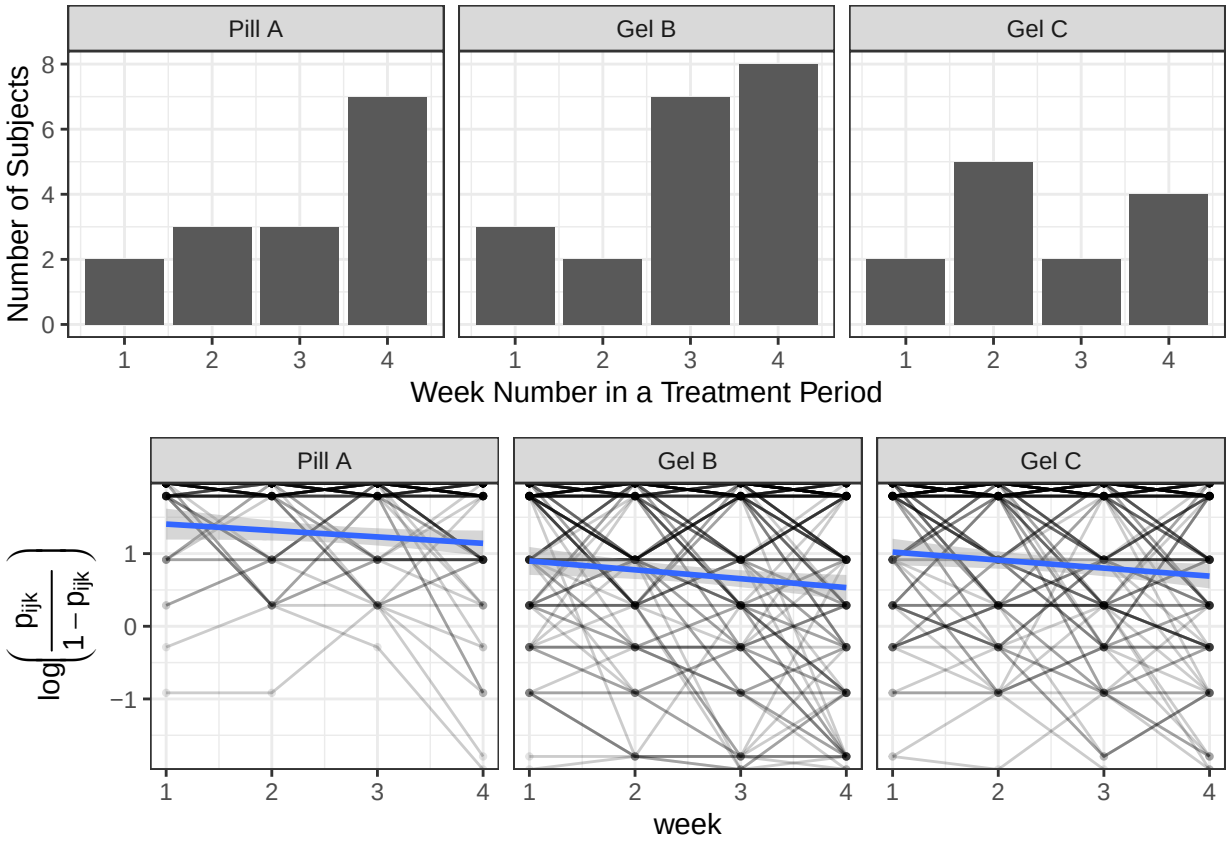

Figure 1: Change of primary outcomes across week in a treatment period. Upper panel: Total number of subject who had experienced adverse events, stratified by treatments. Lower panel: Change of logarithm of odds of adherence, stratified by treatments, the blue line is the population trend fitted by linear model.

adherence rate. We didn't observe a clearly relationship between gender/race and adherence rate, however, we did found a increase in adherence rate as age increases.

