Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

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eTable 1. Enrolling Hospital Characteristics

Enrolling Hospital (arranged by number of enrollments)	Number of In-patient Hospital Beds	Type of Hospital	Enrolled Participants in the ORCHID trial
1	1046	Teaching Hospital Affiliated with a University	79
2	999	Teaching Hospital Affiliated with a University	49
3	800	Teaching Hospital Affiliated with a University	41
4	697	Teaching Hospital Affiliated with a University	34
5	673	Teaching Hospital Affiliated with a University	29
6	678	Teaching Hospital Affiliated with a University	26
7	1300	Teaching Hospital not Affiliated with a University	24
8	500	Teaching Hospital Affiliated with a University	24
9	716	Teaching Hospital Affiliated with a University	21
10	413	Teaching Hospital Affiliated with a University	18
11	678	Teaching Hospital Affiliated with a University	13
12	555	Teaching Hospital Affiliated with a University	11
13	555	Teaching Hospital Affiliated with a University	10
14	777	Teaching Hospital Affiliated with a University	9
15	1125	Teaching Hospital Affiliated with a University	9
16	750	Teaching Hospital Affiliated with a University	8
17	479	Teaching Hospital Affiliated with a University	7
18	80	Teaching Hospital Affiliated with a University	7
19	850	Teaching Hospital Affiliated with a University	7
20	724	Teaching Hospital Affiliated with a University	7
21	520	Teaching Hospital Affiliated with a University	7
22	1509	Teaching Hospital Affiliated with a University	6

23	562	Teaching Hospital Affiliated with a University	6
24	421	Teaching Hospital Affiliated with a University	5
25	660	Teaching Hospital Affiliated with a University	4
26	957	Teaching Hospital Affiliated with a University	4
27	550	Teaching Hospital Affiliated with a University	3
28	637	Teaching Hospital Affiliated with a University	3
29	1043	Teaching Hospital Affiliated with a University	2
30	613	Teaching Hospital Affiliated with a University	2
31	584	Teaching Hospital Affiliated with a University	2
32	330	Teaching Hospital Affiliated with a University	1
33	>750	Teaching Hospital Affiliated with a University	1
34	>750	Teaching Hospital Affiliated with a University	1

eTable 2. ORCHID Trial Eligibility Criteria
(final version of the protocol, version 4)

Inclusion criteria	1. Age ≥18 years. 2. Currently hospitalized or in an emergency department with anticipated hospitalization. 3. Symptoms of acute respiratory infection, defined as one or more of the following: a. Cough b. fever (> 37.5° C / 99.5° F) c. shortness of breath (operationalized as any of the following: subjective shortness of breath reported by patient or surrogate; tachypnea with respiratory rate ≥22 /minute; hypoxemia, defined as SpO2 <92% on room air, new receipt of supplemental oxygen to maintain SpO2 ≥92%, or increased supplemental oxygen to maintain SpO2 ≥92% for a patient on chronic oxygen therapy) d. sore throat 4. Laboratory-confirmed SARS-CoV-2 infection within the past 10 days prior to randomization
Exclusion criteria	1. Prisoner 2. Pregnancy 3. Breast feeding 4. Unable to randomize within 10 days after onset of acute respiratory infection symptoms 5. Unable to randomize within 48 hours after hospital arrival 6. Seizure disorder 7. Porphyria cutanea tarda 8. QTc >500 ms on electrocardiogram within 72 hours prior to enrollment 9. Diagnosis of Long QT syndrome 10. Known allergy to hydroxychloroquine, chloroquine, or amodiaquine 11. Receipt in the 12 hours prior to enrollment, or planned administration during the 5-day study period that treating clinicians feel cannot be substituted for another medication, of any of the following: amiodarone; cimetidine; dofetilide; phenobarbital; phenytoin; sotalol 12. Receipt of >1 dose of hydroxychloroquine or chloroquine in the 10 days prior to enrollment 13. Inability to receive enteral medications 14. Refusal or inability to be contacted on Day 15 for clinical outcome assessment if discharged prior to Day 15 15. Previous enrollment in this trial 16. The treating clinical team does not believe equipoise exists regarding the use of hydroxychloroquine for the treatment of this patient

Differences in eligibility criteria in earlier versions of the protocol	<u>Protocol Version 1 (active from trial start (April 2) – April 21, 2020)</u> 1. Inclusion criterion #3: Shortness of breath did not include an operationalized definition, which was later added as the parenthetical phase listed above in inclusion criterion #3. 2. Inclusion criterion #4 stated: Laboratory-confirmed SARS-CoV-2 infection within the past 10 days or SARS-CoV-2 laboratory test result pending plus a high clinical suspicion for COVID-19 as indicated by fulfilling all of the following: o Cough with duration ≤10 days o Bilateral pulmonary infiltrates on chest imaging (radiograph, computed tomography or ultrasound) or new hypoxemia defined as SpO2 ≤94% on room air o No alternative explanation for symptoms of acute respiratory infection 3. Exclusion criterion #16 did not exist. <u>Protocol Version 2 (active from April 21 – May 28, 2020)</u> 1. Inclusion criterion #3: Shortness of breath did not include an operationalized definition, which was later added as the parenthetical phase listed above in inclusion criterion #3. <u>Protocol Version 3 (active from May 28 – June 12, 2020)</u> Same eligibility criteria as in final protocol (version 4 listed above) <u>Protocol Version 4 (active from June 12 – trial end (June 19, 2020))</u> Final protocol (version 4 listed above)
Summary of eligibility criteria changes	1. Beginning with protocol version 2, participants were required to have laboratory confirmed SARS-CoV-2 infection rather than laboratory confirmed or clinically suspected SARS-CoV-2 infection. 2. Beginning with protocol version 2, an exclusion criterion has added that stated a patient was excluded if: "The treating clinical team does not believe equipoise exists regarding the use of hydroxychloroquine for the treatment of this patient." 3. Beginning with protocol version 3, the definition of shortness of breath was clarified and operationalized.

eTable 3. Protocol Guidance to Prevent Drug-Drug Interactions With the Trial Drug (Hydroxychloroquine)

