Statistical Analysis Plan

HERO-HCQ

Healthcare Worker Exposure Response and Outcomes of Hydroxychloroquine Trial (HERO-HCQ Trial)

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Summary of Changes

Date	Description
8/25/2020	• DRAFT
9/4/2020	• Final, ready for signature

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1. Introduction

The HERO-HCQ is a phase 3, randomized, double-blind, placebo controlled study of the efficacy and safety of Hydroxychloroquine to prevent COVID-19 clinical infection in healthcare workers (HCWs). Screening and randomization will be followed by a total of 30 days of blinded, placebo-controlled treatment and 30 more days of follow-up. This document describes data analysis methods and data summaries for the primary manuscript. Analysis approaches detailed within supersede the protocol with respect to the analyses and summaries.

1.1 Objectives of Study

1.1.1 Primary

To evaluate the efficacy of HCQ to prevent COVID-19 clinical infection in healthcare workers (HCWs)

1.1.2 Secondary

- To evaluate the efficacy of HCQ to prevent viral shedding of SARS-CoV-2 among HCWs
- Evaluate safety and tolerability of HCQ

1.1.3 Exploratory

- Evaluate SARS-CoV-2 seroconversion in participants taking HCQ

1.2 Study Population and Stratification

Randomization will be stratified by site and occur onsite. Both participants and the study team will remain blinded to assignment throughout the study.

1.3 Sample Size Determination

The sample size of approximately 2,000 randomized participants was selected to yield high power for testing the primary outcome of clinical infection with COVID-19. Please reference section 10.2 of the clinical study protocol for further details about the sample size calculations.

1.4 Blinding

1.4.1 Blinding Method

The statistical team working on the final analyses as governed by this SAP will be blinded to treatment through data base lock.

1.4.2 Interim Analyses

Regular DSMB reviews will be conducted to ensure the safety of study participants and evaluate the accumulating endpoint data by treatment group.

It is expected that both internal and external factors will influence the decisions of the DSMB. The Statistical Analysis Plan for the DSMB will describe the planned interim analyses and futility monitoring in greater detail.

2. General Analysis Considerations

This report will utilize participant data through their most recent mortality status or last visit date in the 60 day follow-up period unless specified otherwise.

Any reference to new-onset of symptom in context of this trial is defined as reporting of a symptom at a visit. Any negative or unknown result COVID-19 test with missing or unknown date will not be used while defining clinically confirmed or suspected COVID-19. Data from all sites will be pooled for analyses.

Analyses will be performed using SAS software version 9.4 or higher (SAS Institute, Inc., Cary, NC).

2.1 Analysis Populations

2.1.1 Intention-to-treat (ITT) analysis set

The ITT population (ITT) is defined as all randomized participants. The ITT population will be used for all secondary and exploratory efficacy analysis and for safety analyses. Participants will be analyzed according to their assigned randomized treatment.

2.1.2 Modified Intention-to-treat (mITT) analysis set

The mITT population includes participants in the ITT with baseline negative RT-PCR test. Subjects will be analyzed according to their assigned randomized treatment. The modified ITT population (mITT) will be used for analysis of the primary efficacy endpoint

2.2 Study Day Derivation

The day of the study is the day relative to randomization date, (study date – randomization date)+1.

2.3 Handling of Dropouts and Missing data

Missing data will not be imputed for the primary efficacy analysis of clinical infection with COVID-19.

2.4 Type 1 Error Rate

All the Type 1 error will be used for the primary analysis. Hence, the statistical significance of the secondary analyses is dependent on first achieving statistically significant results in the primary efficacy analysis.

3. Enrollment and Study Conduct

Descriptive summaries of enrollment, baseline characteristics, medical history, participant status, retention, adherence to randomized treatment, and concomitant medication will be presented in table and graphical format as applicable.

4. Efficacy Evaluations

4.1 Primary Endpoint

The primary endpoint for the study is clinical infection with COVID-19 through day 30 visit. It is defined as a binary composite outcome of :

(1) clinically confirmed COVID-19 identified as new-onset of fever, or cough, or dyspnea along with a positive COVID-19 test result via local or central laboratory test results, or
(2) a suspected COVID-19 identified as new-onset of fever, or cough or dyspnea in the absence of negative COVID-19 test result within 7 days following any reported symptoms, via local or central laboratory test results.

The possible values of the endpoint are :
Yes : confirmed or suspected COVID-19
No : neither confirmed nor suspected COVID-19

4.1.1 Primary Efficacy Analysis

The primary efficacy analysis conducted in mITT will test for treatment effect presented as difference in the proportion of participants with COVID-19 clinical infection between the treatment groups. The 95% CI for this difference will be constructed using Miettinen-Nurminen method and Chang-Zhang exact method.
Additionally, we will use a logistic regression model with an indicator for the treatment group as supportive analysis. The estimated odds ratio and associated 95% confidence interval as well as the P value testing the null hypothesis will be reported.
The primary hypothesis is:

H0 (null hypothesis): Allocation to HCQ results in no change in COVID-19 infection among HCWs at risk for COVID-19 infection

Ha (alternative hypothesis) Allocation to HCQ results in prevention of COVID-19 infection among HCWs at risk for COVID-19 infection.

The primary hypothesis will be formally tested (two-tailed) at the alpha level of 0.05.

4.2 Secondary Endpoint

4.2.1 Viral Shedding of SARS-CoV-2

Viral shedding of SARS-CoV-2 data at 30 days received as a binary response from the central lab and collected via nasal swabs will be analyzed in ITT to assess the efficacy of

HCQ to prevent viral shedding of SARS-CoV-2 among HCWs. This viral shedding endpoint is independent of reported symptoms.

