Statistical Analysis Plan for the COVID-19 Antiviral Therapy Domain for Patients with COVID-19 Pandemic Infection Suspected Or Proven (PISOP)

COVID-19 Antiviral Domain SAP Version 1.0 dated 14 January 2021

COVID-19 Antiviral Domain SAP Version 1.1, with Amendment dated 29 January 2021

CONTENTS

1. COVID-19 ANTIVIRAL DOMAIN SAP VERSION

The version is in this document's header and on the cover page.

1.1 VERSION HISTORY

Version 1: Draft dated January 5, 2021.

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3. INTRODUCTION

This statistical plan for the analysis of the COVID-19 Antiviral Therapy Domain in the pandemic stratum of REMAP-CAP is an appendix to the Pandemic Appendix to Core (PAtC) Statistical Analysis Plan (SAP). This plan details the statistical analyses in the original REMAP-CAP core SAP and the pandemic stratum SAP applied to the analysis of the COVID-19 Antiviral Therapy Domain interventions in the Severe State. This plan is prespecified for the imminent unblinding of the data for the COVID-19 Antiviral Therapy Domain interventions within the pandemic infection suspected or proven (PISOP) (COVID-19) stratum.

Enrollment in the COVID-19 Antiviral Therapy Domain started on April 8th, 2020. The hydroxychloroquine arms (including hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir arms) in the COVID-19 Antiviral Therapy Domain were halted in the PISOP stratum on May 23rd, 2020, based on concerns regarding the safety and efficacy of hydroxychloroquine which was later substantiated by the press release of the results of the RECOVERY trial (https://www.recoverytrial.net/files/hcq-recovery-statement-050620-final-002.pdf). The lopinavir/ritonavir arm in the COVID-19 Antiviral Therapy Domain was halted in the PISOP stratum on Nov 19th, 2020 after reaching a prespecified futility threshold.

The authors of this document are blinded to the data and results in REMAP-CAP other than those already publicly disclosed results.

4. DESIGN CONSIDERATIONS

REMAP-CAP is designed with Bayesian analyses as the primary analysis method for the trial. There is one overarching Bayesian model, prespecified in the SAP, driving all adaptations, platform conclusions, and result summaries. Similar to the SAP used for the Corticosteroids and the Immune Modulation Therapy Domains, the primary statistical analysis model will be used to report the results for the severe state in the COVID-19 Antiviral Therapy Domain within the PISOP stratum. At the time of concluding enrollment in the lopinavir/ritonavir, hydroxychloroquine and lopinavir/ritonavir plus hydroxychloroquine arms, there were <100 patients enrolled in the moderate state, therefore it was decided to only report descriptive data by assignment for this state to facilitate future systematic reviews by others.

The decision to use a Bayesian analysis in REMAP-CAP was driven in part by the uncertainty of the extent of the pandemic. The sample size could be small, or large, and there may be unexpected external events, that alter the design of REMAP-CAP. Given the expected

evolution of the design, and uncertain sample size, a Bayesian approach was deemed more appropriate.

REMAP-CAP defines several statistical triggers within the trial that, at any analysis of the trial, would result in public disclosure and a declaration of a platform conclusion.

The following internal statistical triggers were pre-defined for the interventions in the COVID-19 Antiviral Therapy Domain:

1. **Domain Superiority**. If an intervention in the COVID-19 Antiviral Therapy Domain has at least a 99% posterior probability of being in the best regimen for patients in state s of the PISOP stratum (i.e. superior to all other interventions in the domain), this would trigger domain superiority of that intervention within that state.
2. **Intervention Efficacy**. If an intervention in the COVID-19 Antiviral Therapy Domain is deemed to have at least a 99% posterior probability of being superior to the control in state s, then a declaration of efficacy of that intervention would be declared for state s. This statistical trigger is active for each of the non-control arms in the COVID-19 Antiviral Therapy Domain.
3. **Intervention Equivalence**. If two non-control interventions have a 90% probability of equivalence, this would trigger a public disclosure of intervention equivalence.
4. **Intervention Futility**. Because the hydroxychloroquine arms have been stopped for external reasons, no futility analyses will be reported for this arm. For lopinavir/ritonavir, if an intervention is deemed to have a less than 5% probability of at least a 20% odds ratio improvement compared to the control, then a declaration of futility would be declared.

The 99% threshold for efficacy was selected to have good properties for potential outbreak sample sizes. For example, the type I error rate of any conclusion of efficacy for a single intervention 'A' vs. control is less than 2.5% for approximately less than 1000 patients on intervention 'A' with multiple interim analyses (see main and pandemic SAP).

Importantly, the ITSC halted the hydroxychloroquine and the combination of hydroxychloroquine and lopinavir/ritonavir arms of REMAP-CAP before the first interim analysis. At the time of analysis, being halted early does not change the Bayesian statistical triggers of the domain; the same thresholds apply. However, since there will be no further

enrollment into the hydroxychloroquine and the combination of hydroxychloroquine and lopinavir/ritonavir arms of the COVID-19 Antiviral Therapy Domain for patients within the pandemic stratum, the results are still of value regardless of whether they support any particular internal trigger. Thus, we emphasize the posterior probabilities (and 95% credible intervals) are more informative in contributing to overall knowledge about hydroxychloroquine in COVID-19 than whether a particular posterior probability exceeded a pre-defined threshold in REMAP-CAP.

5. UNBLINDING

REMAP-CAP has multiple domains to which patients can be randomized and multiple interventions within domains. At the unblinding of the COVID-19 Antiviral Therapy Domain, there are other interventions to which patients have been randomized that will not be unblinded at this analysis unless a statistical trigger is hit at the time of the primary analysis. In the analysis plan, there will be analyses conducted by the Statistical Analysis Committee (SAC) using additional randomizations and also unblinding of other randomizations. The SAC is unblinded to all arms/domains in their function for REMAP-CAP. There will also be analyses that are conducted with only knowledge of unblinded interventions and domains. At this time, that includes the COVID-19 Antiviral Therapy Domain allocation, the Corticosteroid Domain allocation, and the reported arms of the Immune Modulation Therapy Domain. These may be conducted by investigators who are blinded to other information about other domains. These analyses are identified below.

6. INTERVENTIONS

There are 4 interventions within the COVID-19 Antiviral Therapy Domain. These are

1. No antiviral for COVID-19
2. Lopinavir/ritonavir
3. Hydroxychloroquine
4. Hydroxychloroquine and lopinavir/ritonavir

For the primary analysis completed by the SAC and all secondary analyses completed by blinded investigators, all four arms will be modeled, and analysis results for all arms will be reported.

