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JWT629 (Hydroxychloroquine)

Clinical Trial Protocol CJWT629A12301 / NCT04358081

A multi-center, randomized, double-blinded, placebo-controlled study to evaluate the safety and efficacy of hydroxychloroquine monotherapy and in combination with azithromycin in patients with moderate and severe COVID-19 disease

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Table of contents

List of tables

List of figures

List of abbreviations

AE	Adverse Event
ALP	Alkaline Phosphatase
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the curve
AZI	Azithromycin
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CL	Clearance
Cmax	Minimum (peak) plasma drug concentration
Cmin	Maximum plasma drug concentration
CMO&PS	Chief Medical Office and Patient Safety
CoV(s)	Coronavirus(es)
CRF	Case Report/Record Form (paper or electronic)
CRO	Contract Research Organization
CSR	Clinical study report
DBP	Diastolic Blood Pressure
DMC	Data Monitoring Committee
ECG	Electrocardiogram
[redacted]	[redacted]
F	Bioavailability (systemic availability of the administered dose)
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-glutamyl transferase
GLDH	Glutamate dehydrogenase
h	Hour
HCQ	Hydroxychloroquine
HCT	Hematocrit
Hgb	Hemoglobin
[redacted]	[redacted]
HSS	Department of Health and Human Services
ICF	Informed Consent Form
ICH	International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use
IEC	Independent Ethics Committee
IN	Investigator Notification
IND	Investigational new drug application
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology

K	Potassium
ka	Absorption rate constant (first order)
KG	Kilogram
LFT	Liver function test
LLOQ	lower limit of quantification
MedDRA	Medical dictionary for regulatory activities
Med hx	Medical history
MERS-CoV	Middle Eastern respiratory syndrome coronavirus
mg	milligram(s)
Mg	Magnesium
mL	milliliter(s)
msec	Millisecond(s)
Na	Sodium
ng	nanogram
o.d.	Once a day
PCR	Polymerase chain reaction
PLT	Platelets
p.o.	oral(ly)
PK	Pharmacokinetic(s)
QMS	Quality Management System
QTcF	QT interval corrected by Fridericia's formula
RBC	red blood cell(s)
RNA	Ribonucleic acid
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SARS-CoV	severe acute respiratory syndrome coronavirus
sCR	serum creatinine
SD	standard deviation
SMQ	Standardized MedDRA Query
SoC	Standard of care
SpO2	Peripheral capillary oxygen saturation
SUSAR	Suspected Unexpected Serious Adverse Reaction
t.i.d.	Three times a day (ter in die)
μg	Microgram
ULOQ	Upper limit of quantification
ULN	upper limit of normal
μM	Micro Molar Unit
USPI	United States package insert
WBC	white blood cell(s)
WHO	World Health Organization
WoC	Withdrawal of Consent

Glossary of terms

Additional treatment	Medicinal products that may be used during the clinical trial as described in the protocol, but not as an investigational medicinal product (e.g. any background therapy)
Assessment	A procedure used to generate data required by the study
Biologic Samples	A biological specimen including, for example, blood (plasma, serum), saliva, tissue, urine, stool, etc. taken from a study participant
Control drug	A study drug (active or placebo) used as a comparator to reduce assessment bias, preserve blinding of investigational drug, assess internal study validity, and/or evaluate comparative effects of the investigational drug
Dosage	Dose of the study treatment given to the participant in a time unit (e.g. 100 mg once a day, 75 mg twice a day)
Electronic Data Capture (EDC)	Electronic data capture (EDC) is the electronic acquisition of clinical study data using data collection systems, such as Web-based applications, interactive voice response systems and clinical laboratory interfaces. EDC includes the use of Electronic Case Report Forms (eCRFs) which are used to capture data transcribed from paper source forms used at the point of care
End of the clinical trial	The end of the clinical trial is defined as the last visit of the last participant or at a later point in time as defined by the protocol
Enrollment	Point/time of participant entry into the study at which informed consent must be obtained
Estimand	A precise description of the treatment effect reflecting the clinical question posed by the trial objective. It summarizes at a population-level what the outcomes would be in the same patients under different treatment conditions being compared. Attributes of an estimand include the population, variable (or endpoint) and treatment of interest, as well as the specification of how the remaining intercurrent events are addressed and a population-level summary for the variable.
Intercurrent events	Events occurring after treatment initiation that affect either the interpretation or the existence of the measurements associated with the clinical question of interest.
Investigational drug/ treatment	The drug whose properties are being tested in the study
Medication number	A unique identifier on the label of medication kits
Mis-randomized participants	Mis-randomized participants are those who were not qualified for randomization and who did not take study treatment, but have been inadvertently randomized into the study
Other treatment	Treatment that may be needed/allowed during the conduct of the study (i.e. concomitant or rescue therapy)
Participant	A trial participant (can be a healthy volunteer or a patient)
Participant number	A unique number assigned to each participant upon signing the informed consent. This number is the definitive, unique identifier for the participant and should be used to identify the participant throughout the study for all data collected, sample labels, etc.
Period	The subdivisions of the trial design (e.g. Screening, Treatment, Follow-up) which are described in the Protocol. Periods define the study phases and will be used in clinical trial database setup and eventually in analysis