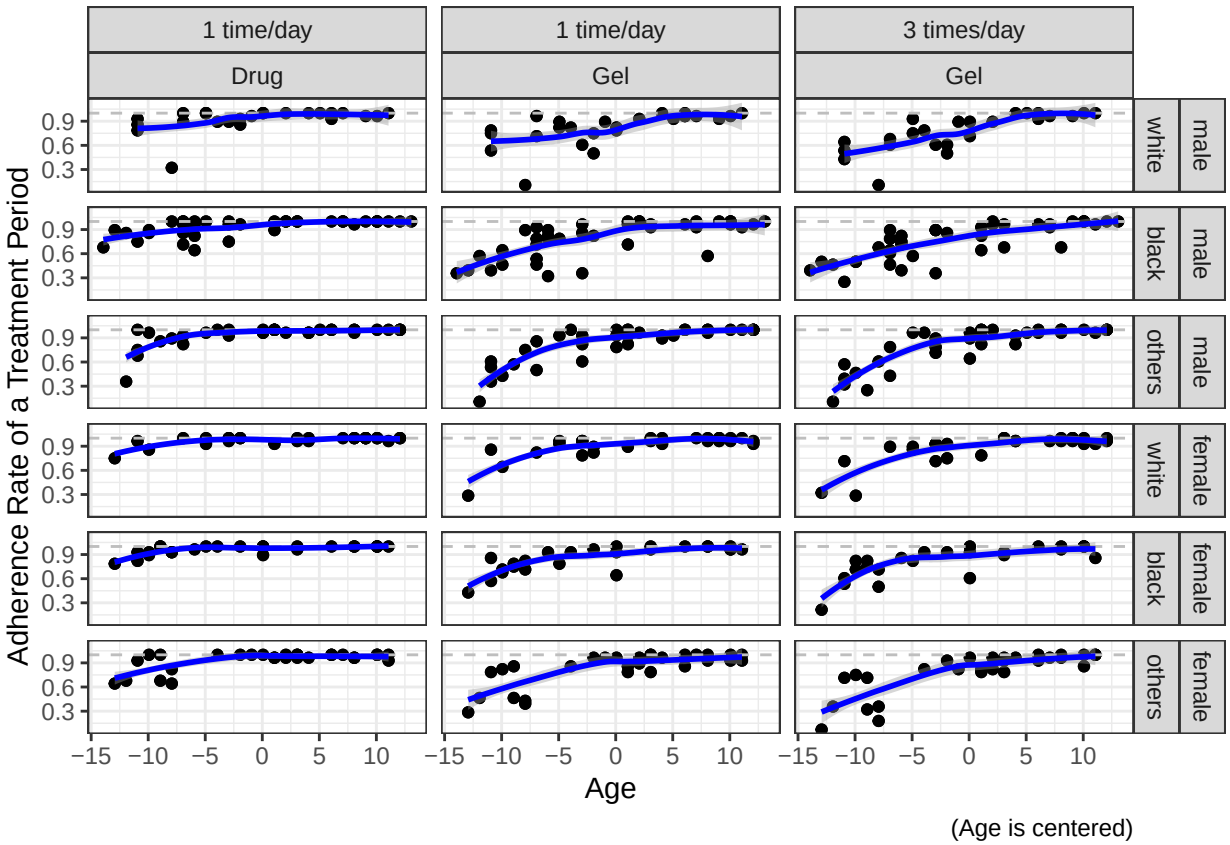

Figure 2: Adherence rate of a treatment period across different age, stratified by product type/regimen and demographic factors, with loess smoothing curve.

For the secondary endpoint, figure 3 shows the overall viral loads change of different treatment groups. We found that Gel C achieved a higher viral loads reduction in both skin viral load and blood viral load compared to Gel B and Gel C. We also found that the occurence of adverse event is associated with a higher reduction in viral loads, while higher adherence is associated with a lower reduction in viral loads.

3.3 Carry-over Effects

Table 4-7 shows the coefficients estimates of the fixed effects of the model analyzing carry-over effects of the treatments on the occurrence of adverse events, the adherence and the PK

