Statistical Analysis Plan

A Trial of Favipiravir therapy in Adults with mild Coronavirus Disease COVID-19

Study Code : RC20/220/R

Study Protocol Version/ Date : 3.0 / 14, March 2021

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Signature Page

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Name	Role& Organization	Signature	Approval Date
Omar Aldibasi, PhD	Project Biostatistician KAIMRC	Omar Aldibasi	7Jun2021
Mohammad Bosaeed, MD	Principal Investigator KAIMRC		7Jun2021

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LIST OF ABBREVIATIONS

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AE : Adverse Event/Adverse Experience

CRF : Case Report Form

COVID-19 : Coronavirus disease 2019

DMC : Data Monitoring Committee

DSMB : Data and Safety Monitoring Board

FDA : Food and Drug Administration

GCP : Good Clinical Practice

ICH : International Conference on Harmonization

ICU : Intensive Care Unit

IRB : Institutional review board

MAP : Mean arterial pressure

PCR : Polymerase chain reaction

PK : Pharmacokinetic

SAE : Serious adverse event

SAP : Statistical Analysis Plan

1. INTRODUCTION

The Statistical Analysis Plan (SAP) purpose is to provide a framework that addresses the protocol objectives in a statistically rigorous fashion, with minimized bias or analytical deficiencies. Specifically, this plan has the following purpose: To evaluate Favipiravir's effect on the timing of PCR test conversion (from positive to negative).

The final study report will follow the guidelines of the Consolidated Standards of Reporting Trials (CONSORT) for reporting randomized controlled trials. [1, 2]

The trial is being conducted according to the standard requirements of Good Clinical Practice E6.[3] The SAP is developed in accordance with the International Council for Harmonisation guidelines (E9 Statistical principles for clinical trials and E3 clinical study reports guidelines)[4, 5] and with Guidelines for the Content of Statistical Analysis Plans in Clinical Trials.[6]

2. STUDY Outcomes

2.1. Primary Outcome

To evaluate the effect of Favipiravir on the timing of PCR test conversion (from positive to negative). **

[Time Frame: 15 days after starting medicine]

**Viral clearance is defined as polymerase chain reaction (PCR) negative results.

2.2. Secondary Outcomes

1. To evaluate Favipiravir's effect on clinical recovery.
2. Evaluate symptoms severity and the progression in the disease course in both arms. [Time Frame: 28 days after starting medicine]
3. To evaluate Favipiravir's effect on the requirement of the use of antipyretics, analgesics, or antibiotics. [Time Frame: 15 days after starting medicine]
4. To evaluate Favipiravir's effect on disease complications (hospitalization, ICU admission or Mechanical ventilation). [Time Frame: 28 days after starting medicine]
5. Evaluate the safety of investigational therapeutics as compared to the control arm. [Time Frame: 15 days after starting medicine]

3. STUDY DESCRIPTION

3.1. Study Design

This is a Double-blinded multicenter, randomized controlled clinical trial, to evaluate the safety and efficacy of novel therapeutic agents in adults diagnosed with mild COVID-19. Double-blinded means that the participants and investigators with other study staff are unaware of the treatment assignment. The Sponsor's investigational drug unit, not part of the study team, holds the information for treatment allocation. It compares Favipiravir (experimental arm) to a control arm (Placebo).

3.2. Randomization Procedure

Patients will be randomly assigned to one of the two intervention arms by stratified block randomization, which will ensure that the two arms contain equal numbers of patients. Randomization will be stratified according to center and according to at the time of enrollment. The web-based data entry system (REDCAP) will be used to randomized patients in two groups.

3.3. Sample Size

Assumptions and Study Hypothesis:

1. The current study's primary hypothesis is H0: HR =1 vs. H1: HR ≠1; and HR is the hazard ratio of treatment compared to the control arm.

2. Time to viral clearance
3. In patients with mild COVID19, 90% of the patients clear the virus by day 10 of onset (1). If we assume an exponential hazard, we estimate the median time of viral clearance in the placebo group to be eight days.
4. The exact treatment effect from Favipiravir is not known but can be approximated using prior clinical studies. A study comparing Favipiravir's effect to lopinavir/ritonavir on virus clearance has shown a 64% reduction in the time to viral clearance in the Favipiravir arm(7). To stay on the conservative side, we assume that Favipiravir will reduce the median time to virus clearance to six days, equivalent to a hazard ratio of 1.33.
5. We further assume that 90% of the control group patients will have viral clearance within 15 days, and 90% will have viral clearance in the treatment arm.
6. It is anticipated that very few of these subjects will be randomized and not start study treatment (and so be excluded from the primary analysis) or be lost to follow-up (and so have missing data for the primary endpoint). Given certain uncertainties, however, we have included a nominal 10% dropout rate.