Personal data	Participant information collected by the Investigator that is coded and transferred to Novartis for the purpose of the clinical trial. This data includes participant identifier information, study information and biological samples.
Premature participant withdrawal	Point/time when the participant exits from the study prior to the planned completion of all study drug administration and/or assessments; at this time all study drug administration is discontinued and no further assessments are planned
Randomization number	A unique identifier assigned to each randomized participant
Screen Failure	A participant who did not meet one or more criteria that were required for participation in the study
Source Data/Document	Source data refers to the initial record, document, or primary location from where data comes. The data source can be a database, a dataset, a spreadsheet or even hard-coded data, such as paper or eSource
Start of the clinical trial	The start of the clinical trial is defined as the signature of the informed consent by the first participant
Study treatment	Any drug or combination of drugs or intervention administered to the study participants as part of the required study procedures; includes investigational drug(s), control(s) or background therapy
Study treatment discontinuation	When the participant permanently stops taking any of the study drug(s) prior to the defined study treatment completion date (if any) for any reason; may or may not also be the point/time of study discontinuation
Treatment arm/group	A treatment arm/group defines the dose and regimen or the combination, and may consist of 1 or more cohorts.
Treatment of interest	The treatment of interest and, as appropriate, the alternative treatment to which comparison will be made. These might be individual interventions, combinations of interventions administered concurrently, e.g. as add-on to standard of care, or might consist of an overall regimen involving a complex sequence of interventions. This is the treatment of interest used in describing the related clinical question of interest, which might or might not be the same as the study treatment.
Variable (or endpoint)	The variable (or endpoint) to be obtained for each participant that is required to address the clinical question. The specification of the variable might include whether the participant experiences an intercurrent event.
Withdrawal of study consent (WoC)	Withdrawal of consent from the study occurs only when a participant does not want to participate in the study any longer and does not allow any further collection of personal data

Protocol summary

Protocol number	JWT629A12301
Full Title	A multi-center, randomized, double-blinded, placebo-controlled study to evaluate the safety and efficacy of hydroxychloroquine monotherapy and in combination with azithromycin in patients with moderate and severe COVID-19 disease
Brief title	Hydroxychloroquine monotherapy and in combination with azithromycin in patients with moderate and severe COVID-19 disease
Sponsor and Clinical Phase	Novartis III
Investigation type	Drug
Study type	Interventional
Purpose and rationale	Recently, there has been excitement to repurpose chloroquine and hydroxychloroquine (HCQ) for the treatment of the patients with COVID-19, therefore there is an urgent need to conduct prospective, randomized, double-blind, controlled clinical trials to definitively establish the benefit of hydroxychloroquine and the combination of hydroxychloroquine with azithromycin in patients with COVID-19 disease. This clinical trial is designed to evaluate the efficacy and safety of HCQ and HCQ in combination with azithromycin compared to a placebo in adult participants hospitalized with moderate to severe COVID-19 disease, excluding critically ill participants (i.e. those needing ICU admission or mechanical ventilation at study start).
Primary Objective(s)	The primary objective of this study is to demonstrate superiority of hydroxychloroquine or hydroxychloroquine plus azithromycin compared to placebo in achieving clinical response by Day 15. The primary clinical question of interest is: What is the effect of the hydroxychloroquine and hydroxychoroquine plus azithromycin versus placebo on the percentage of participants achieving clinical response by Day 15 in participants with moderate to severe COVID-19 disease excluding critically ill participants (i.e. those needing ICU admission or mechanical ventilation at study start) who are receiving standard of care?
Secondary Objectives	The secondary objectives are: To demonstrate superiority of hydroxychloroquine or hydroxychloroquine plus azithromycin compared to placebo in achieving viral clearance by Day 15 by assessing SARS-COV-2 PCR qualitative testing by day 15 To evaluate the time to discharge from the hospital in participants receiving hydroxychloroquine or hydroxychloroquine plus azithromycin relative to placebo by assessing time to discharge (or ready for discharge) To evaluate the time to return to pre-morbid supplemental oxygen requirement in participants receiving hydroxychloroquine or hydroxychloroquine plus azithromycin relative to placebo by assessing the time to return to pre-morbid supplemental oxygen requirements To evaluate the time to SARS-COV-2 negativity in participants receiving hydroxychloroquine or hydroxychloroquine plus azithromycin relative to placebo by assessing the time to SARS-COV-2 negativity