In addition, the models in this SAP will estimate and report the interaction effects of the interventions in the COVID-19 Antiviral Therapy Domain with the Corticosteroid Domain and reported arms of the Immune Modulation Therapy Domain.

7. DISEASE STATES

There are 2 disease states in the PAtC, which are **moderate** and **severe**. In most participating sites, the COVID-19 Antiviral Therapy Domain randomized to patients in the severe state, and as indicated earlier, this SAP describes the analysis of patients in the severe state. In one site, patients were randomized to the hydroxychloroquine and no antiviral therapy arms in the moderate state. Descriptive data on these patients will be reported separately.

8. ANALYSIS POPULATIONS

1. REMAP-COVID intent-to-treat (ITT). All patients within the PISOP stratum initially randomized in the severe state randomized within at least one domain.
2. Unblinded ITT. All patients within the PISOP stratum initially randomized in the severe state randomized to an intervention in the COVID-19 Antiviral Therapy Domain, the Corticosteroid Domain, or reported arms of the Immune Modulation Therapy Domain. Note the assignment to the interventions mentioned above will be unblinded, the other intervention assignments will not be unblinded to the analysis team.
3. Unblinded ITT Non-negative. All patients within the Unblinded ITT population after removing those with $\geq$1 negative test for COVID **and** no positive tests.
4. Antiviral specific ITT. All patients within the PISOP stratum initially randomized in the severe state randomized to an intervention or no antiviral for COVID-19 Antiviral Therapy Domain.
5. Antiviral specific ITT Moderate State. All patients within the PISOP stratum in the moderate state randomized to an intervention or no antiviral for COVID-19 Antiviral Therapy Domain.

9. ENDPOINTS

The following endpoints will be analyzed, graphically displayed, and/or summarized through descriptive statistics.

A. **Organ-Support Free-Days** (OSFD)
   a. An ordinal endpoint with mortality as the worst outcome. The primary endpoint for the REMAP-CAP PISOP stratum. The types of organ support considered are cardiovascular (vasopressor/inotrope support) and respiratory support. See Appendix A for a detailed description.

B. **In-Hospital Mortality**
   a. A dichotomous endpoint of survival/in-hospital death where the death component corresponds to a –1 on the OSFD endpoint.

C. **Mortality**
   a. This is a time-to-event endpoint through 90-days.
   b. Any patient currently in the hospital or transferred on organ support to an alternative care facility will be censored at their last known status alive.
   c. Any patient successfully discharged from hospital, alive, without organ support, will be censored at the date of discharge, if 90-day mortality data are not yet recorded.

D. **Progression to intubation and mechanical ventilation, extracorporeal membrane oxygenation (ECMO), or death**
   a. A dichotomous endpoint of whether a patient progresses to intubation and mechanical ventilation, ECMO or death in hospital.
   b. This endpoint will only be analyzed for subjects that are not on intubation, mechanical ventilation, or ECMO at baseline.

E. **Cardiovascular (Vasopressor/Inotrope) Free-Days**
   a. An ordinal outcome of number of days free of Vasopressor/Inotropes. This is the exact calculation of OSFD, with Vasopressor/Inotropes as the only organ support category. In-hospital death is considered a –1.

F. **Respiratory support Free-Days**
   a. An ordinal outcome of number of days free of respiratory support. This is the exact calculation of OSFD, with respiratory support as the only organ support category. In-hospital death is considered a –1.

G. **Duration of ICU stay**
   a. A time-to-event endpoint of leaving the ICU alive. If a patient is known to leave the ICU and return to the ICU within 14-days that intervening time will be ignored.

b. This variable will be truncated at 90-days: all deaths in ICU will be considered 90-days with no liberation of ICU.
c. Patients still in the ICU at data snapshot will be considered censored.

H. **Duration of hospital stay**

a. A time-to-event endpoint of leaving the hospital alive. If a patient is known to leave and return to the hospital within 14-days that intervening time will be ignored.
b. This variable will be truncated at 90-days and all deaths in-hospital will be considered 90-days with no events.
c. Patients still in the hospital at data snapshot will be considered censored.

I. **At least one serious adverse event (SAE)**

a. A dichotomous endpoint of SAE.
b. This endpoint will be summarized descriptively. Counts and proportions of SAEs will be provided by intervention.

J. Serious ventricular arrhythmia (including ventricular fibrillation) or sudden unexpected death in hospital.

a. A dichotomous endpoint
b. This endpoint will be summarized descriptively. Counts and proportions will be provided by intervention.

K. **The World Health Organization (WHO) 8-point ordinal scale, measured at day 14.**

A modified WHO ordinal scale will be used:

0 + 1 + 2 = No longer hospitalized

3 = Hospitalized, no oxygen therapy

4 = Oxygen by mask or nasal prongs

5 = Non-invasive ventilation or high-flow oxygen

6 = Intubation and mechanical ventilation

7 = Ventilation + additional organ support: vasopressors, renal replacement therapy (RRT), ECMO

8 = Death

L. Time to SARS-CoV-2 RNA clearance

a. A time-to-event endpoint of time to SARS-CoV-2 RNA clearance

b. This variable is calculated for COVID-19 positive patients as the time from enrollment to the first negative test not followed by a positive test (Appendix B).

10. GRAPHICAL DATA SUMMARIES

1. Ordinal endpoints will be graphed using stacked cumulative bar plots.
2. Time-to-event endpoints will be plotted using Kaplan-Meier plots. Positive clinical event outcomes will be plotted as the cumulative rate of event, and negative events will be plotted as the cumulative rate of event-free.

11. DESCRIPTIVE STATISTICS

1. Ordinal endpoints will be summarized by the cumulative frequency of each outcome for each state. The 25th, 50th, and 75th percentiles will be summarized.
2. Dichotomous endpoints will be summarized by the proportion in each category for each state.
3. Time-to-event outcomes will summarize the 2.5th, 10th, 25th, 50th, 75th, 90th, and 97.5th percentiles from the Kaplan-Meier estimates by state.

12. BASELINE CHARACTERISTICS

The following demographics will be summarized across arms. More may be added as baseline summaries.

Age, sex, BMI, ethnicity, APACHE II score (measured from hospital admission to randomization), confirmed SARS CoV-2 infection, preexisting conditions, baseline use of high-flow nasal oxygenation, non-invasive ventilation, invasive mechanical ventilation, ECMO, vasopressors/inotropes, renal replacement therapy, randomization to corticosteroids, tocilizumab or sarilumab within REMAP-CAP and miscellaneous physiological values.