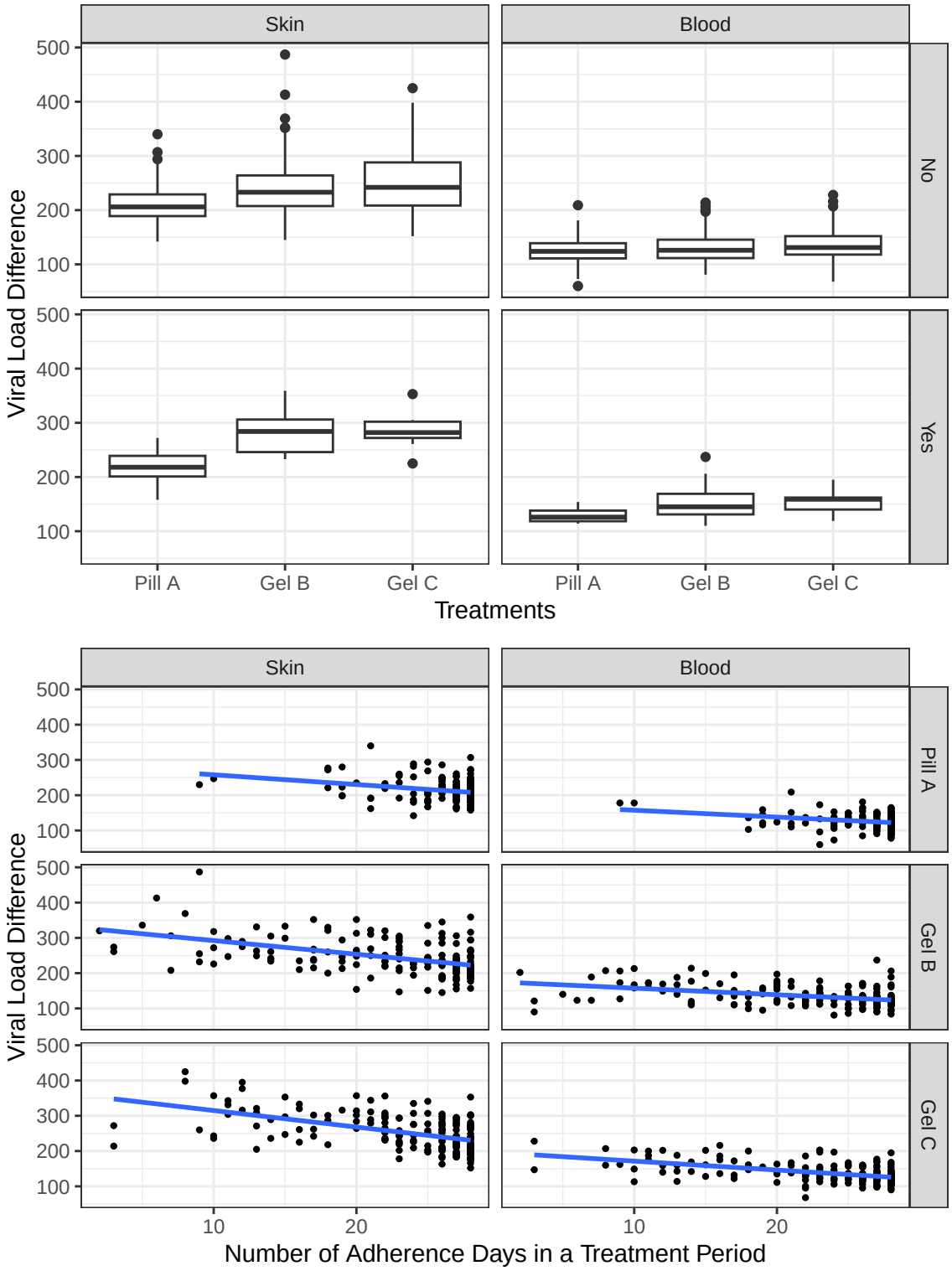

Figure 3: Viral loads change of different treatment groups. Upper panel: stratified by measurement type and occurence of adverse event. Lower panel: change in viral loads versus the number of adherence days, stratified by treatments and measurement types.

(blood and skin), respectively. We did not find any significant carry-over effects of treatments on both outcomes. The p-value of the test against the null hypotheses of no carry-over effects (with degree of freedoms equal 2) on safety outcome, adherence and PK (blood and skin) are 0.761, 0.891, 0.990, and 0.774, respectively, which means that we cannot reject the null of no carry-over effects at $\alpha = 0.05$ significant level in both cases.

Table 4: Coefficent estimates of the carry-over effect model of adverse events.

Characteristics	OR	95% CI	p-value
Period	1.06	0.66, 1.72	0.8
Sequence			
AB	—	—	
AC	0.62	0.12, 3.26	0.6
BC	1.13	0.23, 5.50	0.9

Table 5: Coefficent estimates of the carry-over effect model of adherence.

Characteristics	OR	95% CI	p-value
Period	1.00	0.93, 1.06	0.9
week	0.75	0.71, 0.78	<0.001
Sequence			
AB	—	—	
AC	0.93	0.48, 1.80	0.8
BC	1.10	0.57, 2.12	0.8

Table 6: Coefficent estimates of the carry-over effect model of blood viral loads.