	To assess safety of participants receiving hydroxychloroquine or hydroxychloroquine plus azithromycin as compared to placebo by assessing the number of participants with adverse events, serious adverse events, clinically significant changes in laboratory measures, ECG and vital signs The clinical question of interest is: What is the effect of the hydroxychloroquine and hydroxychloroquine plus azithromycin versus placebo on the presence or absence of virus which will be represented by the percentage of participants achieving viral clearance by Day 15 in participants with moderate to severe COVID-19 disease excluding critically ill participants (i.e. those needing ICU admission or mechanical ventilation at study start) who are receiving standard of care?
Study design	This study is a multi-center, randomized, blinded, three-arm parallel-group, placebo-controlled trial to evaluate the safety and efficacy of hydroxychloroquine monotherapy or in combination with azithromycin in participants with moderate and severe COVID-19 disease excluding critically ill participants (i.e. those needing ICU admission or mechanical ventilation at study start). The study will include: Screening period of up to four days to obtain the informed consent and assess participant's eligibility; Treatment period of 10 days; and an observation period of an additional 30 days (until Day 40) with Day 40 being the end of study visit.
Study population	The study population will consist of approximately 444 male and female adult participants with moderate to severe COVID-19 disease excluding critically ill participants (i.e. those needing ICU admission or mechanical ventilation at study start) receiving standard of care to be randomized into hydroxychloroquine, hydroxychloroquine plus azithromycin, or placebo in 1:1:1 ratio (148 participants / arm).
Key Inclusion criteria	• Informed consent must be obtained prior to participation in the study • Adult patient ≥ 18 years old • Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)-2 infection confirmed by polymerase chain reaction (PCR) test or rapid test from respiratory tract specimen (e.g. nasopharyngeal swab) within 4 days prior to randomization • Currently hospitalized or requiring hospitalization due to COVID-19 disease
Key Exclusion criteria	• Use of other investigational drugs within 5 half-lives or 30 days of enrollment • Participation in any other clinical trial of an experimental treatment for COVID-19 within 5 half-lives or 30 days of enrollment • Expectation of concurrent treatment with other agents with actual or potential direct acting antiviral activity against SARS-CoV-2 • History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes. • Requires, in the judgement of the investigator, admission to the intensive care unit (ICU) or mechanical ventilatory support (invasive or non-invasive) prior to the initiation of study drug • Evidence of cytokine storm syndrome or multi-organ system failure or confirmed co-infection with influenza • History or current diagnosis of ECG abnormalities

	• Pregnant or lactating women
Study treatment	Hydroxychloroquine and matching placebo, azithromycin and matching placebo

Treatment of interest	The study treatment consists of:
	• Investigational drug
	  • Hydroxychloroquine (HCQ): doses of 200 mg or placebo
	  • Azithromycin (AZI): dose of 250 mg or placebo
	All participants will receive best standard of care as background therapy.
	Further details about the investigational treatment and control treatment are provided in Section 6.

Efficacy assessments	COVID-19 participant status [redacted]), SARS-COV-2 testing
Key safety assessments	Adverse event monitoring, Physical examinations, vital signs, monitoring of laboratory markers in blood and urine etc. ECGs
Other assessments	[redacted]
Data analysis	The primary efficacy endpoint (percentage of participants with clinical response by Day 15) is defined: • for participants with a pre-morbid oxygen requirement: as discharge (or ready to discharge as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤ 2L supplemental oxygen) OR survival without need for mechanical ventilation • for participants without a pre-morbid oxygen requirement: as discharge (or ready for discharge) OR survival without need for mechanical ventilation or oxygen supplementation for the last 24 hours. The primary analysis will use a logistic regression model. The secondary endpoint controlled for multiplicity, will be the percentage of participants with viral clearance (SARS-CoV-2 negativity) by day 15. This endpoint will be analyzed using a logistic regression model.
Key words	COVID-19, corona virus, SARS-CoV

1 Introduction

1.1 Background

Coronavirus (CoVs) are positive-sense single stranded enveloped RNA viruses, many of which are commonly found in humans and cause mild symptoms. Over the past two decades, emerging pathogenic CoVs capable of causing life-threatening disease in humans and animals have been identified, namely severe acute respiratory syndrome coronavirus (SARS-CoV) and Middle Eastern respiratory syndrome coronavirus (MERS-CoV).

In December 2019, the Wuhan Municipal Health Committee (Wuhan, China) identified an outbreak of viral pneumonia cases of unknown cause. Coronavirus RNA was quickly identified in some of these patients. This novel coronavirus has been abbreviated as SARS-CoV-2 and has 89% nucleotide identity with bat SARS-like-CoVZXC21 and 82% with that of human SARS-CoV-1. Initially, most of the infections outside China were travel-associated cases in those who had recently visited the city of Wuhan, and thought to have acquired the virus through contact with infected animals or contact with infected people. However, in recent weeks, the world has seen an increasing number of cases (> 800,000 confirmed cases worldwide and > 180,000 confirmed cases in the US by 31st March 2020), primarily the result of community transmission according to World Health Organization (WHO 2020).

The novel coronavirus has been designated SARS-CoV-2, and the disease caused by it has been designated COVID-19, which leads to substantial morbidity and mortality. Outbreak forecasting and mathematical modeling suggests that these numbers will continue to rise (Ferguson et al 2020). Global efforts to evaluate novel antivirals and therapeutic strategies to treat COVID-19 have intensified. There are currently no vaccine or therapies to prevent or treat SARS-CoV-2 infection. Therefore, there is an urgent public health need for rapid research and development of novel therapeutics.