Class	Action	Drugs
Class A	Medications considered contraindicated with ORCHID trial drug (hydroxychloroquine). If ordered on an inpatient during the 5-day ORCHID trial drug period, study personnel discussed with treating clinicians whether not administering the drug was appropriate. If this drug was not stopped, trial drug was withheld. Clinicians did not have a choice of continuing the ORCHID trial drug along with this concomitant drug.	amiodarone; chloroquine; cimetidine; dofetilide; phenobarbital; phenytoin; sotalol.
Class B	Medications considered to present a potential interaction with ORCHID trial drug (hydroxychloroquine). If ordered on an inpatient during the 5-day study period, study personnel discussed with treating clinicians the risk-benefit assessment of adding this drug to ORCHID study drug. If this drug was not withheld, ORCHID trial drug could continue after the treating team was alerted to potential drug-drug interactions. Clinicians had the choice of continuing both ORCHID trial drug and this drug.	ampicillin, antacids, cyclosporine, digoxin, flecainide, mefloquine, methotrexate, mexilitine, rifampicin, rifapentine.

eTable 4. Recommendations for Stopping the Trial

Recommendations from the investigators to the DSMB for stopping enrollment in the trial at any of the interim analyses included the following criteria:

- >95% probability of the odds ratio for the primary outcome is >1.0 → stop for efficacy
- >90% probability that the odds ratio for the primary outcome is <1.1 → stop for futility
- >70% probability that the odds ratio for the primary outcome is <0.70 → stop for harm

For calculation of posterior probabilities for tests of efficacy, we used a prior distribution for the odds ratio such that there is an equal chance of harm (OR < 1.0) as for benefit (OR > 1.0) with log(OR) having a normal distribution with mean zero and standard deviation 0.352 (this is a skeptical prior). This skeptical prior assumed a 5% probability of an extremely negative effect (more than halving of the aOR) and a 5% probability of an extremely positive effect (more than doubling the aOR). We used a normal prior distribution for the log odds ratio to achieve that. This estimate was based on extensive discussions among the investigator group, the history of positive trials in pulmonary/critical care, and the reality that a skeptical prior serves primarily to avoid declaring early success on the basis of extreme data that has not yet regressed to the mean. We anticipated that the sample size employed would mean that the data itself would largely overcome the skeptical prior by the second interim analysis.

For tests of futility and harm, we used a non-informative prior.

This table displays the probability of stopping the trial at each planned interim analysis based on the stopping criteria outlined above under two hypothetical scenarios: (1) a true odds ratio of 1.0 [no difference in the primary outcome between the hydroxychloroquine and placebo groups] and (2) a true odds ratio of 1.8 [substantially better primary outcome in the hydroxychloroquine group compared with the placebo group].

Probabilities of continuing or stopping the trial on or before each planned interim analysis based on a true odds ratio of 1.0 or 1.8.							
	True Odds Ratio = 1.0				True Odds Ratio = 1.8		
Planned sample size at analysis	Continue	Stop for Efficacy	Stop for Futility		Continue	Stop for Efficacy	Stop for Futility
102	0.844	0.006	0.150		0.840	0.154	0.006
204	0.744	0.021	0.235		0.494	0.500	0.007
306	0.667	0.036	0.297		0.254	0.740	0.007
408	0.606	0.0509	0.344		0.122	0.871	0.007
510	0.556	0.061	0.383		0.056	0.937	0.007

eTable 5. Interim Analyses

An independent data and safety monitoring board (DSMB) oversaw the conduct of the trial and reviewed four interim analyses. The date of each interim analysis, number of patients reviewed at each interim analysis, and the outcome of each interim analysis are listed in the table below.

Interim Analysis Number (date)	Enrolled patients with primary outcome data in dataset, no.	Enrolled patients with baseline data in dataset, no.	DSMB Recommendation
#1 (May 19, 2020)	110	275	Continue trial as planned
#2 (May 29, 2020)	240	348	Continue trial as planned
#3 (June 9, 2020)	306	409	Continue trial as planned
#4 (June 19, 2020)	371	452	Stop trial due to very low probability of efficacy[a]
Total Enrollment (final dataset)	479	479[b]	

a. At the time of the 4th interim analysis (n=371 with primary outcome data available at the time), the posterior probability for the aOR being >1.0 was 47% with a skeptical prior, for being <1.1 was 81% with a non-informative prior, and for being <0.70 was 7.8% with a non-informative prior. A post hoc conditional power analysis with these data showed <1.0% probability of reaching the efficacy stopping threshold (defined as >95% probability for an aOR >1.0 with a skeptical prior) if the trial continued to a sample size of 510 participants with each of three different assumptions for the aOR for the remaining participants to be enrolled up to 510: (i) the skeptical prior, (ii) the non-informative prior, and (iii) an aOR set at 1.5.

b. 27 patients were enrolled between preparation of the dataset for the 4th interim analysis and cessation of enrollment. Using data from all enrolled patients (n=479), the posterior probability for the aOR being >1.0% was 57% with a skeptical prior, for being <1.1 was 67% with a non-informative prior, and for being <0.70 was 1.5% with a non-informative prior.

eTable 6. Chronic Comorbidities
(baseline characteristics in addition to those listed in Table 1)

Comorbidity – no. (%)	Hydroxychloroquine (N=242)	Placebo (N=237)
Acquired immune deficiency syndrome	1 (0)	0 (0)
Leukemia	2 (1)	1 (0)
Malignant lymphoma	2 (1)	1 (0)
Hemiplegia	2 (1)	0 (0)
Cerebrovascular disease	18 (7)	16 (7)
Prior myocardial infarction	9 (4)	12 (5)
Congestive heart failure	18 (7)	17 (7)
Peripheral vascular disease	11 (5)	8 (3)
Dementia	17 (7)	12 (5)
Chronic obstructive pulmonary disease	18 (7)	21 (9)
Asthma	26 (11)	23 (10)
Chronic receipt of supplemental oxygen	10 (4)	9 (4)
Connective tissue disease	2 (1)	0 (0)
Peptic ulcer disease	5 (2)	4 (2)
Hypertension	136 (56)	117 (49)
Human immunodeficiency virus infection	3 (1)	5 (2)
Alcoholism	8 (3)	12 (5)
Coronary artery disease	19 (8)	23 (10)
Rapidly fatal disease	1 (0)	1 (0)
Solid tumor without metastases	4 (2)	7 (3)
Solid tumor with metastasis	4 (2)	2 (1)
Liver disease without portal hypertension or variceal bleeding	5 (2)	1 (0)
Liver disease with portal hypertension or variceal bleeding	2 (1)	2 (1)
Diabetes mellitus without end-organ damage	73 (30)	66 (28)
Diabetes mellitus with end-organ damage	15 (6)	12 (5)
Moderate to severe kidney disease without dialysis*	17 (7)	8 (3)
Kidney disease with dialysis	11 (5)	6 (3)