13. COMPLIANCE

The compliance to lopinavir/ritonavir and hydroxychloroquine use will be summarized descriptively as the fraction of use, the amount, and duration for each randomized arm.

14. ANALYTIC APPROACH

Each inferential analysis will be done using a Bayesian model. Some default frequentist methods are used for exploration and description. A summary of the analysis methods is provided below.

14.1 PRIMARY ANALYSIS OF PRIMARY ENDPOINT

The **primary analysis model** is a Bayesian cumulative logistic model for the ordinal primary endpoint. The model is described below. The primary endpoint for the severe state has 24 possible, ordered outcomes. Let the outcome for a patient by labeled as $Y_{i,s}$, with possible values, –1 (death), 0, 1, …, 21, 22. The outcome of 22 (never received organ support) for the severe state is not possible. Hence there are 23 possible outcomes in the severe state. A cumulative logistic model is specified. The model is structured so that an odds-ratio >1 implies patient benefit. The full details of the model are specified in the Current State Version 2.3 AV. The model has factors for:

- Each level of the ordinal endpoint
- Each Global site, nested within country
- Age; ≤39, 40-49, 50-59, 60-69, 70-79, 80+
- Sex
- Time; 2-week buckets of time working backwards from the last enrolled patient, with the most recent bucket being 4 weeks. Time buckets are defined to be the same time periods for both moderate and severe patients.
- For each domain an effect for being randomized to the domain
- An effect for each intervention within each domain
- Specified interactions in the model between domains

The primary analysis for the lopinavir/ritonavir and hydroxychloroquine uses the following rules:

- All sites within a country that have <5 patients randomized in a state will have their results combined into a single site within that country.
- If there is an outcome in the ordinal scale that did not occur in the data, then that outcome will be combined to a single outcome with a neighboring outcome (the worse outcome). This is done by state for model stability. For example, if the outcome 11 never

occurred in moderate a combined outcome of 10 & 11 will be modeled for the moderate analysis.

- If a time bucket has <5 patients in a state, the bucket will be collapsed with the adjacent earlier bucket in that state.
- The high-dose 7-day hydrocortisone arm will be combined with the 7-day hydrocortisone arm (fixed-duration). They were originally nested, which allows their pooling, and there were very few patients randomized to the high-dose 7-day hydrocortisone arm.
- All interactions between the shock-based steroid arm and other domains will be dropped (assumed to be zero)
- The two IL-6 receptor agonists, Tocilizumab and Sarilumab, will be combined in to a single IL-6ra arm
- For patients who were randomized as part of REMAP-CAP COVID-19 severe state ITT after the closure of Corticosteroid Domain (June 17, 2020), the subjects are coded as receiving fixed-dose hydrocortisone.

The primary analysis model will be referenced with certain model assumptions for sensitivity analyses. For example, the “time effects” in the model could be assumed to be 0.

14.2 PROPORTIONAL ODDS ASSUMPTION

The primary analysis model is based on an assumption of a proportional effect of treatment across the scale of the ordinal outcome. In order to assess the robustness of the results to this assumption, a dichotomous model is fit to every level of the ordinal outcome across the scale and the odds-ratio for each dichotomous break is presented. For tail events, if the cumulative probabilities are less than 5% or greater than 95% these dichotomous may be ignored. No statistical test of proportional odds is conducted.

14.3 ANALYTIC APPROACH FOR SECONDARY DICHOTOMOUS ENDPOINTS

A Bayesian logistic regression model will be used for each dichotomous outcome. The model will always specify the “event” as the negative outcome, so that an odds-ratio >1 implies benefit to patients within each model. The model is the standard logistic link function model with state-specific intercept, α_s and state-specific coefficients for all factors in the model:

$$\log\left(\frac{\pi_s}{1-\pi_s}\right) = \alpha_s - [\text{factors}_s]$$

References will be made to the factors in the model and their prior distribution. Many of these factors will be the same as the primary analysis model, with the same priors, as the parameters have similar interpretation. If not otherwise specified, the prior distribution for the main effect is $\beta \sim N(0, 1.82^2)$ (similar to a uniform prior on the probability scale).

14.4 ANALYTIC APPROACH FOR SECONDARY TIME-TO-EVENT ENDPOINTS

All inferential time-to-event analyses will be done using a Bayesian piecewise exponential model. The Bayesian time-to-event model is intended to mirror a Cox proportional hazards model, with the underlying state-specific hazard rate modeled with a piecewise exponential model. The underlying hazard will be modeled with a hazard rate for 10-day period each day in the model. The prior distribution for each day hazard rate is a gamma distribution with 1 day of exposure and a mean equal to the total exposure divided by the total number of events for each state. This prior will have very little weight but will provide numerical stability to the model. Each factor is incorporated as a proportional hazard rate through an additive linear model of the log-hazard. The default prior for each factor is the same as for the log-odds in the ordinal model. If other non-specified variables are added to the model, then a normal distribution with mean 0 and standard deviation 10 will be utilized.

14.5 MARKOV CHAIN MONTE CARLO (MCMC) MODEL STABILITY

The Bayesian models have many parameters and there may be risk of poor model stability, including convergence of the MCMC and the mixing behavior. These instabilities may be based on sparse data on the outcome or covariates. The statisticians running the model may make changes that do not affect the overall outcome but provide reliable model diagnostics and scientific rigor. Any alterations will be noted.

14.6 MODEL OUTPUTS

The standard model outputs for each treatment effect will be the mean, standard deviation, median, and 95% credible intervals (all credible intervals will range from equal-tailed percentiles, so 95% credible intervals will range from the 2.5th percentile to the 97.5th percentile). For the ordinal model the odds-ratio will be summarized for each state. For the dichotomous endpoints, the odds-ratio will be summarized for each state. For the time-to-event model the hazard ratio will be summarized for each state. For consistency, all models

will be parameterized so that an odds-ratio or hazard-ratio greater than 1 indicates clinical benefit.

For each inferential model, a posterior probability that one arm is superior will be provided for each comparison between arms and for each state. This posterior probability has been identified as the primary analysis metric between arms. A posterior probability greater than 99% of superiority has been identified as statistically significant in REMAP-CAP.

14.7 EXPLORATORY ANALYSES

Exploratory analyses after unblinding will not be considered inferential and no p-values will be presented. Any post-hoc exploratory analyses will use the following methods:

1. Ordinal endpoints will be compared using a cumulative proportional odds model with summaries of the odds-ratio, with 95% confidence intervals and Wilcoxon test for robustness against a lack of proportional odds.
2. Time-to-Event analyses will utilize a Cox proportional hazards model, summarizing the hazard ratios and 95% confidence intervals.
3. Continuous endpoints will compare means with 95% confidence intervals based on two-sample t-test procedures.
4. Dichotomous proportions will be compared using logistic regressions summarizing the odds-ratio and 95% confidence intervals. Differences between proportions will be summarized using observed differences and normal approximations for the 95% credible intervals.