Recently, there has been excitement to repurpose chloroquine and hydroxychloroquine (HCQ) for the treatment of the patients with COVID-19; these are products that were originally approved for malaria in 1949 and 1955, respectively. Both products have well-established safety profiles, with marketed use over 60 years for treatment of malaria, rheumatoid arthritis, and systemic lupus erythematosus. Both have anti-viral as well as immunomodulatory effects, including effects on innate immune pathways and downstream cytokines like IL-6 (van den Borne et al 1997). Further, there are several publications out of China on the use of chloroquine, and there are 16 clinical studies ongoing with chloroquine according to the clinical trial registry in China (accessed on March 22nd, 2020).

HCQ is reported to have a more favorable safety profile, with less toxicity and drug interactions compared to chloroquine. In addition, a recent publication has reported that compared to chloroquine, HCQ also has greater potency *in vitro* against SARS-CoV-2 (Liu et al 2020). However, hydroxychloroquine has potential short and long-term toxicities, and definitive benefit needs to be established to outweigh the known potential risks.

Data from a small open label study in France using HCQ, with or without addition of azithromycin, was recently reported (Gautret et al 2020). In this study 26 patients with COVID-19 were treated with 600 mg daily of HCQ (200 mg t.i.d.) for 10 days (with 6 of these patients also receiving azithromycin). The endpoint was virologic clearance from nasopharyngeal swabs

at Day 6. External controls included patients at another center, or patients at the same center who declined participation, or had an exclusion criteria. Six of the 26 patients were lost to follow-up (3 to ICU; 1 death; 1 left the hospital; 1 stopped treatment due to nausea). Of the remaining 20 who completed, 70% of patients with HCQ were virologically cured compared with only 12.5% of the sixteen control subjects. Further, a recent re-analysis of the data suggests a potential benefit of the combination (Lover 2020).

In addition, a small blinded, randomized, controlled study from Wuhan in patients with COVID-19 pneumonia (31 patients in the treatment group and 31 in the control group), reported after five days of treatment with hydroxychloroquine, significant improvements in the treatment group in fever, cough, and in pneumonia (Chen et al 2020). There is an urgent need to conduct prospective, randomized, double-blind, controlled clinical trials to definitively establish the benefit of hydroxychloroquine and the combination of hydroxychloroquine with azithromycin in patients with COVID-19 disease.

1.2 Purpose

This clinical trial is designed to evaluate the efficacy and safety of HCQ and HCQ in combination with azithromycin compared to a placebo in adult participants hospitalized with moderate to severe COVID-19 disease.

Patients with moderate COVID-19 disease are considered to be those with peripheral capillary oxygen saturation (SpO2) > 94% on room air and requiring hospitalization; patients with severe COVID-19 disease are those requiring hospitalization with peripheral capillary oxygen saturation (SpO2) ≤ 94% on room air, or the need for oxygen supplementation; respiratory rate >24 breaths per min; heart rate >100 beats per min; systolic blood pressure <90 mm Hg). However, in this study, participants critically ill who require mechanical ventilation or admission to an intensive care unit prior to the initiation of study treatment are excluded.

This study is being conducted to determine whether oral hydroxychloroquine can safely and effectively be used to mitigate, treat, or cure COVID-19 or limit the harm of the COVID-19 pandemic in accordance with the Secretary of the Department of Health and Human Services' (HHS's) Declaration under the Public Readiness and Emergency Preparedness Act for medical countermeasures against COVID-19 (COVID-19 Declaration) effective February 4, 2020. In addition, the purpose of this study is to test whether oral hydroxycholorquine drug product, either as a monotherapy or in combination with azithromycin, results in clinical benefit in patients hospitalized with COVID-19. This study is authorized to proceed under an approved investigational new drug application (IND) in accordance with the public health and medical response of FDA, an Authority Having Jurisdiction as described under the PREP Act, to prescribe, administer, deliver, distribute or dispense this Covered Countermeasure as defined by and following the HHS's COVID-19 Declaration.

2 Objectives and endpoints

Table 2-1 Objectives and related endpoints

Objectives	Endpoints

Primary Objective
• To demonstrate superiority of hydroxychloroquine or hydroxychloroquine plus azithromycin compared to placebo in achieving clinical response by Day 15
	Endpoints for primary objective
	The percentage of participants who achieve clinical response by Day 15 defined as:
	• For participants with a pre-morbid oxygen requirement:
	  • Discharge (or ready for discharge as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤ 2L supplemental oxygen) OR
	  • Survival without need for mechanical ventilation
	• For participants without a pre-morbid oxygen requirement:
	  • Discharge (or ready for discharge); OR
	  • Survival without need for mechanical ventilation or oxygen supplementation for the last 24 hours