Characteristics	$\hat\beta$	95% CI
Period	0.74	-1.8, 3.3
Sequence		
AB	—	—
AC	0.32	-6.1, 6.8
BC	0.46	-6.0, 6.9

Table 7: Coefficent estimates of the carry-over effect model of skin viral loads.

Characteristics	$\hat\beta$	95% CI
Period	0.75	-3.6, 5.1
Sequence		
AB	—	—
AC	-2.9	-16, 9.7
BC	-4.5	-17, 8.1

3.4 Safety of the Treatments

Table 8 shows the coefficient estimates of the treatment effects, as well as effects of demographic factors, on the safety outcome. From the table we can see that after controlling for time variable and demographic factors, none of the treatments shows a significant effect on the occurrence of adverse event. However, we found that age has a significant effect on the occurrence of adverse event (OR = 1.22 with 95% CI 1.12-1.32), which means that on average, an additional year of age beyond the mean age of the study population (31.933 years old) is associated with 22% increase in the odds of experiencing at least one adverse event within the treatment period.

Table 8: Coefficent estimates of the treatment effects on the safety outcome.

Characteristics	OR	95% CI	p-value
Treatment			
Pill A	—	—	
Gel B	1.20	0.53, 2.74	0.7
Gel C	0.82	0.34, 1.96	0.7
Period	1.06	0.70, 1.62	0.8
Age	1.22	1.12, 1.32	<0.001
Gender			
male	—	—	
female	1.11	0.48, 2.56	0.8
Race			
white	—	—	
black	0.59	0.20, 1.75	0.3
others	1.00	0.38, 2.64	>0.9

3.5 Adherence of the Treatments

Table 9 shows the coefficient estimates of the treatment effects, as well as effects of demographic factors, on the adherence of treatments. From the table we can see that after controlling for time variable and demographic factors, both Gel B and Gel C have significant effects on the adherence of treatments. Specifically, compared to Pill A, patients who were using Gel B has a 85% lower odds of adherence (OR = 0.15 with 95% CI 0.12-0.17), while patients who were using Gel C has a 79% lower odds of adherence (OR = 0.21 with 95% CI 0.18-0.24). Age still has a significant effect on the adherence (OR = 1.22 with 95% CI 1.19-1.25), which means that on average, for each additional year of age beyond the mean age of the study population, the odds of adhering to the treatment is increase by 22%.

Table 9: Coefficent estimates of the treatment effects on the adherence.

Characteristics	OR	95% CI	p-value
Period	1.02	0.95, 1.09	0.6
Week	0.73	0.69, 0.76	<0.001
Treatment			
Pill A	—	—	
Gel B	0.15	0.12, 0.17	<0.001
Gel C	0.21	0.18, 0.24	<0.001
Age	1.22	1.19, 1.25	<0.001
Gender			
male	—	—	
female	1.29	0.92, 1.80	0.14
Race			
white	—	—	
black	1.11	0.73, 1.69	0.6
others	0.99	0.65, 1.51	>0.9

3.6 Assessment and Comparison Pharmacokinetics of the Treatments

Table 10 shows the coefficients estimates from the two models analyzing the effects of treatments, occurrence of adverse events and adherence on the systemic (blood) and local (skin)

pharmacokinetics. From the results we can see that on average, Gel B and Gel C achieved a higher reduction on both skin and blood viral loads, and these effects are significant except for Gel B on blood viral loads. We also found that for each additional day of adherence beyond the average within a period, the viral load reduction decreased by 1.3 in blood and 2.8 in skin, which are significant. The occurrence of adverse events within the period increase the viral loads reduction by 28 and 56 in blood and skin, respectively, which are also significant. For demographic factors, we found that age is negatively associated with viral loads reduction and female patients had a higher viral loads reduction compared to male patients.

Table 10: Coefficent estimates of the treatment effects on the pharmacokenitics.