Comorbidity – no. (%)	Hydroxychloroquine (N=242)	Placebo (N=237)
Tobacco smoking		
Current	13 (5)	12 (5)
Former	54 (22)	51 (22)
Never	172 (71)	172 (73)
Vaping		
Current	1 (0)	0 (0)
Former	2 (1)	1 (0)
Never	236 (98)	234 (99)

*Moderate to severe kidney disease without dialysis is defined as a plasma creatinine concentration greater than 3 mg/dL, an estimated glomerular filtration rate <15 mL/min/1.73m^2, or a diagnosis of end-stage renal disease in the electronic health record.

eTable 7. Medications Prior to Hospital Presentation
(baseline characteristics in addition to those listed in Table 1)

Medication – no. (%)	Hydroxychloroquine (N=242)	Placebo (N=237)
Corticosteroids	25 (10)	22 (9)
Angiotensin converting enzyme inhibitor	41 (17)	34 (14)
Angiotensin receptor blocker	19 (8)	22 (9)
Non-steroidal anti-inflammatory drugs	32 (13)	32 (14)

eTable 8. Physiologic Measurements in the 12 Hours Prior to Randomization
(baseline characteristics in addition to those listed in Table 1)

Physiologic Measure	Hydroxychloroquine (N=242)	Placebo (N=237)
Highest heart rate, median [IQR], beats per minute	93 [81-103]	95 [84-105]
Lowest systolic blood pressure, median [IQR], mmHg	111 [99-123]	110 [101-126]
Receipt of vasopressors, no. (%)	8 (3)	20 (8)
Highest respiratory rate, median [IQR], breaths per minute	24 [20-30]	24 [20-30]
Lowest SpO2, median [IQR]	92 [90-95]	92 [90-94]
Highest FIO2, median [IQR]	0.27 [0.21-0.33]	0.27 [0.21-0.36]
Respiratory support, no. (%)		
Invasive mechanical ventilation	13 (5)	19 (8)
Noninvasive mechanical ventilation	2 (1)	5 (2)
High-flow nasal cannula	27 (11)	26 (11)
Face mask	5 (2)	5 (2)
Standard nasal cannula	106 (44)	97 (41)
No supplemental oxygen	83 (34)	83 (35)
Other/unspecified	6 (2)	2 (1)

eTable 9. Sequential Organ Failure Assessment (SOFA) Prior to Randomization
(baseline characteristics in addition to those listed in Table 1)

Measurement	Hydroxychloroquine (N=242)	Placebo (N=237)
Total SOFA Score, median [IQR]	2 [1-4]	2 [1-4]
Respiratory SOFA Score, median [IQR]	1 [1-2]	1 [1-2]
Lowest PaO2, median [IQR], mm Hg (number of patients with available values)	62 [58-74] (26)	62 [53-90] (35)
Associated FIO2, median [IQR]	0.36 [0.21-0.60]	0.44 [0.30-0.90]
Lowest SpO2, median [IQR] (number of patients with available values)	92 [88-94] (236)	92 [89-94] (234)
Associated FIO2, median [IQR]	0.23 [0.21-0.30]	0.24 [0.21-0.33]
Coagulation SOFA Score, median [IQR]	0 [0-0]	0 [0-1]
Lowest platelet count, median [IQR], thousand cells per mm^3 (number of patients with available values)	199 [151-247] (237)	201 [147-251] (230)
Liver SOFA Score, median [IQR]	0 [0-0]	0 [0-0]
Highest bilirubin, median [IQR], mg/dL (number of patients with available values)	0.5 [0.4-0.7] (186)	0.5 [0.4-0.7] (193)
Cardiovascular SOFA Score, median [IQR] (number of patients with available values)	0 [0-0] (225)	0 [0-0] (219)
Receipt of vasopressors, no. (%)	8 (3)	20 (8)
Central Nervous System SOFA Score, median [IQR] (number of patients with available values)	0 [0-0] (241)	0 [0-0] (237)
Lowest Glasgow Coma Scale score, median [IQR] (number of patients with available values)	15 [15-15] (219)	15 [15-15] (202)
Renal SOFA Score, median [IQR]	0 [0-1]	0 [0-1]
Highest creatinine, median [IQR], mg/dL (number of patients with available values)	0.95 [0.75-1.47] (235)	0.90 [0.75-1.25] (231)

eTable 10. Laboratory Values in the 24 Hours Prior to Randomization
(baseline characteristics in addition to those listed in Table 1)

Laboratory measurement	Hydroxychloroquine (N=242)	Placebo (N=237)
Highest white blood cell count, median [IQR], thousand cells per mm^3 (number of patients with non-missing values)	6.5 [4.7-8.3] (230)	6.1 [4.5-8.6] (223)
Lowest white blood cell count, median [IQR], thousand cells per mm^3 (number of patients with non-missing values)	6.0 [4.3-7.9] (224)	5.9 [4.1-7.7] (218)
Lowest hemoglobin, median [IQR], g/dL (number of patients with non-missing values)	12.5 [11.4-13.9] (234)	13.2 [11.6-14.5] (224)
Highest sodium, median [IQR], mmol/L (number of patients with non-missing values)	137 [135-139] (235)	137 [135-139] (226)
Lowest sodium, median [IQR], mmol/L (number of patients with non-missing values)	136 [133-138] (229)	136 [134-138] (221)
Lowest bicarbonate, median [IQR], mmol/L (number of patients with non-missing values)	23 [20-24] (216)	23 [21-25] (198)
Highest creatinine, median [IQR], mg/dL (number of patients with non-missing values)	0.95 [0.75-1.47] (235)	0.90 [0.75-1.25] (231)
Highest troponin, median [IQR], ng/dL (number of patients with non-missing values)	0.01 [0.00-0.09] (137)	0.01 [0.00-0.16] (136)
Highest aspartate aminotransferase, median [IQR], units/L (number of patients with non-missing values)	39 [29-62] (173)	45 [31-70] (184)
Highest alanine aminotransferase, median [IQR], units/L (number of patients with non-missing values)	30 [18-47] (174)	34 [22-62] (183)
Highest alkaline phosphatase, median [IQR], IU/L (number of patients with non-missing values)	74 [55-93] (171)	76 [61-102] (176)
Lowest albumin, median [IQR], g/dL (number of patients with non-missing values)	3.5 [3.2-3.9] (172)	3.6 [3.1-3.9] (174)
Highest partial thromboplastin time, median [IQR], seconds (number of patients with non-missing values)	33.4 [28.4-37.4] (64)	31.8 [27.6-36.0] (69)
Highest international normalized ratio, median [IQR] (number of patients with non-missing values)	1.1 [1.0-1.2] (98)	1.1 [1.0-1.2] (105)

eTable 11. Medications Received Between Hospital Presentation and Randomization (baseline characteristics in addition to those listed in Table 1)