Secondary Objectives	**Endpoints for secondary objectives**
• To demonstrate superiority of hydroxychloroquine or hydroxychloroquine plus azithromycin compared to placebo in achieving viral clearance by Day 15	• The percentage of participants with negative or below LLOQ SARS-COV-2 based on polymerase chain reaction (PCR) test by Day 15
• To evaluate the time to discharge from the hospital in participants receiving hydroxychloroquine or hydroxychloroquine plus azithromycin relative to placebo	• Time to discharge (or ready for discharge)
• To evaluate the time to return to pre-morbid supplemental oxygen requirement in participants receiving hydroxychloroquine or hydroxychloroquine plus azithromycin relative to placebo	For the subset of patients who require supplemental oxygen at the time of randomization: • Time to return to pre-morbid supplemental oxygen requirement
• To evaluate the time to SARS-CoV-2 negativity in participants receiving hydroxychloroquine or hydroxychloroquine plus azithromycin relative to placebo	• Time to SARS-CoV-2 negativity
• To assess safety of participants receiving hydroxychloroquine or hydroxychloroquine plus azithromycin as compared to placebo	• Number of participants with adverse events (AE), serious adverse events (SAE), clinically significant changes in laboratory measures, ECG and vital signs

Objectives	Endpoints
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

Objectives	Endpoints
[redacted]	[redacted]
[redacted]	[redacted]

2.1 Primary estimand

The primary clinical question of interest is: What is the effect of the hydroxychloroquine and hydroxychoroquine plus azithromycin versus placebo on the percentage of participants achieving clinical response by Day 15 in participants with moderate to severe COVID-19 disease who are receiving standard of care?

The justification for the primary estimand is that it will capture both the effect of the study treatments and the effect of any standard of care treatments, dosed as required that they are receiving at the time of randomization, mirroring the conditions in clinical practice. Further details can be found in Section 12.

The primary estimand is described by the following attributes:

Population: Adults at least 18 years of age, with SARS-COV-2 confirmed by PCR or rapid test ≤ 4 days prior to randomization who are currently hospitalized or who require hospitalization for COVID-19 disease. Further details about the population are provided in Section 5.

Endpoint: Clinical response by Day 15 defined for participants with a pre-morbid oxygen requirement as: Discharge (or ready for discharge as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤ 2L supplemental oxygen) OR survival without need for mechanical ventilation.

Clinical response by Day 15 defined for participants without a pre-morbid oxygen requirement as: Discharge (or ready for discharge) OR survival without need for mechanical ventilation or oxygen supplementation for the last 24 hours.

Treatment of interest: The randomized treatment (hydroxychloroquine or hydroxychloroquine plus azithromycin or placebo) added to concomitant standard of care treatments used to treat moderate-severe COVID-19 disease. Further details about the investigational treatment and control treatment are provided in Section 6.

Based on the definition of the endpoint there are no intercurrent events which need to be accounted for outside of the treatment of interest attribute of the estimand.

The summary measure: Odds-ratio comparing experimental treatments of interest to placebo

2.2 Secondary estimands

The clinical question of interest is: What is the effect of the hydroxychloroquine and hydroxychloroquine plus azithromycin versus placebo on the presence or absence of virus which will be represented by the percentage of participants achieving viral clearance by Day 15 in participants with moderate to severe COVID-19 disease who are receiving standard of care?

The justification for the secondary estimand is that it will capture both the effect of the study treatments and the effect of any standard of care treatments, dosed as required at the time of randomization, mirroring the conditions in clinical practice. Further details can be found in Section 12.

The secondary estimand is described by the following attributes:

Population: Adults at least 18 years of age, with SARS-COV-2 confirmed by PCR or rapid test ≤4 days prior to randomization who are currently hospitalized or who require hospitalization for COVID-19 disease. Further details about the population are provided in Section 5.

Endpoint: The percentage of participants with negative or below LLOQ - SARS-COV-2 based on PCR by Day 15

Treatment of interest: the randomized treatment (hydroxychloroquine or hydroxychloroquine plus azithromycin or placebo) added to concomitant standard of care, used to treat moderate-severe COVID-19 disease. Further details about the investigational treatment and control treatment are provided in Section 6.

Handling of remaining intercurrent events will be considered as treatment failures (Composite strategy):

- Death

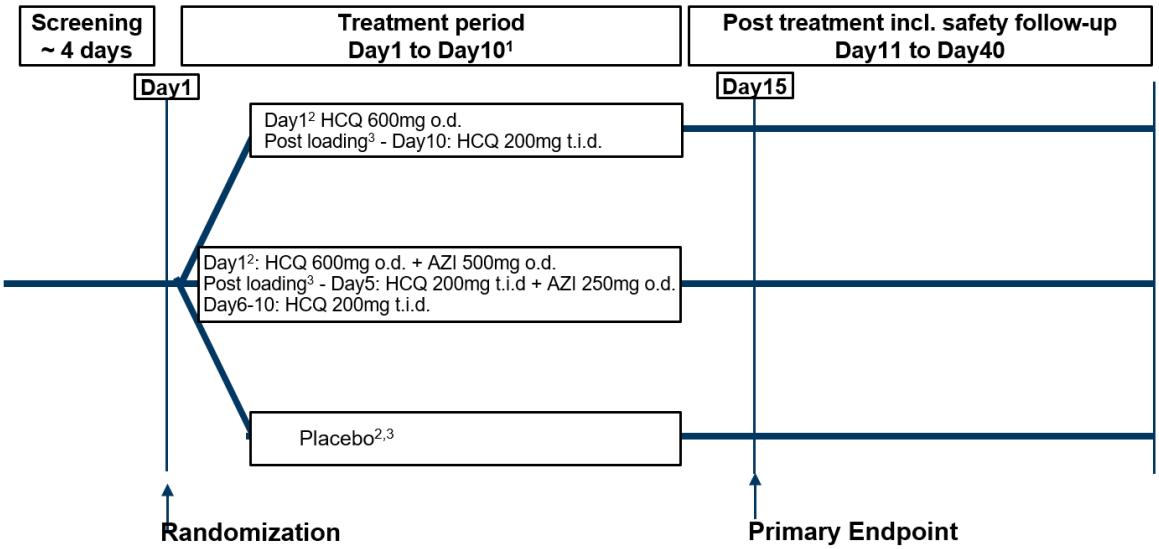
The summary measure: Odds-ratio comparing experimental treatments of interest to placebo