9.2.2 Sample Size Estimation for Classical Two Arm Parallel Design:

Under the classical two-arm parallel design, a one-sided test of whether the hazard ratio is 1 with an overall sample size of 576 subjects (of which 288 are in the control group and 288 are in the treatment group) achieves 90% power at a 0.025 significance level when the hazard ratio is 1.330. The number of events (i.e., subjects with viral clearance) required to achieve this power is 517.5. The proportions of events during the study are anticipated to be 0.900 for the control group and 0.900 for the treatment group. We anticipate a 10% dropout rate, and therefore we expect that the trial will recruit 317 subjects per arm. These results assume that the hazard ratio is constant throughout the study and that Cox proportional hazards regression is used to analyze the data.

9.2.3 Interim analysis and sample size Re-estimation

The current study will have a single interim analysis, which will occur after the recruitment and follow-up of 40% of the total number of subjects (i.e. 230 subjects). The interim analysis is designed to test for early stopping for futility or efficacy and sample size re-	Decision

estimation. The interim analysis and final analysis will be based on the sum of the stage-wise p-value discussed in Mark and Chang, 2008. The table below describes the interim analysis testing boundaries. Boundary	
Alpha1 = 0.01	Stop the trial for early efficacy if the interim analysis p-value is less than 0.01
Beta1 =0.25	Stop the trial for futility if the interim analysis P-value is equal to or larger than 0.25
Alpha2=0.1832	Declare the trial significant if the sum of the interim analysis and final stage P-values are less than 0.1832

The sample size Re-estimation will be based on the ratio of the planned effect size (1.33) to the observed effect size from the interim analysis according to the following formula:

$$N = \left(\frac{E_0}{E}\right)^a N_0$$

where ‘a’ is a constant which will be set to 2 and $'N'_0$ is a number chosen to be slightly larger than the classical sample size per group, E_0 is the planned effect size of 1.33, and E is the observed effect size from the interim analysis.

3.4. Study Duration

The study interventions will continue for 7 days. Patients will be followed up daily until day 14 and then once at day 28.

4. INCLUSION, EXCLUSION AND WITHDRAWAL CRITERIA

4.1. Inclusion Criteria

1. Should be at least 18 years of age.

2. Male or non-pregnant female,

3. Diagnosed with Mild COVID-19* confirmed by positive PCR test for SARS-2-CoV at the time of recruitment, a result within the last 5 days.

4. Able to sign the consent form and agree to clinical samples collection (or their legal surrogates if subjects are or become unable to make informed decisions).

5. Patients had to be enrolled within five days of disease onset.

6. Must agree not to enroll in another study of an investigational antiviral agent before completing Day 28 of the study.

*Mild COVID-19 cases are defined as a patient presenting with a mild illness (absent or mild pneumonia), oxygen saturation >94% at room air, and not requiring ICU admission.

4.2. Exclusion Criteria

Patients are excluded from participation in the study if they meet any of the following exclusion criteria:

1. Patients with concomitant documented bacterial pneumonia

2. Patients who are pregnant or breastfeeding.

3. Known sensitivity/allergy to Favipiravir

4. Significant comorbidities increasing the risk of study drug including:

i. Hematologic malignancy, ii. Advanced (stage 4-5) chronic kidney disease or dialysis therapy, Severe liver damage (Child-Pugh score ≥ C, AST> 5 times the upper limit), HIV.

5. Gout/history of Gout or hyperuricemia (two times above the ULN-upper limit normal)

6. Having used Favipiravir or participated in any other interventional drug clinical study within 30 days before the first dose of the study drug.

7. The investigator believes that participating in the trial is not in the patient's best, or the investigator considers unsuitable for enrollment (such as unpredictable risks or subject compliance issues

8. Clinical prognostic non-survival, palliative care, or a deep coma and have no response to supportive treatment within three hours of admission.

9. Hospitalized patients for moderate or severe COVID-19

5. STUDY POPULATIONS

5.1. Intention-to-treat (ITT) population

The Intention-to-treat population consists of all randomized patients ignoring noncompliance, protocol deviations, withdrawal, and anything criteria that may take place randomization.