Medication, no. (%)	Hydroxychloroquine (N=242)	Placebo (N=237)
Azithromycin	78 (32)	72 (30)
Corticosteroids	17 (7)	18 (8)
Hydroxychloroquine[a]	3 (1)	1 (0)
Chloroquine*	0 (0)	1 (0)
Interferon beta	1 (0)	0 (0)
Remdesivir	12 (5)	12 (5)
Tocilizumab	1 (0)	4 (2)
SARS-CoV-2 convalescent plasma[b]	5/229 (2)	7/227 (3)

a. Patients who received one dose of hydroxychloroquine or chloroquine as part of routine clinical care were eligible for enrollment. Patients who received more than one dose of hydroxychloroquine or chloroquine as part of routine clinical care in the 10 days prior to randomization were not eligible.

b. Data collection of SARS-CoV-2 convalescent plasma did not begin immediately at trial launch; 23 patients did not have data on use of SARS-CoV-2 convalescent plasma collected.

eTable 12. Receipt of Trial Drug

Population/Characteristic	Hydroxychloroquine	Placebo
All enrolled patients	**n = 242**	**n = 237**
Total doses of trial drug received, median [IQR]	10 [9-10]	10 [9-10]
Received ≥ 1 dose of trial drug – no. (%)	242 (100)	231 (97)
Received 10 doses of trial drug – no. (%)	168 (69)	175 (74)
Enrolled patients who survived through Study Day 5	**n = 240**	**n = 235**
Total doses of trial drug received, median [IQR]	10 [9-10]	10 [9-10]
Received ≥ 1 dose of trial drug – no. (%)	240 (100)	229 (97)
Received 10 doses of trial drug – no. (%)	168 (70)	175 (74)

eTable 13. Reasons Trial Drug Not Administered

Characteristics	Hydroxychloroquine	Placebo
Total potential doses of trial drug (no. of patients x 10), count	2420	2370
Doses of trial drug administered, count (% of total potential doses)	2149 (89)	2038 (86)
Doses of trial drug not administered, count (% of total potential doses)	271 (11)	332 (14)
Reason dose of trial drug was not administered, count (% of doses of trial drug not administered)		
Patient died before scheduled dose	11 (4)	8 (2)
On-study monitoring with QTc > 500ms	38 (14)	21 (6)
On-study monitoring with drug-drug interaction	6 (2)	21 (6)
Dose held by clinical team	15 (6)	13 (4)
Study drug unavailable	2 (1)	3 (1)
Negative SARS-CoV-2 test and alternative cause of clinical syndrome	0 (0)	9 (3)
Patient declined dose	90 (33)	104 (31)
Unable to be logistically administered during the scheduled window	26 (10)	36 (11)
Adverse event	12 (4)	22 (7)
Other	71 (26)	95 (29)

eTable 14. Receipt of Concomitant Medications After Randomization During Hospitalization

Class / Medication	Hydroxychloroquine (N=242)	Placebo (N=237)
Antiviral		
Open-label hydroxychloroquine, no. (%)	4 (2)	1 (0)
Remdesivir, no. (%)	56 (23)	48 (20)
Other antiviral, no. (%)	6 (2)	7 (3)
Immunomodulator		
Corticosteroids, no. (%)	39 (16)	49 (21)
Tocilizumab, no. (%)	10 (4)	17 (7)
Other immunomodulator, no. (%)	1 (0)	3 (1)
Antibacterial		
Azithromycin, no. (%)	47 (19)	44 (19)
SARS-CoV-2 convalescent plasma, no. (%)	19 (8)	25 (11)

eTable 15. Receipt of Respiratory Support After Randomization During Hospitalization

Respiratory Support[a]	Hydroxychloroquine (N=242)	Placebo (N=237)
High-flow nasal cannula, no. (%)	58 (24)	65 (27)
Non-invasive ventilation, no. (%)	19 (8)	26 (11)
Invasive mechanical ventilation, no. (%)	41 (17)	47 (20)
Extra-corporeal membrane oxygenation, no. (%)	6 (2)	5 (2)

a. Categories are not mutually exclusive

eTable 16. Sensitivity Analyses for the Primary Outcome

Population / Outcome	Hydroxychloroquine (n=242 randomized)	Placebo (n=237 randomized)	Adjusted odds ratio (95% CI)[a]
Population limited to laboratory-confirmed SARS-CoV-2 infection	n=242	n=235	
Score on COVID Outcomes Scale at 14 days, median [IQR]	6 [4-7]	6 [4-7]	1.04 (0.75-1.45)
Population limited to patients with ≥1 dose of trial drug (modified intention to treat population)	n=242	n=231	
Score on COVID Outcomes Scale at 14 days, median [IQR]	6 [4-7]	6 [4-7]	1.03 (0.74-1.44)
Full trial population with enrolling site included in the model as a random effect (post-hoc analysis)	n=242	n=237	
Score on COVID Outcomes Scale at 14 days, median [IQR]	6 [4-7]	6 [4-7]	1.01 (0.73-1.40)

a. Proportional odds model with study group as the independent variable, COVID Outcomes Scale scores as the dependent variable, and the following co-variables: age, sex, baseline COVID Outcome Scale category, baseline Sequential Organ Failure Assessment (SOFA) score, and duration of acute respiratory infection symptoms prior to randomization.

eTable 17. Post Hoc Subgroup Analyses of the Primary Outcome
The primary outcome is the COVID Outcomes Scale at 14 days after randomization.