3 Study design

This study is a multi-center, randomized, blinded, three-arm parallel-group, placebo-controlled trial to evaluate the safety and efficacy of hydroxychloroquine monotherapy or in combination with azithromycin in participants with moderate and severe COVID-19 disease.

The study will include: Screening period of up to four days to obtain the informed consent and assess participant's eligibility; Treatment period of 10 days; and an observation period of an additional 30 days (until Day 40) with Day 40 being the end of study visit. All participants are expected to be treated with available standard of care (SoC) therapy for COVID-19 disease throughout the study. Approximately 444 participants will be randomized into either of three arms with 1:1:1 ratio. The clinical visit schedule and the details of procedures to be performed at each visit are listed in Table 8-1.

Figure 3-1 Study design



All participants will be treated with the best available standard of care for COVID-19 disease throughout the study

[1] The total treatment duration of hydroxychloroquine will be 10 days. The total treatment duration of azithromycin will be 5 days. In case a participant is discharged before the end of treatment period (Day 10) he/she may continue study medication at home until Day 10 if QTcF ≤ 480 ms at the time of discharge based on the local ECG data. Otherwise, treatment will be discontinued at the time of discharge (before Day 10).

[2] The loading dose of AZI/matching placebo (Day 1) should be taken 4 hours after loading dose of HCQ/matching placebo

[3] After HCQ/matching placebo loading dose on Day 1, the following HCQ/matching placebo doses as a maintenance therapy should be initiated within approximately 8 hours (not to exceed 12 hours).

HCQ: hydroxychloroquine, AZI: azithromycin, o.d.: once a day, t.i.d: three times a day

4 Rationale

4.1 Rationale for study design

The study is designed as a prospective randomized, double blind, placebo-controlled trial in order to reduce the likelihood of imbalances in the study population, and bias in the evaluation of clinical response. The three-arm parallel design allows contemporaneous evaluations of three treatment regimens, and mitigates confounders related to the rapidly changing landscape of therapies and outcomes across various healthcare systems.

Inclusion of hospitalized patients allows for careful assessment of clinical response and monitoring of safety. The study includes a population who is moderately to severely ill, and at risk for developing complications of COVID-19 disease, in order to demonstrate the potential benefit in the clinical response and impact on the progression of disease. The study excludes patients who are critically ill at screening to reduce efficacy and safety confounders and as there is no evidence at this stage to assume the study treatment would be beneficial at this stage of the disease.

4.1.1 Rationale for choice of background therapy

All participants will receive best standard of care as background therapy. Although there are no specific therapies approved for the treatment of COVID-19, participants with moderate and severe disease are expected to receive supportive care as dictated by local treatment guidelines. Depending on the disease severity, supportive care may include the use of oxygen supplementation, antibiotic prophylaxis, and other concomitant medications for comorbidities, ventilator support, and intensive care management in the event of disease progression.

4.2 Rationale for dose/regimen and duration of treatment

4.2.1 Rationale for hydroxychloroquine

Hydroxychloroquine is a medication approved by the US Food and Drug Administration for a variety of indications, including treatment of malaria, rheumatoid arthritis, and systemic lupus erythematosus (Schrezenmeier and Dorner 2020). Hydroxychloroquine and chloroquine are alkalinizing lysosomatropic drugs that accumulate in lysosomes (Vincent et al 2005 and Ponticelli and Moroni 2017) and block viral infection by increasing endosomal pH, which is required for viral participles to fuse with a cell. The effect of hydroxychloroquine on the replication of SARS-CoV-2 and similar coronaviruses has been recently described in the laboratory (Yao et al 2020). In addition to its antiviral properties, hydroxychloroquine treatment may inhibit several pathways relevant to COVID-19 pathology, including inhibition of viral nucleic acid-mediated activation of various innate immune pathways (Toll-like receptors 7, 8 and 9) (Schrezenmeier and Dorner 2020). Modulation of these pathways would result in inhibition of viral nucleic acid-induced cytokine production, reducing levels of interleukin (IL)-6, IL-1b, type 1 interferons (IFNs) and tumor necrosis factor (TNF), and potentially reducing the clinical sequelae of excessive immune activation, including cytokine release syndrome (CRS) (Mehta et al 2020). Furthermore, hydroxychloroquine would be expected to block other immune effector functions dependent on lysosomal-endosomal function, including antigen presentation, which in the context of excessive tissue inflammation, may also reduce tissue damage mediated by T cells. Recent small clinical studies and clinical case series in COVID-19-infected patients have suggested that hydroxychloroquine and chloroquine are superior to control treatments in inhibiting the exacerbation of pneumonia, shortening the disease, improving lung imaging findings and viral clearance. (Gao et al 2020 and Gautret et al 2020). Taken together these data suggest that hydroxychloroquine may be beneficial in the treatment of patients with moderate to severe COVID-19 disease (Colson et al 2020).