5.2.Modified ITT population

The modified ITT population will include all randomized patients but will exclude patients who were judged ineligible after randomization or patients who withdrew consent, or certain patients who never started treatment.

ENDPOINTS/ ANALYSIS	POPULATION /ANALYSIS SETS
Demographic and Baseline Characteristics	Intention-to-treat population
Efficacy Analysis	Intention-to-treat population and/or Modified ITT Population
Safety Analysis	Intention-to-treat population

5.3.Treatment Misallocations

If a patient was:

- Randomized but not treated: the patient will be accounted for in the patient disposition table. The patient will be reported under the randomized treatment group for efficacy analysis. The patient will not be included in safety analyses.
- Treated but not randomized: the patient will be reported under the treatment they actually received for the safety analyses. The patient will not be included in efficacy analyses.
- Randomized but received incorrect treatment: if a patient received the incorrect treatment they will be reported under the treatment they actually received for safety analyses; and they will be reported under the

randomized treatment group for efficacy analysis. The patient will be excluded from the modified ITT population if this is deemed as a major protocol deviation. Patient profiles on safety (demographics, adverse events, laboratory data, concomitant medications) may be generated for further assessments.

6. STATISTICAL CONSIDERATIONS

6.1. Statistical Significance

Hypothesis testing for the primary outcome will be done using a two-sided, 0.05 level of significance.

Statistical tests for variables other than the primary outcome will be performed using a two-sided alpha value of 5% to denote significance level.

As appropriate, the Chi-square test or Fisher's exact test will be used to compare the categorical variables, which will be reported as numbers and percentages. Student's t-test or the Mann–Whitney U test will be used as appropriate to compare the continuous variables, which will be reported as means and standard deviations or as medians and interquartile ranges.

6.2. Handling Dropouts and Missing Data

All missing data will be reviewed and characterized in terms of their pattern (e.g. Missing completely at random, missing at random, etc.). All analyses will be based on a list-wise deletion approach where observation will complete values will be only considered for analysis for missing completely

at random. For variables with values missing at random, multiple imputation techniques will be utilized to impute the missing values as suggested by Rubin's [9].

6.3. Adjustment for multiplicity

To adjust for multiple testing, we will use the False Discovery Rate (FDR) as described by Benjamini and Hochberg [10]. In this procedure, all hypothesis tests will be sorted in an ascending order based on their calculated p-value. All hypothesis tests below an index K will be rejected where K calculated as follows:

$$K = max\left\{i: p(i) \leq \frac{i}{m}.q\right\}$$

Where i=m, …1 ; m is the number total number of tested hypotheses ; q =.05.

6.4. Statistical Software

All analyses including the interim and final analysis will be analyzed using SAS version 9.4 NC.

7. DESCRIPTION OF TABLES AND FIGURES

7.1. Subject Disposition

7.1.1. Subject Disposition

The number and percentage of randomized patients to each group will be reported. We will report the number of randomized patients who received the interventions. We will also report the number of screened patients (defined as all hospitalized patients with covid-19), who met the eligibility criteria but not enrolled and reasons for non-enrollment. A CONSORT flow diagram of the trial progress will be constructed.

7.1.2. Protocol Violations/ Deviations

Potential violations that may result in the exclusion of a patient from the Per-Protocol population include:

- Patient compliance with study medication is <80%,
- Premature discontinuation of treatment

7.2. Baseline and Demographic Characteristics

All analyses will be performed using SAS version 9.4. We will summarize and report the demographics and baseline clinical characteristics using descriptive statistics. Baseline characteristics will be presented for the two study groups, including age, ethnicity, gender, body mass index, and center. We will report comorbidities and the interventions received before randomization for patients in each group. We will report baseline vital signs

(temperature, Heart rate (HR), Respiratory rate (RR), systolic blood pressure (SBP), diastolic blood pressure (DBP), Oxygen Saturation, mode of Oxygen Saturation and amount of Oxygen Saturation via facemask), sign and symptoms in addition to the location of the patient at time of randomization. Categorical variables will be summarized by treatment group using number (n) and percentage (%). Descriptive statistics such as mean, standard deviation (SD) or median (Q1, Q3) will be calculated for continuous variables.