Population / Outcome	Hydroxychloroquine (N=242 randomized)	Placebo (N=237 randomized)	Primary outcome adjusted odds ratio[a] (95% CI)
Open label clinical remdesivir use at any time during hospitalization	n=56	n=48	1.01 (0.49-2.07)
No open label clinical remdesivir use at any time during hospitalization	n=186	n=189	1.03 (0.71-1.51)
Open label azithromycin use at any time during hospitalization	n=47	n=44	0.80 (0.37-1.74)
No open label azithromycin use at any time during hospitalization	n=195	n=193	1.05 (0.73-1.52)
Open label corticosteroid use at any time during hospitalization	n=39	n=49	0.94 (0.44-2.02)
No open label clinical corticosteroid use at any time during hospitalization	n=203	n=188	1.05 (0.73-1.53)

a. Adjusted odds ratios were calculated with proportional odds models with study group as the independent variable, COVID Outcomes Scale at 14 days as the dependent variable, and the following co-variables: age, sex, baseline COVID Outcome Scale category, baseline Sequential Organ Failure Assessment (SOFA) score, and duration of acute respiratory infection symptoms prior to randomization.

eTable 18. COVID Outcomes Scale Over Time by Study Group

***Days after randomization*/ COVID Outcomes Scale**	**Hydroxychloroquine (N=242)**	**Placebo (N=237)**	**Adjusted odds ratio* (95% CI)**
At Randomization			1.04 (0.72-1.49)
COVID Outcomes Scale Category – no. (%)			
2 – Hospitalized, receiving ECMO or invasive mechanical ventilation	13 (5)	19 (8)	
3 – Hospitalized, receiving noninvasive mechanical ventilation or nasal high-flow oxygen therapy	28 (12)	27 (11)	
4 – Hospitalized, receiving supplemental oxygen	116 (48)	108 (46)	
5 – Hospitalized, not receiving supplemental oxygen	85 (35)	83 (35)	
At 2 days after randomization (Study Day 3)			1.28 (0.90-1.81)
COVID Outcomes Scale Category – no. (%)			
1 – Death	1 (0)	0 (0)	
2 – Hospitalized, receiving ECMO or invasive mechanical ventilation	22 (9)	30 (13)	
3 – Hospitalized, receiving noninvasive mechanical ventilation or nasal high-flow oxygen therapy	38 (16)	35 (15)	
4 – Hospitalized, receiving supplemental oxygen	93 (38)	96 (41)	
5 – Hospitalized, not receiving supplemental oxygen	57 (24)	56 (24)	
6 – Not hospitalized, and unable to perform normal activities	31 (13)	20 (8)	
At 7 days after randomization (Study Day 8)			1.16 (0.84-1.61)
COVID Outcomes Scale Category – no. (%)			
1 – Death	9 (4)	9 (4)	
2 – Hospitalized, receiving ECMO or invasive mechanical ventilation	27 (11)	33 (14)	
3 – Hospitalized, receiving noninvasive mechanical ventilation or nasal high-flow oxygen therapy	15 (6)	20 (8)	
4 – Hospitalized, receiving supplemental oxygen	41 (17)	30 (13)	
5 – Hospitalized, not receiving supplemental oxygen	29 (12)	24 (10)	
6 – Not hospitalized, and unable to perform normal activities	56 (23)	73 (31)	
7 – Not hospitalized, and able to perform normal activities	65 (27)	48 (20)	

***Days after randomization*/ COVID Outcomes Scale**	**Hydroxychloroquine (N=242)**	**Placebo (N=237)**	**Adjusted odds ratio* (95% CI)**
At 14 days after randomization (Study Day 15) [primary outcome]			1.02 (0.73-1.42)
COVID Outcomes Scale Category – no. (%)			
1 – Death	18 (7)	14 (6)	
2 – Hospitalized, receiving ECMO or invasive mechanical ventilation	18 (7)	24 (10)	
3 – Hospitalized, receiving noninvasive mechanical ventilation or nasal high-flow oxygen therapy	5 (2)	7 (3)	
4 – Hospitalized, receiving supplemental oxygen	22 (9)	18 (8)	
5 – Hospitalized, not receiving supplemental oxygen	21 (9)	16 (7)	
6 – Not hospitalized, and unable to perform normal activities	80 (33)	89 (38)	
7 – Not hospitalized, and able to perform normal activities	78 (32)	69 (29)	
At 28 days after randomization (Study Day 29)			0.97 (0.69-1.38)
COVID Outcomes Scale Category – no. (%)			
1 – Death	25 (10)	25 (11)	
2 – Hospitalized, receiving ECMO or invasive mechanical ventilation	11 (5)	12 (5)	
4 – Hospitalized, receiving supplemental oxygen	9 (4)	10 (4)	
5 – Hospitalized, not receiving supplemental oxygen	6 (2)	5 (2)	
6 – Not hospitalized, and unable to perform normal activities	75 (31)	72 (30)	
7 – Not hospitalized, and able to perform normal activities	116 (48)	113 (48)	

*Proportional odds model with study group as the independent variable, COVID Outcomes Scale scores as the dependent variable, and the following co-variables: age, sex, baseline COVID Outcome Scale category, baseline Sequential Organ Failure Assessment (SOFA) score, and duration of acute respiratory infection symptoms prior to randomization. Baseline COVID Outcomes Scales score was not used as a co-variable in the model to calculate the adjusted odds ratio for the baseline (at randomization) time point.