15. SPECIFIC PROSPECTIVE ANALYSES

There are 32 specific prospective analyses, summarized in the table and described in detail below.

#	Status	Population	Endpoint	Other
15.1	Primary	REMAP-CAP COVID-19 severe state ITT	OSFD	Includes all interventions and interactions.
15.2	Primary	REMAP-CAP COVID-19 severe state ITT	In-Hospital Mortality	Includes all interventions and interactions.
15.3	Sensitivity	REMAP-CAP COVID-19 severe state ITT	OSFD	Includes all interventions and interactions. Includes less informative standard normal priors on pre-specified combinations of antivirals, steroids, tocilizumab and sarilumab.

#	Status	Population	Endpoint	Other
15.4	Sensitivity	REMAP-CAP COVID-19 severe state ITT	Dichotomized OSFD	A logistic regression will be run for each dichotomization of OSFDs as a robustness check.
15.5	Secondary	Unblinded ITT	OSFD	
15.6	Secondary	Unblinded ITT	In-Hospital Mortality	
15.7	Subgroup*	Unblinded ITT	OSFD	Including differential treatment effects by the presence or absence of shock at enrollment
15.8	Subgroup	Unblinded ITT	In-Hospital Mortality	Including differential treatment effects by the presence or absence of shock at enrollment
15.9	Subgroup	Unblinded ITT	OSFD	Including differential treatment effects by invasive mechanical ventilation at enrollment
15.10	Subgroup	Unblinded ITT	In-Hospital Mortality	Including differential treatment effects by invasive mechanical ventilation at enrollment
15.11	Sensitivity	Unblinded ITT	OSFD	Remove site and time effects
15.12	Sensitivity	Unblinded ITT	In-Hospital Mortality	Remove site and time effects
15.13	Sensitivity	Unblinded ITT	OSFD	Alternative coding of steroid interventions after closure of steroid domain.
15.14	Sensitivity	Unblinded ITT	In-Hospital Mortality	Alternative coding of steroid interventions after closure of steroid domain.
15.15	Secondary	Unblinded ITT Non-negative	OSFD	
15.16	Secondary	Unblinded ITT Non-negative COVID-19	In-Hospital Mortality	
15.17	Secondary	Antiviral therapy specific ITT	OSFD	
15.18	Secondary	Antiviral therapy specific ITT	In-Hospital Mortality	
15.19	Sensitivity	Antiviral therapy specific per protocol	OSFD	
15.20	Sensitivity	Antiviral therapy specific per protocol	In-Hospital Mortality	
15.21	Secondary	Unblinded ITT	Mortality	
15.22	Secondary	Unblinded ITT not on MV, ECMO at baseline	Progression to intubation, ECMO, death	
15.23	Secondary	Unblinded ITT	Days-Free of vasopressor/inotropes	
15.24	Secondary	Unblinded ITT	Respiratory support free days	
15.25	Secondary	Unblinded ITT	Length of ICU Stay	
15.26	Secondary	Unblinded ITT	Length of Hospital Stay	
15.27	Secondary	Unblinded ITT	WHO Scale at 14 days	

#	Status	Population	Endpoint	Other
15.28	Secondary	Unblinded ITT	Time to SARS-CoV-2 RNA clearance	
15.29	Primary Safety Analysis	Antiviral therapy specific ITT	Serious adverse events per patient	Time effects removed from model.
15.30	Primary Safety Analysis	Antiviral therapy specific ITT	Serious ventricular arrhythmia	Time effects removed from model.
15.31	Graphical Summaries	Antiviral therapy specific ITT	All endpoints	Including combinations across unblinded domains.
15.32	Descriptive summaries	Antiviral therapy specific ITT, moderate state	All endpoints	

* There are 2 additional subgroups defined in the DSA based on the co-infection with influenza and bacterial pathogens that will not be perused, due to the small numbers.

15.1 THE PRIMARY ANALYSIS FOR THE COVID-19 ANTIVIRAL THERAPY DOMAIN

- Population: REMAP-COVID severe state ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids, and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Analysis: Conducted by the unblinded SAC

Notes

a. The primary summary for the domain will be the probability that lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
c. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility
d. Only information on the Corticosteroid Domain, the COVID-19 Antiviral Therapy Domain and the reported arms of the Immune Modulation Therapy Domain will be disclosed.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ * IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.2 THE PRIMARY MORTALITY ANALYSIS FOR THE COVID-19 ANTIVIRAL THERAPY

- Population: REMAP-COVID severe state ITT
- Endpoint: In-Hospital Mortality
- Model: Primary dichotomous model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-

based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.

- Analysis: Conducted by the unblinded SAC

Notes

a. The primary summary for the domain will be the probability that lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
c. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility
d. Only information on the Corticosteroid Domain, the COVID-19 Antiviral Therapy Domain and the reported arms of the Immune Modulation Therapy Domain will be disclosed.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.3 A SENSITIVITY ANALYSIS OF THE PRIMARY ANALYSIS OF THE COVID-19 ANTIVIRAL THERAPY WITH LESS INFORMATIVE PRIORS ON INTERACTION EFFECTS

- Population: REMAP-CAP COVID-19 severe state ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model with weaker priors for the interaction effects
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Analysis: Conducted by the unblinded SAC

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between each antiviral and corticosteroid intervention and tocilizumab and sarilumab will be reported relative to control.
d. The prior distributions will be set to N(0,1) for the following interactions: each antiviral intervention with fixed-dose corticosteroid intervention, each antiviral intervention with IL-6.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported :

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.4 A SENSITIVITY ANALYSIS OF THE PRIMARY ANALYSIS OF THE COVID-19 ANTIVIRAL THERAPY FOR THE PROPORTIONAL ODDS ASSUMPTIONS

- Population: REMAP-CAP COVID-19 severe state ITT

- Endpoint: Dichotomized Organ Support-Free Days
- Model: Primary dichotomous model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Analysis: Conducted by the unblinded SAC

Notes

a. For this analysis, the primary dichotomous model will be fit to each dichotomization of OSFDs and the summaries of the odds-ratio of lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir will be reported.