	Blood viral loads model		Skin viral loads model	
Characteristics	$\hat{\beta}$	95% CI	$\hat{\gamma}$	95% CI
Treatment				
Pill A	—	—	—	—
Gel B	3.3	-1.6, 8.2	20	13, 27
Gel C	8.6	3.8, 13	32	25, 39
Period	0.67	-1.6, 2.9	0.60	-2.7, 3.9
Days of adherece (within a period, centered)	-1.3	-1.8, -0.81	-2.8	-3.6, -2.0
Occurence of adverse effects				
No	—	—	—	—
Yes	28	21, 35	56	45, 67
Age	-1.3	-1.6, -0.97	-2.4	-2.9, -1.8
Gender				
male	—	—	—	—
female	7.2	3.5, 11	25	18, 31
Race				
white	—	—	—	—
black	-3.0	-7.6, 1.7	0.26	-8.0, 8.5
others	-1.5	-6.1, 3.1	-2.6	-11, 5.5

3.7 Demographic Factors associated with Adherence

Table 11 shows the coefficient estimates of the models investigating demographic factors associated with adherence and the effects of product type and regimen on adherence. In both

models, age is associated with a increase in the odds of adherence and week is associated with a decrease in the odds of adherence, which are in align with the results from the primary analyses. For product type, the odds of adherence for patients using gels, on average, is 77% lower than patients using pills, no significant interactions with demographic factors are found. For treatment regimen, patients who are prescribed take treatments three times a day has a 51% lower odds of adherence than patients who are prescribed to take treatments once a day. Age has a significant interaction with treatment regimen.

4 Discussion

The analysis of the Phase II trial data provides a robust foundation for advancing to Phase III. In this discussion, we synthesize the results and delineate the implications for future trials, particularly in the context of treatment efficacy, safety, and patient adherence.

The Phase II trial's balanced baseline characteristics across treatment groups reinforce the effectiveness of the randomization procedure, which is crucial for the internal validity of the study. This balance minimizes confounding factors, thereby enabling a more accurate assessment of the treatments' true effects. Notably, the trend towards increased adverse events over time necessitates close monitoring in subsequent studies.

In considering treatments for a Phase III trial, the data suggests that Pill A exhibits a superior adherence profile compared to Gels B and C. Given the importance of adherence in chronic conditions management, Pill A emerges as a strong candidate for further investigation. However, the higher viral load reductions associated with Gel C cannot be overlooked, as this indicates a potent therapeutic effect.

For the Phase III trial design, a randomized controlled trial (RCT) remains the gold standard to confirm these findings. The RCT should be adequately powered to detect differences in adherence and viral load reductions, taking into account the observed effects from Phase II. Additionally, stratification by demographic factors, as indicated by the increased adherence with age, could be beneficial.

Information from Phase II that will be valuable for planning Phase III includes the adherence

Table 11: Coefficent estimates of the effects of demographic factors and product used on the adherence.

	Model for product type			Model for regimen		
Characteristics	OR	95% CI	p-value	OR	95% CI	p-value
Period	0.99	0.92, 1.06	0.7	0.99	0.90, 1.09	0.8
Week	0.76	0.73, 0.79	<0.001	0.76	0.74, 0.79	<0.001
Age	1.21	1.17, 1.25	<0.001	1.19	1.16, 1.22	<0.001
Product type						
Pill	—	—				
Gel	0.23	0.15, 0.36	<0.001			
Gender						
male	—	—		—	—	
female	1.56	0.98, 2.48	0.064	1.50	1.08, 2.07	0.015
Race						
white	—	—		—	—	
black	1.34	0.68, 2.63	0.4	1.07	0.66, 1.72	0.8
others	0.88	0.45, 1.74	0.7	0.87	0.55, 1.39	0.6
Age × Product type						
Age * Gel	0.99	0.96, 1.02	0.6			
Product type × Gender						
Gel * female	0.92	0.67, 1.25	0.6			
Product type × Race						
Gel * black	0.77	0.50, 1.19	0.2			
Gel * others	0.98	0.62, 1.56	>0.9			
Regimen						
once				—	—	
three times				0.49	0.39, 0.61	<0.001
Age × Regimen						
Age * three times				1.02	1.00, 1.04	0.033
Regimen × Gender						
three times * female				0.90	0.74, 1.09	0.3
Regimen × Race						
three times * black				1.01	0.77, 1.32	>0.9
three times * others				1.01	0.77, 1.31	>0.9

rates over time, the incidence and pattern of adverse events, and the demographic factors influencing treatment outcomes. Additional data that would be beneficial includes long-term follow-up for safety and efficacy, quality of life assessments, and pharmacoeconomic analyses to inform the broader impact of the treatments.