eTable 19. Additional Clinical Outcomes by Study Group

Outcome	Hydroxychloroquine (N=242)	Placebo (N=237)
Total SOFA Score, median [IQR]		
At randomization	2 [1-4]	2 [1-4]
2 days after randomization (Study Day 3)	2 [1-5]	2 [1-4]
Respiratory SOFA Score, median [IQR]		
At randomization	1 [1-2]	1 [1-2]
2 days after randomization (Study Day 3)	1 [1-2]	1 [1-2]
Coagulation SOFA Score, median [IQR]		
At randomization	0 [0-0]	0 [0-1]
2 days after randomization (Study Day 3)	0 [0-0]	0 [0-0]
Liver SOFA Score, median [IQR]		
At randomization	0 [0-0]	0 [0-0]
2 days after randomization (Study Day 3)	0 [0-0]	0 [0-0]
Cardiovascular SOFA Score, median [IQR] (patients with available values)		
At randomization	0 [0-0] (225)	0 [0-0] (219)
2 days after randomization (Study Day 3)	0 [0-1] (201)	0 [0-1] (208)
Central Nervous System SOFA Score, median [IQR] (patients with available values)		
At randomization	0 [0-0] (241)	0 [0-0] (237)
2 days after randomization (Study Day 3)	0 [0-1] (180)	0 [0-1] (182)
Renal SOFA Score, median [IQR] (patients with available values)		
At randomization	0 [0-1]	0 [0-1]
2 days after randomization (Study Day 3)	0 [0-2] (196)	0 [0-1] (184)
Readmitted between hospital discharge and 28 days, no (%)	17/201 (8)	13/196 (7)
Emergency department visit between discharge from index hospitalization and 28 days, no (%)	26/201 (13)	21/196 (11)
Diagnosed with a deep vein thrombosis between randomization and earlier of hospital discharge or 28 days, no (%)	6 (2)	10 (4)
Diagnosed with a pulmonary embolism between randomization and earlier of hospital discharge or 28 days, no (%)	4 (2)	5 (2)

eTable 20. Symptoms of Respiratory Infection by Study Group

Follow-up time / Symptom*	Hydroxychloroquine (N=242)	Placebo (N=237)
14 Days after Randomization (Study Day 15)		
Cough, no (%)	34 (14)	34 (14)
Fever (T >99.5F measured), no (%)	2 (1)	1 (0)
Feverishness (subjective symptom), no (%)	4 (2)	3 (1)
Shortness of breath, no (%)	32 (13)	35 (15)
Chest tightness, no (%)	9 (4)	6 (3)
Sore throat, no (%)	0 (0)	4 (2)
Weakness or fatigue, no (%)	44 (18)	38 (16)
Other, no (%)	21 (9)	21 (9)
Any symptom attributed to COVID-19 (composite of above symptoms), no (%)	84 (35)	78 (33)
28 Days after Randomization (Study Day 29)		
Cough, no (%)	25 (10)	23 (10)
Fever (T >99.5F measured), no (%)	1 (0)	2 (1)
Feverishness (subjective symptom), no (%)	1 (0)	2 (1)
Shortness of breath, no (%)	24 (10)	25 (11)
Chest tightness, no (%)	4 (2)	6 (3)
Sore throat, no (%)	3 (1)	3 (1)
Weakness or fatigue, no (%)	33 (14)	28 (12)
Other, no (%)	19 (8)	31 (13)
Any symptom attributed to COVID-19 (composite of above symptoms), no (%)	69 (29)	72 (30)

eTable 21. Laboratory Values Through Day 5 by Study Group

Laboratory value, median [IQR] (number of patients with available data)	Hydroxychloroquine (N=242)	Placebo (N=237)
White blood cell count, thousand per mm^3		
At randomization (lowest in prior 24 hours)	6.0 [4.3-7.9] (224)	5.9 [4.1-7.7] (218)
Lowest through Day 5	4.9 [3.5-6.6] (234)	5.0 [3.6-6.5] (233)
Highest through Day 5	7.9 [5.7-10.2] (238)	7.8 [5.9-10.8] (235)
Hemoglobin, g/dL		
At randomization (lowest in prior 24 hours)	12.5 [11.4-13.9] (234)	13.2 [11.6-14.5] (224)
Lowest through Day 5	11.7 [10.4-13.1] (242)	12.1 [10.4-13.6] (236)
Platelet count, thousand per mm^3		
At randomization (lowest in prior 24 hours)	199 [151-247] (237)	201 [147-251] (230)
Lowest through Day 5	210 [163-265] (212)	211 [144-279] (211)
Sodium, mmol/L		
At randomization (lowest in prior 24 hours)	137 [135-139] (235)	137 [135-139] (226)
Lowest through Day 5	135 [133-137] (238)	135 [132-137] (233)
Highest through Day 5	139 [138-140] (242)	139 [137-142] (236)
Potassium, mmol/L		
At randomization (lowest in prior 24 hours)	3.8 [3.6-4.2] (228)	3.8 [3.5-4.2] (221)
Lowest through Day 5	3.7 [3.4-3.9] (237)	3.6 [3.4-3.9] (233)
Highest through Day 5	4.30 [4.0-4.7] 241	4.30 [4.0-4.7] 236
Chloride, mmol/L		
At randomization (highest in prior 24 hours)	102 [98-106] (235)	102 [98-105] (227)
Highest through Day 5	105 [102-107] (242)	104 [101-108] (236)
Bicarbonate, mmol/L		
At randomization (lowest in prior 24 hours)	23 [200-24] (216)	23 [21-25] (198)
Lowest through Day 5	21 [19-23] (228)	22 [20-24] (221)
Highest through Day 5	25 [23-28] (232)	26 [24-29] (224)
Blood urea nitrogen, mg/dL		
At randomization (highest in the prior 24 hours)	14 [11-26] (235)	14 [10-24] (224)
Creatinine, mg/dL		
At randomization (highest)	0.95 [0.75-1.47] (235)	0.90 [0.75-1.25] (231)
Highest through Day 5	0.89 [0.70-1.40] (218)	0.90 [0.71-1.30] (216)

Laboratory value, median [IQR] (number of patients with available data)	Hydroxychloroquine (N=242)	Placebo (N=237)
Troponin, ng/dL		
At randomization (highest in prior 24 hours)	0.01 [0.00-0.09] (137)	0.01 [0.00-0.16] (136)
Highest through Day 5	0.01 [0.00-0.20] (148)	0.01 [0.00-0.37] (151)
Aspartate aminotransferase (AST), units/L		
At randomization (highest in prior 24 hours)	39 [29-62] (173)	45 [31-70] (184)
Highest through Day 5	45 [31-78] (213)	53 [38-88] (219)
Alanine aminotransferase (ALT), units/L		
At randomization (highest in prior 24 hours)	30 [18-47] (174)	34 [22-62] (183)
Highest through Day 5	33 [20-63] (214)	42 [24-73] (218)
Total bilirubin, mg/dL		
At randomization (highest in prior 24 hours)	0.5 [0.4-0.7] (186)	0.5 [0.4-0.7] (193)
Highest through Day 5	0.5 [0.4-0.7] (160)	0.6 [0.4-0.8] (170)
Albumin, g/dL		
At randomization (lowest in prior 24 hours)	3.5 [3.2-3.9] (172)	3.6 [3.1-3.9] (174)
Lowest through Day 5	3.2 [2.7-3.5] (211)	3.1 [2.8-3.5] (209)
Partial thromboplastin time (PTT), seconds		
At randomization (highest in prior 24 hours)	33.4 [28.4-37.4] (64)	31.8 [27.6-36.0] (69)
Highest through Day 5	34.6 [29.1-39.8] (95)	33.6 [28.8-39.8] (104)
International normalized ratio (INR)		
At randomization (highest in prior 24 hours)	1.1 [1.0-1.2] (98)	1.1 [1.0-1.2] (105)
Highest through Day 5	1.2 [1.1-1.4] (75)	1.2 [1.1-1.3] (85)