7.3. Efficacy Analysis

7.3.1. Analysis of the primary outcome and continuous planning of the trial

The primary endpoint of the current study is the time to viral clearance. The number and percent of subjects who met the endpoint by day 15 of follow-up will be calculated and tabulated. The primary outcome will be compared in the intention-to-treat and modified ITT population using the unadjusted Cox proportional hazard model test the null hypothesis. We define the hazard function at time t as the instantaneous probability of a negative RT-PCR test result at time t given the patient was positive as per the RT-PCR test up to that time. Negative results from the RT-PCR nucleic acid test will be considered as events. Specifically, we will censor patients who are still positive by the end of the 15-day of randomization, those who die before day 15, and those lost to follow-up (dropouts and lost to follow-up before day

15). We will report hazard ratio (HR) with 95% CI. Kaplan-Meier curves will be generated for the alternative treatment groups, and a log-rank test will be used to compare distributions. Although imbalances in baseline characteristics are possible, we will conduct an adjusted Cox proportional hazard model with center/site as a random effect to adjust for the following factors (defined a priori):

Age, Sex, BMI, and Symptoms onset to enrollment.

Supportive analyses can be used including chi-square or fisher's exact test. Results will be reported as RR with 95% CI . there is the possibility that some of the study centers may have few events; we will use a generalized linear mixed-model (GLMM) to estimate adjusted RR after incorporating center/site as random effect. If there is a significant difference, we will report relative risk reduction (RRR), absolute risk reduction (ARR) or increase, and the number needed to treat (or harm) with 95% CIs.

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7.3.2. Secondary outcomes and subgroups.

Analysis of secondary outcomes, including safety outcomes, will be compared in the intention-to-treat cohort and will be reported as relative risk with the corresponding 95% CI.

A secondary adjusted analysis will be conducted using multiple logistic regression analysis in which death within 28 days will be modeled as the dependent variable and a set of baseline variables that are strongly believed to affect the outcome of Covid-19 infection will be included as independent variables. These independent variables will be same covariates as considered for primary endpoint. The other secondary outcomes such as requirement of hospitalization. ICU admission or Mechanical ventilations will be analyzed in similar fashion as defined above for 28 days mortality.

The hospital length of stay (LOS) which is defined as “number of days patient stayed at the hospital” and can be calculated by considering the difference between date of discharge to date of admission. The number of days patient stayed in the hospital will be analyzed using a Poisson model with a log link. The model will be adjusted for same covariates as considered for primary analysis.

The time from randomization to clinical recovery will be summarized and analyzed in the same fashion as the primary endpoint.

The symptoms severity and progression based on clinical evaluation, daily requirement of use of antipyretics, analgesics, or antibiotics, and evaluate the safety of investigational therapeutics will be summarised descriptively between two treatment groups.

Subgroup analyses

The following pre-specified subgroup analyses will be conducted on the primary and the other secondary outcomes stratified by:

1.Age

2.Sex

3. BMI

4. Symptoms onset to enrollment.

These subgroups are chosen as they have an implication on the primary and secondary outcomes. Results will be presented as forest plots with interactions results alongside. The interaction test will assess if the treatment effect is modified by the subgroup.

7.4. Safety Analysis

7.4.1. Adverse Events (AE) and Drug reactions

The proportion of subjects experiencing an adverse drug reactions, SAE and the proportion experiencing a Grade 3 or higher AE will be compared between randomized arms using Fisher's Exact Test. All results will be declared statistically significant with P-value <0.05.

Serious adverse events will be summarized by treatment group using number (n) and percentage (%). The relationship with study drugs will also be

summarized. Serious adverse events related to the study drugs will be summarized by treatment group using number (n) and percentage (%).

7.4.2. Vital Signs

Vital signs such as temperature (°C), respiratory rate, systolic blood pressure (mmHg), highest heart rate, lowest mean arterial pressure (mmHg) will be summarized using median (Q1, Q3) at baseline and over time.

7.4.3. Laboratory Parameters

Laboratory values such as hemoglobin, white blood cell count, lymphocyte, neutrophil, platelet count , ALT/SGPT, Total Bilirubin , AST/SGOT , Glucose , Blood Urea Nitrogen , Creatinine , Sodium and Potassium will be summarized using median (Q1, Q3) at baseline. Figures will be presented for the serial measurements Day 1, Day 5, Day 10, and Day 15. The chest x ray , presence of infiltrates and assessment of ECG will be summarized using number (n) and percentages (%) between both groups.

7.4.4. Pathogen Testing

All reported Pathogens will be summarized using number (n) and percentages (%) between both groups.

7.4.5. Complication

All reported complications at day 28 will be summarized using number (n) and percentages (%) between both groups.