4.2.1 Rationale for combination

A recent publication (Gautret et al 2020) suggested that hydroxychloroquine treatment at doses of 600 mg daily (200 mg t.i.d) (with or without azithromycin) resulted in virologic clearance in 70% of treated COVID-19 patients compared with 12.5% of controls by Day 6. The results were most pronounced in the subjects that receive azithromycin in combination with HCQ. The mechanisms by which azithromycin may have contributed to enhanced viral clearance in this small study are unknown (Lover 2020).

Macrolide antibiotics accumulate in polymorphonuclear leukocytes and macrophages reaching high intracellular concentrations (Bosner et al 2005). A number of *in vivo* and *in vitro* studies,

as well as clinical findings, confirm macrophages as one of the target cells of macrolide antibiotics. Inhibitory effects of azithromycin on LPS-induced lung neutrophilia can be explained, at least partially, by inhibition of GM-CSF and IL-1β production by macrophages. Further, their ability to inhibit IL-6 and PGE2 production correlates with macrolide accumulation in cells, as well as with their binding to phospholipids (Banjanac et al 2012). In clinical studies, in addition to its antibacterial properties, azithromycin immunomodulatory effects have been proven beneficial in a variety of inflammatory acute and chronic lung diseases such as, community acquired pneumonia, cystic fibrosis, bronchiectasis, COPD, and others; and may be beneficial in patients with COVID-19 disease (Amsden 2005). Azithromycin will be dosed in accordance to the label for a total duration of 5 days.

4.2.2 Rationale for treatment duration

A short-term duration of 10 days is proposed. Modeling and simulation described in Section 4.2.3 suggest adequate concentrations in the lung for > 28 days. Clinical data suggest that the maximum anti-viral effect may be achieved the first 5-6 days of therapy (Gautret et al 2020), while anti-inflammatory effects may be beneficial over longer periods. When used for short periods, hydroxychloroquine is generally well tolerated, with the most common side effects including nausea, vomiting, diarrhea, rash, and headache (Ponticelli and Moroni 2017). Further, in double-blind trials in patients with rheumatoid arthritis, 6 weeks of treatment with HCQ at 400 mg/day (n =71), 800 mg/day (n= 71), and 1,200 mg/day (n= 66), followed by 18 weeks of open label HCQ treatment at 400 mg/day, toxicity was not dose related and was relatively mild. In particular, 800 mg/day and 1,200 mg/day HCQ dosages were not associated with more ocular toxicity compared with the 400 mg/day (Furst et al 1999). The protocol exclusion criteria will be in place based on the known safety profile of HCQ, and the sponsor will closely monitor safety.

4.2.3 Rationale for dose regimen

The proposed hydroxychloroquine (HCQ) regimen is 600 mg loading dose followed by 200 mg three times daily for the first 10 days of the study. The total treatment duration of hydroxychloroquine will be a maximum of 10 days. The approach includes a loading dose on Day 1 to reach the target concentration in the lung tissue within the first 5 hours. The proposed regimen is expected to enable optimal inhibition of both viral and inflammatory pathways by HCQ. Three times a daily regimen is selected to mitigate Cmax related to cardiac safety risk.

Recently published literature describes the effect of HCQ on the replication of SARS-CoV-2 and similar coronaviruses, *in vitro*. Full dose response curves of the antiviral activity of HCQ in an *in vitro* assay using Vero E6 kidney epithelial cells infected with SARS-CoV-2 have been published (Yao et al 2020). Depending on the time point (24 or 48 hours post infection) the EC50 values range from 0.72 – 6.25 µM and the EC90 values from 1.5 – 15 µM. Furthermore, HCQ EC50 values of 8 µM have been reported in similar *in vitro* assays for other human-tropic coronaviruses (Dyall et al 2014). Based on the totality of in vitro data, we anticipate a significant effect of HCQ on SARS-CoV-2 viral load in patients at an HCQ target concentrations of greater than 15 µM (5040 ng/mL) of free base in lung tissue.

The HCQ PK model was constructed based on published clinical data (Tett et al 1988 and Tett et al 1989). The combined clinical data was best described by a 3-compartment model with

absorption into and linear elimination from the central compartment, and distribution into peripheral compartments. The human PK parameters from the 3-compartment model are summarized in Table 4-1. The simulations took into consideration that an oral dosage form of 200 mg hydroxychloroquine sulfate contains 155 mg hydroxychloroquine. The large volume of distribution indicates that HCQ is highly bound to tissues. To simulate the concentration of HCQ in the lung we assume direct and rapid partitioning from the central compartment with a partition coefficient of Kp = 50.6 (Wei et al 1995).