eTable 22. Pathogen Testing Data

Pathogen testing	Hydroxychloroquine (n=242)	Placebo (n=237)
SARS-CoV-2 polymerase chain reaction: ≥1 positive test for SARS-CoV-2 detection, no. (%)	242 (100)	235 (99)
Source of specimen(s) positive for SARS-CoV-2 detection, no. [not mutually exclusive]		
Nasopharyngeal	232	227
Oral	4	3
Tracheal aspirate	4	6
Sputum	1	1
Bronchoalveolar lavage	1	0
Other	5	4
Blood cultures: ≥1 blood culture positive between hospital presentation and Study Day 7, no. (%)	16 (7)	17 (7)
Pathogen in positive blood culture, no. [not mutually exclusive]		
Staphylococcus aureus	4	5
Enterococcus	2	0
Streptococcus pneumoniae	0	2
Pseudomonas aeruginosa	1	0
Coagulase negative staphylococcus	1	3
Bacillus	0	1
Other	9	7
Viral pathogens: ≥1 virus detected by polymerase chain reaction other than SARS-CoV-2 between hospital presentation and Study Day 7, no. (%)	0	1 (<1%)
Other viral pathogens detected, no.		
Influenza B	0	1

eTable 23. Systematically Collected Safety Events
(assessed between randomization and 28 days later)

Outcome – no. (%)	Hydroxychloroquine (n=242)	Placebo (n=237)	Odds ratio (95% CI)
Seizure	1 (<1)	0	n/a
Atrial tachyarrhythmia	15 (6)	11 (5)	1.36 (0.61-3.02)
Ventricular tachyarrhythmia	5 (2)	6 (3)	0.81 (0.24-2.70)
Cardiac arrest treated with CPR	10 (4)	4 (2)	2.51 (0.78-8.12)
AST or ALT greater than twice upper limit of normal	50 (21)	65 (27)	0.69 (0.45-1.05)
Acute pancreatitis	5 (2)	6 (3)	0.81 (0.24-2.70)
Stage II or greater acute kidney injury	37 (15)	37 (16)	0.97 (0.59-1.59)
Receipt of renal replacement therapy	10 (4)	14 (6)	0.69 (0.30-1.58)
Symptomatic hypoglycemia	10 (4)	8 (3)	1.23 (0.48-3.18)
Neutrophil count < 1000 cells/mm^3	4 (2)	4 (2)	0.98 (0.24-3.96)
Lymphocyte count < 1000 cells/mm^3	92 (38)	87 (37)	1.06 (0.73-1.53)
Hemoglobin < 12 g/dL	139 (57)	120 (51)	1.32 (0.92-1.89)
Platelet count < 50 cells/mm^3	4 (2)	5 (2)	0.78 (0.21-2.94)
Severe dermatologic reaction	1 (<1)	1 (<1)	0.98 (0.06-15.74)

Abbreviations: AST = aspartate aminotransferase; ALT = alanine aminotransferase; CPR = cardiopulmonary resuscitation

eTable 24. Adverse Events by Organ System

Adverse events (AEs) were reported by site investigators, who were blinded to randomized group, to the Clinical Coordinating Center. The site investigator who reported each adverse event classified the adverse event as serious or not serious and the relatedness to study procedures. Individual patients could experience more than one adverse event.

A total of 89 adverse events were reported in the trial. In the hydroxychloroquine group, 50 adverse events among 44 patients were reported. In the placebo group, 39 adverse events among 32 patients were reported.

A serious adverse event (SAE) was defined as an adverse event leading to death, a life-threatening experience, prolongation of hospitalization, or persistent or significant disability or incapacity. A total of 30 serious adverse events were reported in the trial. In the hydroxychloroquine group, 18 serious adverse among 14 patients were reported. In the placebo group, 12 serious adverse events among 11 patients were reported.

Site investigators reported the suspected relatedness of each adverse event to study procedures using the following 5 options: definitely related; probably or possibly related; probably not related; definitely not related; uncertain relationship. All serious adverse events were classified as probably not related or definitely not related.

This table, which begins on the next page, displays all 89 adverse events reported in the trial, whether the adverse event was classified as serious, and the relatedness of the adverse event to study procedures.

Organ System	Adverse Event	SAE?	Relatedness of AE to study procedures	Hydroxychloroquine AEs reported, no.	Placebo AEs reported, no.
Blood and lymphatic system disorders	Leukocytosis	No	Definitely not related	1	0
Cardiac disorders	Atrial Arrythmia	No	Probably or possibly related	1	2
	Bradycardia	No	Probably or possibly related	0	2
	Cardiac Arrest	**Yes**	Probably not related	0	1
		Yes	Definitely not related	0	1
	Cardiac Arrhythmia	No	Probably or possibly related	0	1
	Cardiomyopathy	No	Definitely not related	1	0
	Chest Pain	No	Probably or possibly related	2	0
	Conduction Disorder	No	Probably or possibly related	0	1
	EKG Abnormality: Non-Specific	No	Probably or possibly related	0	1
	Myocardial Infarction	**Yes**	Definitely not related	1	0
	Premature Ventricular Contractions	No	Probably or possibly related	1	1
	Prolonged QTc	No	Probably or possibly related	1	2
		No	Definitely related	1	1
	Sinus Bradycardia	No	Probably not related	0	1
	Ventricular Tachycardia	**Yes**	Probably not related	0	1
Endocrine disorders	Hypoglycemia	No	Definitely not related	0	1