This analysis is not without limitations. The generalizability of the findings is constrained by the sample size and the specific patient population studied. Furthermore, the occurrence of adverse events, though monitored, may not fully encapsulate the long-term safety profile of the treatments. Adherence was self-reported, which can introduce reporting bias. Phase III trials should aim to include objective adherence measures and a more diverse patient population to enhance the external validity of the findings.

Based on the Phase II results, Pill A would be recommended for the Phase III trial given its adherence advantage. However, further investigation into optimizing Gel C's regimen could improve its adherence profile, making it a contender given its efficacy. Phase III should seek to confirm these findings, with a focus on long-term outcomes and real-world adherence patterns.

To prepare for Phase III, further elucidation of the mechanisms driving the differences in adherence and viral load reductions is needed. Additionally, understanding patient preferences and barriers to adherence could inform interventions to enhance compliance. A pivotal Phase III trial should incorporate these considerations to ensure that the selected treatment not only demonstrates efficacy and safety but also aligns with patient needs for long-term disease management.

Appendix

A.2 Code for This Report

```
source(knitr::purl("P9185_project1.Rmd", quiet=TRUE))
# Create a data frame with the table information
table_trt <- data.frame(
  Treatment = c("Pill A", "Gel B", "Gel C"),
  Description = c("200 mg, once a day for 4 weeks",
                  "1% gel concentration; three times a day on affected areas, daily use for 4 weeks",
                  "2% gel concentration; once a day on affected areas, daily use for 4 weeks")
)

# Generate the table with kable and style it with kableExtra
kable(table_trt, "latex", booktabs = TRUE, caption = "Recommended doses/administration schedule") %>%
  kable_styling(position = "center", latex_options = "hold_position") %>%
  column_spec(1, bold = TRUE)
study_regimen <- data.frame(
  Sequence = 1:6,
  `Period 1` = c("Pill A", "Gel C", "Gel B", "Gel B", "Pill A", "Gel C"),
  `Period 2` = c("Gel B", "Pill A", "Gel C", "Pill A", "Gel C", "Gel B"),
  `Period 3` = c("Gel C", "Gel B", "Pill A", "Gel C", "Gel B", "Pill A")
)

# Generate the table with kable and kableExtra
kable(study_regimen, "latex", booktabs = TRUE, col.names = c("Sequence", "Period 1", "period 2", "Perio
  kable_styling(latex_options = c("hold_position"), full_width = FALSE, position = "center")
baseline.demo <-
  left_join(Adhere.demo, baseline.dat %>% select(ptid, bviral0, sviral0)) %>%
  left_join(
    .,
    endpoints.period %>% select(ptid, sequence) %>% distinct()
  )
library(table1)
baseline.demo$gender <- factor(baseline.demo$gender, levels = c("male", "female"), labels = c("Male", "
baseline.demo$race <- factor(baseline.demo$race, levels = c("white", "black", "others"), labels = c("Wh
```

```r
label(baseline.demo$gender) = "Gender"
label(baseline.demo$race) = "Race"
label(baseline.demo$age) = "Age"
label(baseline.demo$bviral0) = "Baseline blood viral load"
label(baseline.demo$sviral0) = "Baseline skin viral load"
label(baseline.demo$sequence) = "Treatment sequence"
library(gt)
demo.tab <-
  table1(~ age + gender + race + bviral0 + sviral0 | sequence,
    data=baseline.demo, caption="Descriptive statistics of baseline characteristics of the 180 subjects
demo.tab
library(latex2exp)
library(ggpubr)

plot.ae <-
endpoints.AE %>%
  filter(AE ==1) %>%
  group_by(drug, week) %>%
  ggplot(aes(x=week))+
  geom_bar()+
  facet_grid(.~factor(drug, levels=c('Pill A','Gel B','Gel C')))+
  theme_bw()+
  ylab("Number of Subjects")+