The following summaries will be reported for the lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir odds-ratios:

OSFD Dichotomization	Mean	SD	Median	95% Credible Interval
Lopinavir/ritonavir				
-1 vs ≥0				
≤0 vs ≥1				
≤1 vs ≥2				
≤2 vs ≥3				
≤3 vs ≥4				
≤4 vs ≥5				
≤5 vs ≥6				
≤6 vs ≥7				
≤7 vs ≥8				
≤8 vs ≥9				
≤9 vs ≥10				
≤10 vs ≥11				
≤11 vs ≥12				
≤12 vs ≥13				
≤13 vs ≥14				
≤14 vs ≥15				
≤15 vs ≥16				
≤16 vs ≥17				
≤17 vs ≥18				
≤18 vs ≥19				
≤19 vs ≥20				
≤20 vs 21				
Hydroxychloroquine				
-1 vs ≥0				
≤0 vs ≥1				

OSFD Dichotomization	Mean	SD	Median	95% Credible Interval
≤1 vs ≥2				
≤2 vs ≥3				
≤3 vs ≥4				
≤4 vs ≥5				
≤5 vs ≥6				
≤6 vs ≥7				
≤7 vs ≥8				
≤8 vs ≥9				
≤9 vs ≥10				
≤10 vs ≥11				
≤11 vs ≥12				
≤12 vs ≥13				
≤13 vs ≥14				
≤14 vs ≥15				
≤15 vs ≥16				
≤16 vs ≥17				
≤17 vs ≥18				
≤18 vs ≥19				
≤19 vs ≥20				
≤20 vs 21				
Hydroxychloroquine combined with lopinavir/ritonavir				
-1 vs ≥0				
≤0 vs ≥1				
≤1 vs ≥2				
≤2 vs ≥3				
≤3 vs ≥4				
≤4 vs ≥5				
≤5 vs ≥6				
≤6 vs ≥7				
≤7 vs ≥8				
≤8 vs ≥9				
≤9 vs ≥10				
≤10 vs ≥11				
≤11 vs ≥12				
≤12 vs ≥13				
≤13 vs ≥14				
≤14 vs ≥15				
≤15 vs ≥16				
≤16 vs ≥17				
≤17 vs ≥18				
≤18 vs ≥19				
≤19 vs ≥20				
≤20 vs 21				

15.5 A SECONDARY ANALYSIS RESTRICTED TO THE UNBLINDED ITT

- Population: Unblinded ITT (COVID-19 Antiviral Therapy Domain, Corticosteroid Domain and the reported arms of the Immune Modulation Therapy Domain)
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention and IL-6 will be reported relative to control.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported :

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.6 A SECONDARY ANALYSIS OF IN-HOSPITAL MORTALITY RESTRICTED TO UNBLINDED ITT

- Population: Unblinded ITT (COVID-19 Antiviral Therapy Domain, Corticosteroid Domain or the reported arms of the Immune Modulation Therapy Domain)
- Endpoint: In-Hospital Mortality
- Model: Primary dichotomous model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.

b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention and IL-6 will be reported relative to control.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.7 A SUBGROUP ANALYSIS OF OSFD RESTRICTED TO THE UNBLINDED ITT WITH DIFFERENTIAL TREATMENT EFFECTS BY SHOCK AT ENROLLMENT

- Population: Unblinded ITT (COVID-19 Antiviral Therapy Domain, Corticosteroid Domain and the reported arms of the Immune Modulation Therapy Domain)
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Each of the intervention effects will be estimated separately by shock status, a fixed effect for shock status at baseline is estimated. All baseline covariate effects, site, and time effects are constant across shock status
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Differential treatment effect for lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir by shock status. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention and IL-6 will be reported relative to control.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is superior to control in patients with shock	
Lopinavir/ritonavir is futile in patients with shock	
HCQ is in superior to control in patients with shock	
HCQ is futile in patients with shock	
Lopinavir/ritonavir and HCQ combination is superior to control in patients with shock	
Lopinavir/ritonavir and HCQ combination is futile in patients with shock	
Lopinavir/ritonavir is superior to control in patients with no shock	
Lopinavir/ritonavir is futile in patients with no shock	
HCQ is superior to control in patients with no shock	
HCQ is futile in patients with no shock	
Lopinavir/ritonavir and HCQ combination is superior to control in patients with no shock	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported :

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir in shock				
Lopinavir/ritonavir in no shock				
Hydroxychloroquine in shock				
Hydroxychloroquine in no shock				
Lopinavir/ritonavir and HCQ combination in shock				
Lopinavir/ritonavir and HCQ combination in no shock				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.8 A SUBGROUP ANALYSIS OF IN-HOSPITAL MORTALITY RESTRICTED TO THE UNBLINDED ITT WITH DIFFERENTIAL TREATMENT EFFECTS BY THE PRESENCE OF SHOCK AT ENROLLMENT

- Population: Unblinded ITT (COVID-19 Antiviral Therapy Domain, Corticosteroid Domain and the reported arms of the Immune Modulation Therapy Domain)
- Endpoint: in-hospital mortality
- Model: Primary analysis ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Each of the intervention effects will be estimated separately by shock status, a fixed effect for shock status at baseline is estimated. All baseline covariate effects, site, and time effects are constant across shock status
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Differential treatment effect for lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir by the presence of shock. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention and IL-6 will be reported relative to control within each shock status.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is superior to control in patients with shock	
Lopinavir/ritonavir is futile in patients with shock	
HCQ is in superior to control in patients with shock	
HCQ is futile in patients with shock	
Lopinavir/ritonavir and HCQ combination is superior to control in patients with shock	
Lopinavir/ritonavir and HCQ combination is futile in patients with shock	
Lopinavir/ritonavir is superior to control in patients with no shock	
Lopinavir/ritonavir is futile in patients with no shock	
HCQ is superior to control in patients with no shock	
HCQ is futile in patients with no shock	
Lopinavir/ritonavir and HCQ combination is superior to control in patients with no shock	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported :

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir in shock				
Lopinavir/ritonavir in no shock				
Hydroxychloroquine in shock				
Hydroxychloroquine in no shock				
Lopinavir/ritonavir and HCQ combination in shock				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Lopinavir/ritonavir and HCQ combination in no shock				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.9 A SUBGROUP ANALYSIS OF OSFD RESTRICTED TO THE UNBLINDED ITT WITH DIFFERENTIAL TREATMENT EFFECTS BY INVASIVE MECHANICAL VENTILATION AT ENROLLMENT