7.4.6. Treatment Exposure and Compliance

We will report the received and duration of study intervention for each group, in addition to the missing or incomplete doses and protocol violations.

7.4.7. Prior and Concomitant Medications and Interventions

We will summarize any use of antiviral agents, the use of antibiotics, antiinterleukin-6 agents and corticosteroid in the study.

The dose of antiviral therapies, antibiotics, Convalescent plasma and Corticosteroid and duration of corticosteroid (days) use will be summarized by treatment group using median (Q1, Q3).

7.5. Model assumptions checks and alternative methods:

The model diagnostic check for the Cox regression model will include checking for influential observations, linearity, and proportional hazards assumptions. For this, established diagnostic procedures which incorporate evaluation of various residuals will be used. Both statistical testing and graphical plotting will be used for this evaluation.

1. For testing the proportional hazards assumption, the scaled Schoenfeld residuals will be plotted against the log of time. The statistical test will be testing for a non-zero slope in a generalized linear regression of the scaled Schoenfeld residuals on the functions of time. If the proportional

hazards assumption is not met then the accelerated failure time (AFT) model will be used. If the fit of the AFT model is not adequate, as demonstrated by a Q-Q plot, then a restricted mean survival time method as demonstrated by Royston & Parmar will be utilized (7). The restricted mean survival time approach is robust as it does not assume proportional hazards.

2. Influential observations or outliers will be checked using deviance residuals which are normalized transformations of the martingale residuals. The plot of these residuals against the observations should symmetrically distribute about zero with a standard deviation of 1.
3. Linearity assumptions for continuous covariates will be checked by plotting the Martingale residuals against the covariate. Fitted lines with loess function should appear linear to satisfy the linearity assumptions. If the same is found to be violated, continuous variables will be expanded by restricted cubic splines with 3 or more knots will be used to model the continuous covariate.
4. In order to evaluate the model discrimination and calibration, bootstrapping with 500 bootstrap samples will be used to derive a calibration plot and optimism corrected C-index

5. For testing the equidispersion assumption for Poisson regression:

   Parameter estimates may be non-robust to the failure of the assumed distribution of the random effects. Therefore diagnostic checking of the residuals will be performed. If data deviates from the assumption of equidispersion (average = variance). The Pearson Chi-Square / DF value should be roughly 1.0. A value greater than 1.0 indicates the data are over-dispersed, i.e., the variance is greater than the mean. In general, a value greater than 2.0 requires remedial action. Therefore, we will be using robust variance estimators to estimate robust standard errors. When the data are from a Poisson process (no violation of equidispersion assumption), the Poisson SE may be preferred. It will generally provide more statistical power in this situation; the P-values and CIs will be smaller.

8. PHARMACOKINETIC ANALYSIS

Pharmacokinetic analysis will not be done for this study.

9. INTERIM REPORT DETAILS

There will be one formal interim analyses in this study, which will occur after the recruitment and follow-up of 40% of the total number of subjects (i.e. 230 subjects). The interim analysis is designed to test for early stopping for futility or efficacy and sample size re-estimation.

Recommendation by the data safety monitoring Board (DSMB) whether to terminate the study based on this interim analysis will be determined by evaluating the overall safety information and efficacy data based on the boundary specified in the sample size Re-estimation section.

10. Data and Safety Management Board (DSMB)

A DSMB will review safety and efficacy data at the interim analyses. The DSMB will provide a recommendation regarding study continuation based on the safety and efficacy parameters. If the study is terminated early based on a DSMB recommendation, KAIMRC will notify the appropriate regulatory authorities. Detailed information regarding the composition of the DSMB and detailed DSMB procedures will be provided in the DMC charter.

11. REPORT GENERATION

Figure Legend

Figure 1: CONSORT flow chart for the AVIMILD trial

Supplemental Table Legends

Supplemental Table 1. Baseline characteristics.

Supplemental Table 2. Summary of interventions and co-interventions.

Supplemental Table 3. Primary Outcome.

Supplemental Table 4. Secondary Outcomes.

Supplemental Table 5. Subgroup analyses.

Supplemental Table 7: Summary of Adverse Events by severity.

Supplemental Table 8: Summary of Protocol Violations.

Supplemental Figure 2: Kaplan Meier Survival Curve for overall survival

Supplemental Figure 3: Forest plot for subgroups.

12.CLINICAL STUDY REPORT APPENDICES

13.REFERENCES

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