  xlab("Week Number in a Treatment Period")

#plot.ae

plot.adhere <-
endpoints.Adhere %>%
  # each line is adherence of a drug taken by a subject
  ggplot(aes(x = week, y = log(Adhere/7/ (1-Adhere/7)))) +
  geom_line(alpha = 0.2,aes(x = week, y = log(Adhere/7/ (1-Adhere/7)),group = interaction(ptid, drug)))
  geom_point(alpha = 0.1, size = 0.8,aes(x = week, y = log(Adhere/7/ (1-Adhere/7)),group = interaction(
  geom_smooth(method = "lm")+
  facet_grid(.~drug)+
  theme_bw() +
```

```
  ylab(TeX("$\\log\\left(\\frac{p_{ijk}}{1-p_{ijk}}\\right)$"))

#plot.adhere

plot.PK <-
endpoints.PK %>%
  ggplot(aes(y=dvalue, x=period))+
  geom_smooth(method = "lm", se = FALSE, show.legend = FALSE) +
  geom_line(alpha = 0.2, aes(group = ptid)) +
  geom_point(alpha = 0.1, size = 0.8) +
  facet_grid(.~measure)+
  xlab("Period")+
  ylab("Viral Load Difference")+
  theme_bw()

#plot.PK

ggarrange(plot.ae, plot.adhere,
          #labels = c("(a)", "(b)"),
          ncol = 1, nrow = 2)
plot.adhere.demo <-
endpoints.PK %>%
  mutate(product_type = if_else(drug=="Pill A", "Drug", "Gel"),
         regimen = if_else(drug== "Gel B", "3 times/day", "1 time/day"),
         product_dosage = case_when(
           drug == "Pill A" ~ "Drug, 1 time/day",
           drug == "Gel B" ~ "Gel, 3 times/day",
           drug == "Gel C" ~"Gel, 1 time/day"
         )) %>%
  ggplot(aes(y = Adhere_rate, x = age))+
  #geom_boxplot()+
  geom_point()+
  geom_hline(yintercept = 1, linetype = 2, color = "grey")+
  geom_smooth(color="blue", method="loess")+
  facet_grid(gender + race~regimen + product_type)+
  theme_bw()+
```

```
  ylab("Adherence Rate of a Treatment Period")+
  xlab("Age") +
  labs(caption = "(Age is centered)")

library(patchwork)
plot.adhere.demo
plot.pk.ae <-
 endpoints.PK %>%
  ggplot(aes(y=dvalue, x=drug))+
  geom_boxplot()+
  facet_grid(AE_ind ~measure)+
  theme_bw()+
  ylab("Viral Load Difference")+
  xlab("Treatments")

plot.pk.adhere <-
 endpoints.PK %>%
  ggplot(aes(y=dvalue, x=Adhere_sum))+
  #geom_boxplot(aes(group = Adhere_sum))+
  geom_point(size=0.8)+
  geom_smooth(method = "lm", se = FALSE, show.legend = FALSE) +
  facet_grid(drug~measure)+
  xlab("Number of Adherence Days in a Treatment Period")+
  ylab("Viral Load Difference")+
  theme_bw()

ggarrange(plot.pk.ae, plot.pk.adhere,
          ncol = 1, nrow =2)
tbl.ae.co.model <-
  AE.crossover.model %>%
  tbl_regression(
    exponentiate = T,
    label = list(
      period ~ "Period",
      seq2 ~ "Sequence"
    )
```

```
  ) %>%
  modify_header(
  update = list(p.value = "p-value", ci = "95% CI", label = "Characteristics", estimate = "OR")
  )



tbl.ae.co.model %>% as_kable(booktabs = T, caption = "Coefficent estimates of the carry-over effect mod
tbl.adhere.co.model <-
  Adhere.crossover.model %>%
  tbl_regression(
    exponentiate = T,
    label = list(
      period ~ "Period",
      seq2 ~ "Sequence"
    )
  ) %>%
  modify_header(
  update = list(p.value = "p-value", ci = "95% CI", label = "Characteristics", estimate = "OR")
  )



tbl.adhere.co.model %>%   as_kable(booktabs = T, caption = "Coefficent estimates of the carry-over effe
tbl.pk.co.model.b <-
  PK.crossover.model.bviral %>%
  tbl_regression(
    exponentiate = F,
    label = list(
      period ~ "Period",
      seq2 ~ "Sequence"
    )
  ) %>%
  modify_header(
  update = list(p.value = "p-value", ci = "95% CI", label = "Characteristics", estimate = "$\\hat\\beta
  )
```

```r
tbl.pk.co.model.b %>%   as_kable(booktabs = T, caption = "Coefficent estimates of the carry-over effect
tbl.pk.co.model.s <-
  PK.crossover.model.sviral %>%
  tbl_regression(
    exponentiate = F,
    label = list(
      period ~ "Period",
      seq2 ~ "Sequence"
    )
  ) %>%
  modify_header(