- Population: Unblinded ITT (COVID-19 Antiviral Therapy Domain, Corticosteroid Domain and the reported arms of the Immune Modulation Therapy Domain)
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Each of the intervention effects will be estimated separately by IMV status, a fixed effect for IMV status at baseline is estimated. All baseline covariate effects, site, and time effects are constant across IMV status
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Differential treatment effect for lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir by invasive mechanical ventilation. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention and IL-6 will be reported relative to control.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is superior to control in patients with invasive mechanical ventilation	
Lopinavir/ritonavir is futile in patients with invasive mechanical ventilation	
HCQ is superior to control in patients with invasive mechanical ventilation	
HCQ is futile in patients with invasive mechanical ventilation	
Lopinavir/ritonavir and HCQ combination superior to control in patients with invasive mechanical ventilation	
Lopinavir/ritonavir and HCQ combination is futile in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir is superior to control in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir is futile in patients with no invasive mechanical ventilation	
HCQ is superior to control in patients with no invasive mechanical ventilation	
HCQ is futile in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir and HCQ combination is superior to control in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir and HCQ combination is futile in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported :

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir with IMV				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Lopinavir/ritonavir with no IMV				
Hydroxychloroquine with IMV				
Hydroxychloroquine with no IMV				
Lopinavir/ritonavir and HCQ combination with IMV				
Lopinavir/ritonavir and HCQ combination with no IMV				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.10 A SUBGROUP ANALYSIS OF IN-HOSPITAL MORTALITY RESTRICTED TO THE UNBLINDED ITT WITH DIFFERENTIAL TREATMENT EFFECTS BY INVASIVE MECHANICAL VENTILATION AT ENROLLMENT

- Population: Unblinded ITT (COVID-19 Antiviral Therapy Domain, Corticosteroid Domain and the reported arms of the Immune Modulation Therapy Domain)
- Endpoint: in-hospital mortality
- Model: Primary analysis ordinal model
- Factors: All interventions and specified interactions, age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.
- Each of the intervention effects will be estimated separately by shock status, a fixed effect for shock status at baseline is estimated. All baseline covariate effects, site, and time effects are constant across shock status
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Differential treatment effect for lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir by invasive mechanical ventilation. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.

b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention and IL-6 will be reported relative to control.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is superior to control in patients with invasive mechanical ventilation	
Lopinavir/ritonavir is futile in patients with invasive mechanical ventilation	
HCQ is superior to control in patients with invasive mechanical ventilation	
HCQ is futile in patients with invasive mechanical ventilation	
Lopinavir/ritonavir and HCQ combination superior to control in patients with invasive mechanical ventilation	
Lopinavir/ritonavir and HCQ combination is futile in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir is superior to control in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir is futile in patients with no invasive mechanical ventilation	
HCQ is superior to control in patients with no invasive mechanical ventilation	
HCQ is futile in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir and HCQ combination is superior to control in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir and HCQ combination is futile in patients with no invasive mechanical ventilation	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported :

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir with IMV				
Lopinavir/ritonavir with no IMV				
Hydroxychloroquine with IMV				
Hydroxychloroquine with no IMV				
Lopinavir/ritonavir and HCQ combination with IMV				
Lopinavir/ritonavir and HCQ combination with no IMV				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.11 A SENSITIVITY ANALYSIS RESTRICTED TO THE UNBLINDED ITT POPULATION WITH SITE AND TIME FACTORS REMOVED

- Population: Unblinded ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined to a single IL-6 arm) and no immune modulation.

- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention and IL-6 will be reported relative to control.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Lopinavir/ritonavir				
Hydroxychloroquine				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.12 A SENSITIVITY ANALYSIS OF IN-HOSPITAL MORTALITY RESTRICTED TO UNBLINDED ITT POPULATION WITH FACTORS FOR SITE AND TIME REMOVED

- Population: Unblinded ITT
- Endpoint: In-Hospital Mortality
- Model: Primary dichotomous model
- Factors: Age, sex, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (as a combined IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention and tocilizumab and sarilumab will be reported relative to control.

The following posterior probabilities will be reported:

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	

Quantity of Interest	Posterior Probability
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.13 A SENSITIVITY ANALYSIS OF OSFD RESTRICTED TO THE UNBLINDED ITT POPULATION WITH DIFFERENT STEROID CODING

- Population: Unblinded ITT
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, antiviral domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids and shock-based steroids combined as a corticosteroid arm and

reported interventions of the Immune Modulation Therapy Domain: tocilizumab and no immune modulation combined as an IL-6 arm.

- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and each corticosteroid intervention and IL-6 will be reported relative to control.
d. Fixed-dose and shock-based steroids are pooled for this analysis.
e. Patients randomized after the closure of the Corticosteroid Domain (June 17, 2020) will be coded as receiving steroids if they received steroids within the first two study days.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * corticosteroids				
HCQ * corticosteroids				
Lopinavir/ritonavir and HCQ combination* corticosteroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.14 A SENSITIVITY ANALYSIS OF IN-HOSPITAL MORTALITY RESTRICTED TO THE UNBLINDED ITT WITH DIFFERENT STEROIDS CODING

- Population: Unblinded ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids and shock-based steroids (combined as a corticosteroid arm) and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and corticosteroid intervention, IL-6 will be reported relative to control.
d. Fixed-dose and shock-based steroids are pooled for this analysis.
e. Patients randomized after the closure of the Corticosteroid Domain (June 17, 2020) will be coded as receiving steroids if they received steroids within the first two study days.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir *corticosteroids				
HCQ * corticosteroids				
Lopinavir/ritonavir and HCQ combination* corticosteroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.15 A SECONDARY ANALYSIS OF OSFD RESTRICTED TO THE UNBLINDED ITT POPULATION NON-NEGATIVE COVID POPULATION

- Population: Unblinded ITT, Non-negative COVID
- Endpoint: Organ-Support Free-Days
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. The primary summary for the domain will be the probability that lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention, IL-6will be reported relative to control.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.16 A SECONDARY ANALYSIS OF IN-HOSPITAL MORTALITY RESTRICTED TO THE UNBLINDED ITT POPULATION NON-NEGATIVE COVID POPULATION

- Population: Unblinded ITT, Non-negative COVID
- Endpoint: In-Hospital Mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.

b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir,

hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.

c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid intervention, IL-6 will be reported relative to control.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.17 A SECONDARY ANALYSIS OF OSFD FOR ANTIVIRAL THERAPY SPECIFIC ITT

- Population: Antiviral Therapy specific ITT
- Endpoint: OSFD
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and no antiviral interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				

