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:

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

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:

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

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:

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

2.4.2 Secondary Analysis

2.4.2.1 Correlation of PK 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:

$$\Delta\text{Skin Viral Load}_{ij} = \beta_0 + \beta_1 \cdot \text{Period}_{ij} + \beta_2 \cdot \mathbf{I}(\text{Sequence } 2_i = 1) + \beta_3 \cdot \mathbf{I}(\text{Sequence } 2_i = 2) + b_{0i},$$
$$\Delta\text{Blood Viral Load}_{ij} = \gamma_0 + \gamma_1 \cdot \text{Period}_{ij} + \gamma_3 \cdot \mathbf{I}(\text{Sequence } 2_i = 1) + \gamma_3 \cdot \mathbf{I}(\text{Sequence } 2_i = 2) + b_{0i}.$$

Here $\Delta\text{Skin Viral Load}_{ij}$ and $\Delta\text{Blood Viral Load}_{ij}$ 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:

$$\begin{aligned}\Delta\text{Skin Viral Load}_{ij} = \ & \beta_0 + \beta_1 \cdot \mathbf{I}\left(\text{Treatment}_{ij} = \text{Gel B}\right) + \beta_2 \cdot \mathbf{I}\left(\text{Treatment}_{ij} = \text{Gel C}\right) + \beta_3 \cdot \text{Period}_{ij} \\ & + \beta_4 \cdot \mathbf{I}\left(\text{Number of adverse event}_{ij} \geq 1\right) + \beta_4 \cdot \text{Number of days of adherence}_{ij} \\ & + \beta_4 \cdot \text{Age}_i + \beta_5 \cdot \mathbf{I}(\text{Gender}_i = \text{female}) + \beta_6 \cdot \mathbf{I}(\text{Race}_i = \text{black}) + \beta_7 \cdot \mathbf{I}(\text{Race}_i = \text{others})\end{aligned}$$