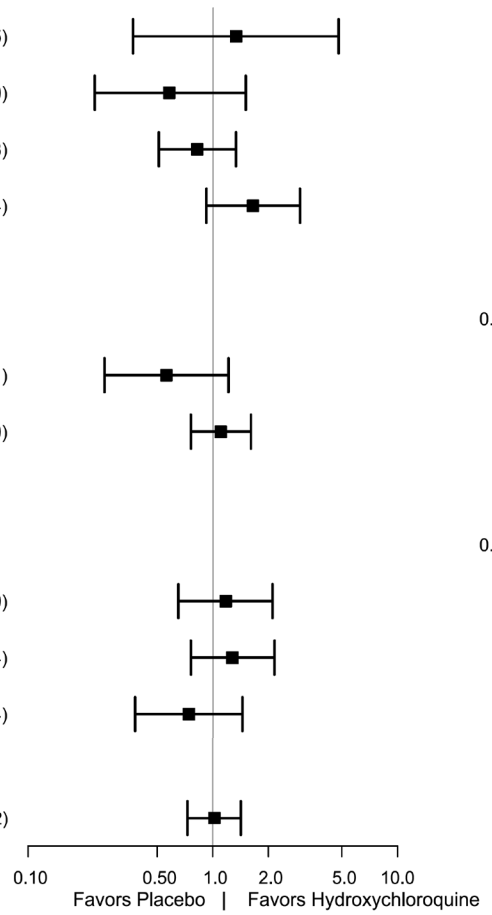
Organ System	Adverse Event	SAE?	Relatedness of AE to study procedures	Hydroxychloroquine AEs reported, no.	Placebo AEs reported, no.
Gastrointestinal disorders	Abdominal Distension	**Yes**	Definitely not related	0	1
	Bleeding Gastrointestinal	**Yes**	Definitely not related	1	0
	Diarrhea	No	Probably or possibly related	0	1
	Gall stones	**Yes**	Definitely not related	0	1
	Nausea	No	Probably or possibly related	2	1
	Nausea, Vomiting	No	Probably or possibly related	1	0
	Nausea, Vomiting, Hematemesis	**Yes**	Definitely not related	1	0
	Nausea, Diarrhea	No	Uncertain relationship	0	1
	Obstruction Bowel	**Yes**	Definitely not related	1	0
General disorders	Contrast Extravasation	No	Definitely not related	1	0
	Death	**Yes**	Definitely not related	2	0
Immune systems disorders	Allergic Reaction	No	Definitely not related	1	0
Investigations (laboratories)	ALT Increased	No	Probably or possibly related	1	0
	AST Increased	No	Probably or possibly related	1	0
	Hypokalemia	**Yes**	Probably not related	0	1
	Multiple Liver Function Tests Abnormal	No	Probably or possibly related	10	3
	Reaction Nonspecific	**Yes**	Probably not related	1	1
Musculoskeletal and connective tissue disorders	Hematoma Muscle	**Yes**	Definitely not related	1	0
	Joint Pain	**Yes**	Definitely not related	1	0

Organ System	Adverse Event	SAE?	Relatedness of AE to study procedures	Hydroxychloroquine AEs reported, no.	Placebo AEs reported, no.
Nervous system disorders	Edema Cerebral	**Yes**	Probably not related	1	0
	Encephalopathy	**Yes**	Definitely not related	1	0
	Headache	No	Probably or possibly related	3	1
		No	Probably not related	0	1
		Yes	Definitely not related	0	1
	Intracranial hemorrhage	**Yes**	Definitely not related	0	1
	Neuropathy Peripheral	No	Definitely not related	0	1
	Stroke	**Yes**	Probably not related	1	0
		Yes	Definitely not related	0	2
Renal and urinary disorders	Kidney Function Abnormal	No	Definitely not related	1	0
Respiratory, thoracic and mediastinal disorders	Hypoxia	No	Probably not related	1	1
		Yes	Probably not related	1	0
		Yes	Definitely not related	1	0
	Pneumothorax	**Yes**	Definitely not related	2	0
	Respiratory Distress	**Yes**	Definitely not related	1	0
	Shortness of Breath	**Yes**	Definitely not related	1	0
Skin and subcutaneous tissue disorders	Itching	No	Definitely not related	0	1
	Rash	No	Probably not related	1	1
Vascular disorders	Flushing	No	Uncertain relationship	0	1
	Hemorrhage Retroperitoneal	**Yes**	Definitely not related	0	1
Vascular or cardiac disorders	Vagal Reaction	No	Definitely not related	1	0
Vascular or respiratory disorders	Nosebleed	No	Probably or possibly related	0	1
TOTAL				**50**	**39**

eFigure. Subgroup Analyses of the Primary Outcome

The adjusted odds ratios and 95% confidence intervals (CI) for the primary outcome (COVID Outcomes Scale 14 days after randomization) are displayed, comparing hydroxychloroquine to placebo after adjusting for pre-specified baseline co-variables, including age, sex, baseline COVID Outcomes Scale, baseline SOFA score, and duration of acute respiratory symptoms prior to randomization. Reported P values represent the interaction between the baseline characteristic used to define subgroups and randomized group (hydroxychloroquine versus placebo) on the primary outcome.

Subgroup	Number of patients			aOR (95% CI) for COVID Scale score at 14 days	P-value for interaction
	Total	HCQ	Placebo		
COVID Outcomes Scale category at randomization					0.18
2: IMV or ECMO	32	13	19	1.33 (0.37, 4.75)	
3: NIV or HFNC	55	28	27	0.58 (0.23, 1.50)	
4: Hospitalized, with O2	224	116	108	0.82 (0.51, 1.33)	
5: Hospitalized, no O2	168	85	83	1.64 (0.92, 2.94)	
Location at randomization					0.12
ICU	91	37	54	0.56 (0.26, 1.21)	
Not in ICU	388	205	183	1.10 (0.76, 1.60)	
SOFA score at randomization					0.43
Highest tertile [score 4 to 17]	146	79	67	1.17 (0.65, 2.09)	
Middle tertile [score 2 to 3]	200	94	106	1.27 (0.76, 2.14)	
Lowest tertile [score 0 to 1]	133	69	64	0.74 (0.38, 1.44)	
Full Population	479	242	237	1.02 (0.73, 1.42)	



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