15.18 A SECONDARY ANALYSIS OF IN-HOSPITAL MORTALITY FOR ANTIVIRAL THERAPY SPECIFIC ITT

- Population: Antiviral specific ITT
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and no antiviral interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.

b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				

15.19A SECONDARY ANALYSIS OF OSFD IN ANTIVIRAL THERAPY SPECIFIC PER PROTOCOL

- Population: Antiviral therapy specific Per Protocol
- Endpoint: OSFD
- Model: Primary analysis ordinal model
- Factors: Age, sex, site, time, lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and no antiviral interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.

b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir and HCQ combination is superior to control	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				

15.20 A SECONDARY ANALYSIS OF IN-HOSPITAL MORTALITY IN ANTIVIRAL SPECIFIC PER PROTOCOL

- Population: Antiviral specific Per Protocol
- Endpoint: In-hospital mortality
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and no antiviral interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.

b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	

Quantity of Interest	Posterior Probability
HCQ is superior to control	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				

15.21 A SECONDARY ANALYSIS OF MORTALITY

- Population: Unblinded ITT
- Endpoint: Time-to-death
- Model: Primary TTE model
- Factors: Age, sex, site, time, lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and no antiviral interventions
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is superior to control	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				

15.22 A SECONDARY ANALYSIS OF PROGRESSION TO INTUBATION, ECMO, OR DEATH, RESTRICTED TO PATIENTS NOT ON MV OR ECMO AT BASELINE

- Population: Unblinded ITT (COVID-19 Antiviral Therapy Domain, Corticosteroid Domain or the reported arms of the Immune Modulation Therapy Domain) not on MV or ECMO at baseline.
- Endpoint: Progression to MV, ECMO, or death
- Model: Primary dichotomous model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. This quantity is the

same as the probability lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir is in the optimal regimen.

b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid, IL-6 interventions will be reported relative to control

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.23 A SECONDARY ANALYSIS OF DAYS-FREE OF VASOPRESSOR/INOTROPES USE

- Population: Unblinded ITT
- Endpoint: Vasopressor/Inotropes free days
- Model: Primary ordinal model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. The primary summary for the domain will be the probability that lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir is in the optimal regimen. A 99% probability of being in the optimal regimen would hit the domain superiority statistical trigger.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
a. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid, IL-6 interventions will be reported relative to control

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * Tocilizumab				
HCQ* Tocilizumab				
Lopinavir/ritonavir and HCQ combination* Tocilizumab				

15.24 A SECONDARY ANALYSIS OF DAYS FREE OF RESPIRATORY SUPPORT

- Population: Unblinded ITT
- Endpoint: Respiratory support free days
- Model: Primary ordinal model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune

Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.

- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. This quantity is the same as the probability lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir is in the optimal regimen.

b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.

a. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid, IL-6 interventions will be reported relative to control

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.25 A SECONDARY ANALYSIS OF LENGTH OF ICU STAY

- Population: Unblinded ITT
- Endpoint: Length of ICU stay
- Model: Primary TTE model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. This quantity is the same as the probability lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir is in the optimal regimen.

b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.

c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid, IL-6 interventions will be reported relative to control

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.26 A SECONDARY ANALYSIS OF LENGTH OF HOSPITAL STAY

- Population: Unblinded ITT
- Endpoint: Length of Hospital stay
- Model: Primary TTE model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
a. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid, IL-6 interventions will be reported relative to control

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.27 A SECONDARY ANALYSIS OF THE MODIFIED WHO SCALE AT DAY 14

- Population: Unblinded ITT
- Endpoint: Modified WHO scale at 14-days
- Model: Primary ordinal model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir,

hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.

c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid, IL-6 interventions will be reported relative to control

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.28 A SECONDARY ANALYSIS OF TIME-TO-SARS-COV-2 RNA CLEARANCE

- Population: Unblinded ITT
- Endpoint: time-to-SARS-CoV-2 RNA clearance
- Model: Primary TTE model
- Factors: Age, sex, site, time, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir, and corticosteroid interventions: no steroids, fixed-duration corticosteroids, and shock-based steroids and reported interventions of the Immune Modulation Therapy Domain: tocilizumab, sarilumab (combined as an IL-6 arm) and no immune modulation.
- Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for efficacy. This quantity is the same as the probability lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir is in the optimal regimen.
b. Lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm for futility. A 95% probability of a smaller than 1.2 odds-ratio for lopinavir/ritonavir, hydroxychloroquine and hydroxychloroquine combined with lopinavir/ritonavir will be compared with the control arm will be used as a statistical trigger for futility.
c. Odds ratio effects and posterior probabilities for the pre-specified interactions between lopinavir/ritonavir, hydroxychloroquine or hydroxychloroquine combined with lopinavir/ritonavir and fixed-dose corticosteroid, IL-6 interventions will be reported relative to control
d. Because repeated rRT-PCR was not done routinely, this analysis will be carried out only if there is sufficient number of patients with follow-up tests.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is in the optimal regimen	
Lopinavir/ritonavir is superior to control (OR > 1)	
Lopinavir/ritonavir is futile (OR < 1.2)	
HCQ is in the optimal regimen	
HCQ is superior to control (OR > 1)	
HCQ is futile (OR < 1.2)	
Lopinavir/ritonavir and HCQ combination is in the optimal regimen	

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir and HCQ combination is superior to control (OR > 1)	
Lopinavir/ritonavir and HCQ combination is futile (OR < 1.2)	
Lopinavir/ritonavir *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir *IL-6 OR > 1	
HCQ *Fixed-dose corticosteroid OR > 1	
HCQ *IL-6 OR > 1	
Lopinavir/ritonavir and HCQ combination *Fixed-dose corticosteroid OR > 1	
Lopinavir/ritonavir and HCQ combination *IL-6 OR > 1	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Lopinavir/ritonavir and HCQ combination				
Lopinavir/ritonavir * fixed-dose steroids*				
HCQ * fixed-dose steroids				
Lopinavir/ritonavir and HCQ combination* fixed-dose steroids				
Lopinavir/ritonavir * IL-6				
HCQ* IL-6				
Lopinavir/ritonavir and HCQ combination* IL-6				

15.29 THE PRIMARY SAFETY ANALYSIS

- Population: Antiviral specific ITT
- Endpoint: Serious Adverse Events (SAE)
- Model: Primary dichotomous model

- Factors: Age, sex, site, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir Analysis: Conducted by the ITSC Analysis Center

Notes

a. Lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for superior safety or inferior safety.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is superior to control	
Lopinavir/ritonavir is inferior to control	
Hydroxychloroquine is superior to control	
Hydroxychloroquine is inferior to control	
Hydroxychloroquine combined with lopinavir/ritonavir is superior to control	
Hydroxychloroquine combined with lopinavir/ritonavir is inferior to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Hydroxychloroquine combined with lopinavir/ritonavir				

15.30 THE PRIMARY SAFETY ANALYSIS-SERIOUS VENTRICULAR ARRHYTHMIA

- Population: Antiviral specific ITT
- Endpoint: Serious ventricular arrhythmia
- Model: Primary dichotomous model
- Factors: Age, sex, site, COVID-19 Antiviral Therapy Domain interventions: control, lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir Analysis: Conducted by the ITSC Analysis Center

Notes

b. Lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir will be compared to the control arm. A posterior probability of superiority of 99% will be used as a statistical trigger for superior safety or inferior safety.