  update = list(p.value = "p-value", ci = "95% CI", label = "Characteristics", estimate = "$\\hat\\beta$
  )


tbl.pk.co.model.s %>%   as_kable(booktabs = T, caption = "Coefficent estimates of the carry-over effect
model.AE %>%
  tbl_regression(
    exponentiate = T,
    label = list(
      drug ~ "Treatment",
      period ~ "Period",
      age ~ "Age",
      gender ~ "Gender",
      race ~ "Race"
    ),
    include = everything()) %>%
  modify_header(
  update = list(p.value = "p-value", ci = "95% CI", label = "Characteristics", estimate = "OR")
  ) %>%
  as_kable(booktabs = T, caption = "Coefficent estimates of the treatment effects on the safety outcome
  kable_styling(latex_options = c("hold_position"))
model.Adhere %>%
  tbl_regression(
    exponentiate = T,
    label = list(
```

```
      week ~ "Week",
      drug ~ "Treatment",
      period ~ "Period",
      age ~ "Age",
      gender ~ "Gender",
      race ~ "Race"
    )) %>%
  modify_header(
  update = list(p.value = "p-value", ci = "95% CI", label = "Characteristics", estimate = "OR")
  ) %>%
  as_kable(booktabs = T, caption = "Coefficent estimates of the treatment effects on the adherence.") %
  kable_styling(latex_options = c("hold_position"))
tab.bviral <-
model.PK.bviral %>%
  tbl_regression(
    exponentiate = F,
    label = list(
      Adhere_sum_centered ~ "Days of adherece (within a period, centered)",
      drug ~ "Treatment",
      period ~ "Period",
      age ~ "Age",
      gender ~ "Gender",
      race ~ "Race",
      AE_ind ~ "Occurence of adverse effects"
    )) %>%
  modify_header(
  update = list(p.value = "p-value", ci = "$95\\%$ CI", label = "Characteristics", estimate = "$\\hat\\
  )
#tab.bviral

tab.sviral <-
model.PK.sviral %>%
  tbl_regression(
    exponentiate = F,
    label = list(
      Adhere_sum_centered ~ "Days of adherece (within a period, centered)",
```

```
      drug ~ "Treatment",
      period ~ "Period",
      age ~ "Age",
      gender ~ "Gender",
      race ~ "Race",
      AE_ind ~ "Occurence of adverse effects"
    )) %>%
  modify_header(
  update = list(p.value = "p-value", ci = "$95\\%$ CI", label = "Characteristics", estimate = "$\\hat\\
  )
#tab.sviral

tbl_merge(
  list(tab.bviral, tab.sviral),
) %>%
  as_kable(booktabs = T, caption = "Coefficent estimates of the treatment effects on the pharmacokeniti
  add_header_above(c("", "Blood viral loads model" = 2, "Skin viral loads model" = 2))
adhere.demo.tab.product <-
  model.Adhere.product.1 %>%
  tbl_regression(
    exponentiate = T,
    label = list(
      product ~ "Product type",
      period ~ "Period",
      age ~ "Age",
      gender ~ "Gender",
      race ~ "Race",
      week~ "Week",
      `age:product` ~ "Age $\\times$ Product type",
      `product:gender` ~ "Product type $\\times$ Gender",
      `product:race` ~ "Product type $\\times$ Race"
    )
  ) %>%
  modify_header(
  update = list(p.value = "p-value", ci = "$95\\%$ CI", label = "Characteristics", estimate = "OR")
  )
```

```r
adhere.demo.tab.freq <-
  model.Adhere.freq.1 %>%
  tbl_regression(
    exponentiate = T,
    label = list(
      freq ~ "Regimen",
      period ~ "Period",
      age ~ "Age",
      gender ~ "Gender",
      race ~ "Race",
      week~ "Week",
      `age:freq` ~ "Age $\\times$ Regimen",
      `freq:gender` ~ "Regimen $\\times$ Gender",
      `freq:race` ~ "Regimen $\\times$ Race"
    )
  ) %>%
  modify_header(
  update = list(p.value = "p-value", ci = "$95\\%$ CI", label = "Characteristics", estimate = "OR")
  )

tbl_merge(list(adhere.demo.tab.product, adhere.demo.tab.freq)) %>%
  as_kable(booktabs = T, caption = "Coefficent estimates of the effects of demographic factors and produ
  add_header_above(c("", "Model for product type" = 3, "Model for regimen" = 3))
```