3 Result

4 Discussion

Appendix

A.2 Code for This Report

```
knitr::opts_chunk$set(echo = FALSE, message = F, warning = F)
options(knitr.kable.NA = '')
library(tidyverse)
library(lme4)
library(nlme)
library(lattice)
library(gtsummary)
library(DHARMa)
library(knitr)
library(kableExtra)
library(webshot)

write_matex <- function(x) {
  begin <- "$$\\begin{bmatrix}"
  end <- "\\end{bmatrix}$$"
  X <-
    apply(x, 1, function(x) {
      paste(
        paste(x, collapse = "&"),
        "\\\\"
      )
    })
  writeLines(c(begin, X, end))
}
theme_set(
  theme_bw()+
  theme(
    plot.title = element_text(size = 16, hjust = 0.5),
    axis.title.x = element_text(size = 12),
    axis.title.y = element_text(size = 12),
    axis.text = element_text(size = 10),
    axis.line = element_line(color = "black", size = 0.5),
  )
)
```

```r
baseline.dat <- read.csv("baseline.csv")
endpoints.dat <- read.csv("endpoints.csv")
endpoints.AE <-
  endpoints.dat %>%
  select(ptid,  AE_pillA_week1:AE_gelC_week4) %>%
  pivot_longer(
    cols = starts_with("AE_"),
    names_to = c("drug", "week"),
    names_pattern = "AE_(.*)_(week\\d+)",
    values_to = "AE"
  ) %>%
  mutate(drug = case_when(
    str_detect(drug, "pillA") ~ "Pill A",
    str_detect(drug, "gelB") ~ "Gel B",
    str_detect(drug, "gelC") ~ "Gel C"
  ),
  week = parse_number(week))

endpoints.Adhere <-
  endpoints.dat %>%
  select(ptid, Adhere_pillA_week1:Adhere_gelC_week4) %>%
  pivot_longer(
    cols = starts_with("Adhere_"),
    names_to = c("drug", "week"),
    names_pattern = "Adhere_(.*)_(week\\d+)",
    values_to = "Adhere"
  ) %>%
  mutate(drug = case_when(
    str_detect(drug, "pillA") ~ "Pill A",
    str_detect(drug, "gelB") ~ "Gel B",
    str_detect(drug, "gelC") ~ "Gel C"
  ),
  week = parse_number(week)) %>%
  mutate(drug = factor(drug, levels = c("Pill A", "Gel B", "Gel C")))

endpoints.period <-
```

```
  endpoints.dat %>%
  select(ptid, period1:period3) %>%
  mutate(sequence = case_when(
    period1 == "Pill A" & period2 == "Gel B" & period3 == "Gel C" ~ "ABC",
    period1 == "Pill A" & period2 == "Gel C" & period3 == "Gel B" ~ "ACB",
    period1 == "Gel B" & period2 == "Gel C" & period3 == "Pill A" ~ "BCA",
    period1 == "Gel B" & period2 == "Pill A" & period3 == "Gel C" ~ "BAC",
    period1 == "Gel C" & period2 == "Pill A" & period3 == "Gel B" ~ "CAB",
    period1 == "Gel C" & period2 == "Gel B" & period3 == "Pill A" ~ "CBA",
    TRUE ~ "Other" # This is the default case
  )) %>%
  mutate(
    seq1 = case_when(
    sequence == "ABC" ~ 1,
    sequence == "CAB" ~ 2,
    sequence == "BCA" ~ 3,
    sequence == "BAC" ~ 4,
    sequence == "ACB" ~ 5,
    sequence == "CBA" ~ 6,
  ),
    seq2 = case_when(
      sequence == "ABC" | sequence == "BAC" ~ 0,
      sequence == "CAB" | sequence == "ACB" ~ 1,
      sequence == "BCA" | sequence == "CBA" ~ 2
    )) %>%
  pivot_longer(
    cols = starts_with("period"),
    names_prefix = "period",
    names_to = "period",
    values_to = "drug"
  ) %>%
  mutate(period = as.numeric(period)) %>%
  mutate(drug = factor(drug, levels = c("Pill A", "Gel B", "Gel C"))) %>%
  mutate(seq2 = factor(seq2, levels = c(0,1,2), labels = c("AB", "AC", "BC")))


endpoints.lag <-
```

```
  endpoints.period %>%
  select(ptid, period, drug) %>%
  group_by(ptid) %>%
  mutate(drug_lag = lag(as.character(drug))) %>%
  ungroup() %>%
  replace_na(list(drug_lag = "None")) %>%
  mutate(
    A_lag = ifelse(drug_lag == "Pill A", 1, 0),
    B_lag = ifelse(drug_lag == "Gel B", 1, 0),
    C_lag = ifelse(drug_lag == "Gel C", 1, 0)
  )%>%
  mutate(drug = factor(drug, levels = c("Pill A", "Gel B", "Gel C")))

endpoints.period <- left_join(endpoints.period, endpoints.lag)

endpoints.AE <- left_join(endpoints.AE, endpoints.period)

endpoints.Adhere <- left_join(endpoints.Adhere, endpoints.period)
endpoints.AE.weeksum <-
  endpoints.AE %>%
  select(-week) %>%
  group_by(ptid,drug,period) %>%
  mutate(AE_sum  = sum(AE)) %>%
  ungroup() %>%
  mutate(AE_ind = as.factor(ifelse(AE_sum > 0, 1, 0))) %>%
  select(-AE) %>%
  distinct() %>%
  mutate(drug = factor(drug, levels = c("Pill A", "Gel B", "Gel C")))

endpoints.Adhere <-
  endpoints.Adhere %>%
  mutate(total_week = period*week,
         nonAdhere = 7-Adhere)
# 0- baseline; 1- 1st treatment; 2- 1st wash out; 3- 2nd treatment;
# 4- 2nd wash out; 5- third treatment; 6- third wash out
endpoints.PK <-
```

```
  baseline.dat %>%
  select(ptid, bviral0:sviral6) %>%
  mutate(
    dbvial1 = -bviral1 - bviral0,
    dsvial1 = -sviral1 - sviral0,
    dbvial2 = -bviral3 - bviral2,
    dsvial2 = -sviral3 - sviral2,
    dbvial3 = -bviral5 - bviral4,
    dsvial3 = -sviral5 - sviral4
  ) %>%
  pivot_longer(
    cols = starts_with("d"),
    names_to = c("measure", "period"),
    names_pattern = "d(.*vial)(\\d+)",
    values_to = "dvalue"
  ) %>%
  select(ptid, measure, period, dvalue) %>%
  mutate(period = as.numeric(period),
         dvalue = -dvalue)



endpoints.Adhere.sum <-
  endpoints.Adhere %>%
  select(ptid, period, week, Adhere) %>%
  group_by(ptid, period) %>%
  summarize(Adhere_sum  = sum(Adhere)) %>%
  mutate(Adhere_rate = Adhere_sum/28)

endpoints.PK <- left_join(endpoints.PK, endpoints.Adhere.sum)
endpoints.PK <-
  left_join(endpoints.PK, endpoints.AE.weeksum) %>%
  mutate(drug = factor(drug, levels = c("Pill A", "Gel B", "Gel C"))) %>%
  mutate(measure = factor(measure, labels = c("Skin", "Blood"),levels = c("svial", "bvial"))) %>%
  mutate(AE_ind = factor(ifelse(AE_ind == 1,"Yes", "No")))

#endpoints.PK.bvial <- endpoints.PK %>% filter(measure == "bvial")
```

```r
#endpoints.PK.svial <- endpoints.PK %>% filter(measure == "svial")
Adhere.demo <-
  baseline.dat %>%
  select(ptid, age, gender, race) %>%
  mutate(
    gender = factor(gender, labels = c("male", "female"), levels = c(0,1)),
    race = factor(race, levels = c("white", "black", "others"))
  )

endpoints.Adhere.total <-
  endpoints.Adhere.sum %>%
  select(ptid, Adhere_sum) %>%
  group_by(ptid) %>%
  summarize(Adhere_total = sum(Adhere_sum))

Adhere.demo <- left_join(Adhere.demo, endpoints.Adhere.total) %>%
  mutate(non_Adhere_total = 84 - Adhere_total)
# 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")
)
```

```r
# 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")
```