The following posterior probabilities will be reported

Quantity of Interest	Posterior Probability
Lopinavir/ritonavir is superior to control	
Lopinavir/ritonavir is inferior to control	
Hydroxychloroquine is superior to control	
Hydroxychloroquine is inferior to control	
Hydroxychloroquine combined with lopinavir/ritonavir is superior to control	
Hydroxychloroquine combined with lopinavir/ritonavir is inferior to control	

The following will be reported:

Odds-Ratio Parameter	Mean	SD	Median	95% Credible Interval
Age < 39				
Age 40, 49				
Age 50, 59				
Age 70-79				
Age 80+				
Female				
Time Bucket 1				
…				
Time Bucket k-1				
Lopinavir/ritonavir				
Hydroxychloroquine				
Hydroxychloroquine combined with lopinavir/ritonavir				

15.31 GRAPHICAL SUMMARIES

The following graphical summaries will be provided for all endpoints:

- Population: Antiviral specific ITT
- Endpoint: all endpoints
- Factors: lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir and control interventions

The following additional graphical summaries will be provided for OSFD and in-hospital mortality:

- Population: Antiviral specific ITT
- Endpoint: OSFD, in-hospital mortality

- Factors:
    - Lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir and control interventions interacted with fixed-dose steroids
    - Lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir and control interventions interacted with IL-6
- Analysis: Conducted by the ITSC Analysis Center

15.32 DESCRIPTIVE ANALYSIS OF THE MODERATE STATE

- Population: Antiviral specific ITT-Moderate State
- Endpoint: all baseline characteristics, interventions and endpoints
- Factors: lopinavir/ritonavir, hydroxychloroquine, hydroxychloroquine combined with lopinavir/ritonavir and control interventions

Appendix A: Definition of organ support-free days

This outcome is an ordinal scale of integers from –1 to 22 for each state (Moderate or Severe) derived from a composite of the patient's vital status at the end of acute hospital admission and days spent receiving organ failure support while admitted to an ICU (including a repurposed ICU) during the 21 days (504 hours) after randomisation.

A patient enrolled in the Severe State while still in an Emergency Department is regarded as 'admitted to an ICU' and the time of commencement of organ failure support is the time of randomisation, as it is for all other patients in the Severe State.

Patents who survive to hospital discharge and are enrolled in one or more domains in the Moderate State and are enrolled in one or more domains in the Severe State have a primary end point value for each state, which may be different.

If deceased between first enrolment and ultimate hospital discharge, code OutcomeDay21 as -1

If not deceased, ModerateOutcomeDay21 = 21 – (the sum of the length of time in days and part-days between time of first commencement of organ failure support while admitted to an ICU and the time of last cessation of organ failure support during that ICU admission plus time between first commencement and last cessation of organ failure support during any and all subsequent readmissions to ICU, censored at the 504 hours after enrolment in the Moderate State)

- A patient who is enrolled in the Moderate State who never receives organ failure support while admitted to an ICU has an ModerateOutcomeDay21 = 22.

- A patient who is enrolled in the Moderate State in a ward location who commences organ failure support on the ward and is transferred to an ICU while receiving organ failure support has a commencement time of organ failure support corresponding to the time of ICU admission.

If not deceased, SevereOutcomeDay21 = 21 – (the sum of the length of time in days and part- days between time of enrolment and the time of last cessation of organ failure support during that ICU admission plus the lengths of time between first commencement and last cessation of organ failure support during any and all subsequent readmissions to ICU, censored at 504 hours after the time of enrolment

Decimals are rounded up or down to nearest whole day.

If transferred between hospitals before the last study day 21 and known to be alive at ultimate hospital discharge use all available information to calculate Outcome Day21 with an assumption that no subsequent organ failure support in an ICU was provided.

If transferred between hospitals before the last study day 21 and vital status at ultimate hospital discharge is not known, code as follows:

- If last known to be on a ward use all available information to calculate Outcome Day 21 with an assumption that the patient has not died prior to ultimate hospital discharge and that there were no subsequent ICU admissions.

- If last known to be in an ICU, code OutcomeDay21 as missing (999)

If a patient is discharged alive from the ultimate hospital before 504 hours from each enrolment, assume all subsequent time is alive and without provision of organ failure support in an ICU.

If the patient is alive at the end of one or both censoring time points, the hours will be calculated as above. If the patient dies after the end of one or both of the censoring time points and before hospital discharge, the value will be updated to -1

A patient who remains admitted to an acute hospital and is still alive at the end of study day 90 no further changes to coding will be made.

Appendix B: Definition of time-to-SARS-CoV-2 RNA clearance.

a) Time-to-SARS-CoV-2 RNA clearance in respiratory samples is assessed in patients who had at least 1 follow-up rRT-PCR performed after the first confirmatory test of SARS-CoV-2.
b) Time-to-SARS-CoV-2 RNA clearance is calculated from the time of enrollment until the final rRT-PCR test, if negative.
c) If the final rRT-PCR test is positive, the follow-up time is censored by the date of that test (survival analysis).

Amendment Dated January 29-2021

A. Definition of the per-protocol cohort:

1. No antiviral for COVID-19 group: Patients who received no dose of lopinavir/ritonavir and no dose of hydroxychloroquine.
2. Lopinavir/ritonavir: Patients who received one dose or more of lopinavir/ritonavir but no dose of hydroxychloroquine.
3. Hydroxychloroquine: Patients who received one dose or more of hydroxychloroquine but no dose of lopinavir/ritonavir.
4. Hydroxychloroquine and lopinavir/ritonavir: Patients who received one dose or more of hydroxychloroquine and one dose or more of lopinavir/ritonavir.

B. The per-protocol cohort and compliance data will be calculated for all patients except those with missing medication data, defined as no information on any medication documented.