Analyses of the viral shedding secondary efficacy endpoint will be conducted using a logistic regression model with an indicator for the treatment group or the Fisher's exact test dependent on distribution of data. Adjustment covariates such as age,sex, race may be used in the logistic regression model if the data allow.

4.3 Other Secondary Endpoints

Additional secondary endpoints, not adjusted for alpha are:

4.3.1 All-Cause Mortality

Analysis of the binary response for all-cause mortality at day 30 in ITT will be conducted using logistic regression model with an indicator for the treatment group or the Fisher's exact test dependent on distribution of data.

4.3.2 All-Cause Hospitalization

Analyses of all-cause hospitalization at day 30 in ITT defined as a hospitalization indicated on the COVID-19 questionnaire or within the SAE/EOSI form will use similar strategy as All-cause mortality

4.3.3 Cause specific Hospitalization

Covid specific hospitalizations in participants defined as those reported on the COVID-19 questionnaire will also be analyzed in ITT using similar strategy as all-cause mortality.

4.4 Exploratory Endpoint

Serology results received as a binary response at baseline and day 30 will be used to define the exploratory endpoint of seroconversion at day 30, measured as change to positive serology at day 30 with negative serology at baseline. The response will be analysed in the ITT population with negative baseline serology using logistic regression model with an indicator for the treatment group or the Fisher's exact test dependent on distribution of data.

4.5 Sensitivity Analysis

Below methods will be used to assess sensitivity of various analyses completed.

4.5.1 Cox proportional hazard model stratified by site

A sensitivity analysis will use the time-to-clinical infection (confirmed or suspected) with COVID-19 outcome in mITT. For this analysis, the treatment groups will be compared using a Cox proportional hazards regression model with the baseline hazard function stratified by site. The estimated hazard ratio and associated 95% confidence interval will be used to summarize the treatment effect. The model will account for clustering of participants within site by using the robust sandwich covariance estimate.

Time-to-clinically confirmed Covid-19 and time-to-clinically suspected Covid-19 will be analyzed similar to the composite of time-to-clinical infection.
Finally, a Kaplan-Meier curve for time to clinical infection with COVID-19 will be included.

5. Subgroup Analysis

Subgroup analyses will be conducted for the following pre-specified sub-groups for the primary endpoint:

- Age (<35, 35-50, >=50)
- Sex (M, F)
- Race (White, Others)
- Ethnicity (Hispanic/Latino, non-Hispanic/Latino)

For each subgroup analysis, a logistic regression model similar to the one described above for the primary analyses will be used, but with additional terms identifying subgroup membership and the intervention by subgroup interaction.

6. Safety Evaluations

6.1 Safety and Tolerability of HCQ

Safety assessments will be based on ITT population and if needed by treated population. Descriptive summaries of SAE, Events of special interest (EOSI), and unanticipated problems will be generated for each randomized treatment group. The statistical comparisons of the randomized arms with respect to the SAEs and EOSI will use Fisher's exact test.

1. Safety and tolerability of HCQ via serious adverse events (SAE)
2. Safety and tolerability of HCQ via events of special interest (EOSI)

Supplementary analyses will only be performed where these summaries suggest that there may be clinically significant differences.
For continuous safety parameters, at least one post-randomization measurement is required for inclusion in the analysis. To assess change from baseline, a baseline measurement is also required.

6.2 Adverse Events

Events of special interest (EOSI) and serious adverse event (SAE) data will be collected on the "Adverse Events" eCRF and coded using the MedDRA dictionary.

A participant level summary table of adverse events by treatment through 60 days will be presented. This table will include:

- Participants who experienced at least one SAE/EOSI
- Serious TEAE

- SAE with fatal outcome
- SAE resulting in permanent treatment discontinuation
- SAE related to study drug
- Severe TEAE

The incidence of each SAE will also be summarized by system organ class, preferred term and treatment assignment. Multiple AEs mapped to the same preferred term will be counted once per participant though the number of events per preferred term may also be presented.

7. Database Sources

The data used for analysis will come from 4 main sources:

- the Interactive Web/Voice Response System (Almac),
- the HERO-HCQ e-CRF includes participant self reported data, call center information and site reported data (Verily),
- limited baseline information from HERO Registry e-CRF (Verily),
- the central laboratory which provides results of nasopharyngeal swab (Covance).
- And the serology data from Duke laboratory.

Data from the IXRS will be used to determine treatment assignment. The e-CRF will be the source for site-level geographic information, all baseline and follow-up data entered by the sites, participants or the call center. The HERO-HCQ clinical database will be housed in EDC (Electronic Data Capture) hosted by Verily Health Sciences. The central laboratory from Covance and the serology data from Duke laboratory will be transferred to the Duke Clinical Research Center (DCRI). DCRI will obtain unblinded randomization data collected in the Interactive Voice/Web Response System (IXRS) from Almac after the 60 day follow-up data are locked for analysis.

8. References

1. Will, G., Constructing Confidence Intervals for the Differences of Binomial Proportions in SAS®
2. Broglio, K., Randomization in Clinical Trials: Permuted Blocks and Stratification. Jama, 2018. 319(21): p. 2223-2224.
3. Cox, D.R., Regression Models and Life-Tables. Journal of the Royal Statistical Society. Series B (Methodological), 1972. 34(2): p. 187-220.
4. Glidden, D.V. and E. Vittinghoff, Modelling clustered survival data from multicentre clinical trials. Stat Med, 2004. 23(3): p. 369-88