The simulated concentration time curves for HCQ in the lung and blood for either 600 mg o.d. HCQ sulfate (light gray, regimen),or a loading dose of 600 mg followed by 200mg t.i.d. (dark red) are presented in Figure 4-1. Additionally, co-administration of azithromycin is not expected to have an effect on HCQ concentrations (Yeates et al 1996 and Mattila et al 1994).

The dosing regimen of 600 mg loading dose followed by 200 mg t.i.d. hydroxychloroquine sulfate enables rapid attainment and maintenance of the target lung concentration of 15 µM. Table 4-2 summarizes the Cmax, Cmin and AUC values for HCQ in blood.

Figure 4-1 Predicted concentrations of hydroxychloroquine in the lung and blood compartments

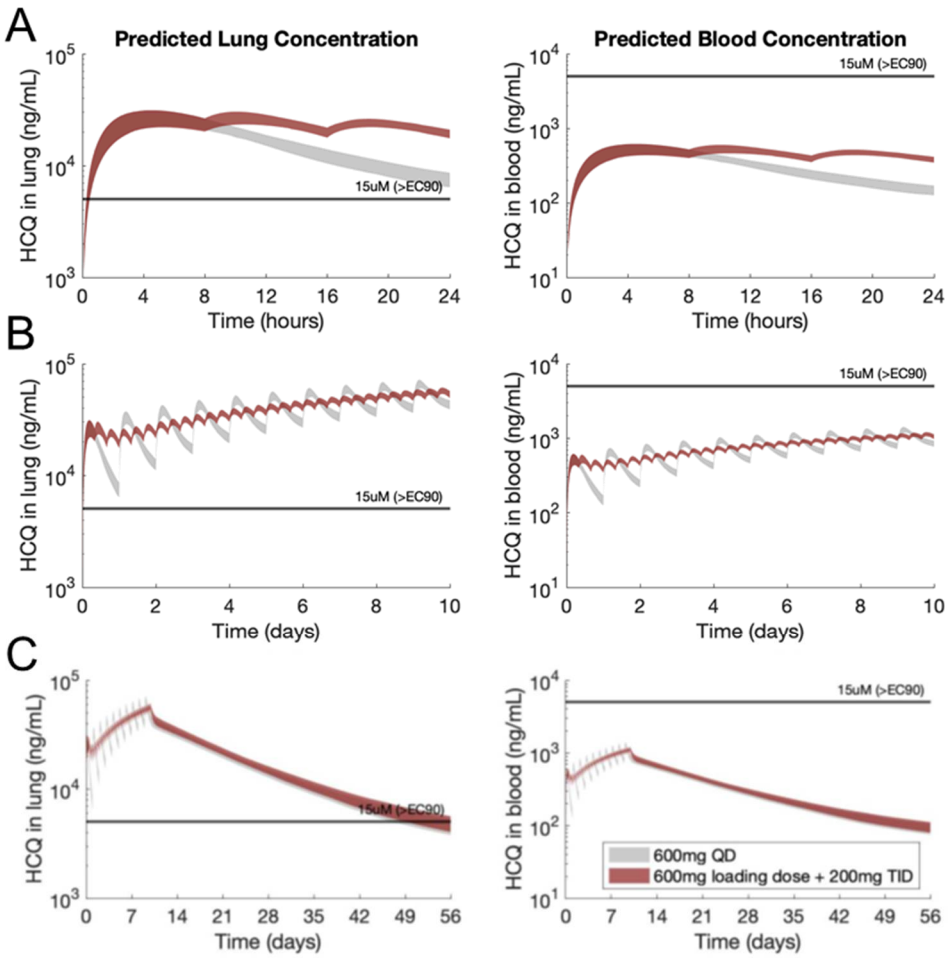


Figure 4-1: A regimen consisting of a 600 mg HCQ sulfate loading dose on Day 1 followed by 200 mg t.i.d. (red) is compared against a 600mg o.d. regimen (grey). While the y-axis represents concentrations of HCQ (free base), doses are expressed as HCQ sulfate tablets. The horizontal line denotes a target threshold of 15 µM (5040 ng/mL). a) Predicted PK profile for day 1 b) Predicted PK profile from day 1 to day 10 C) Predicted PK profile followed by a washout period to reach the threshold of EC90.

Table 4-1 Human PK parameters from 3-compartment model describing human total blood hydroxychloroquine

Parameter	Units	Estimate	95% Confidence Interval
V1	L	193.6	[161.1,228.7]
V2	L	3519.1	[3024.6,4150.2]
CL	L/h	5.67	[5.37,5.99]
Q12	L/h	2.42	[1.95,3.05]
ka	1/h	0.156	[0.125, 0.199]
F	dimensionless	0.79 (fixed)	
V3	L	2274.5	[2021.1,2546.1]
Q13	L/h	47.5	[40.9,54.9]

Table 4-2 Predicted human exposure for 600 mg loading dose and 200 mg t.i.d. maintenance dose of hydroxychloroquine sulfate

		Mean	95% Confidence Interval
Cmax (ng/mL)	Day 1, 0-8hr	511.8	[433.2, 600.3]
	Day 1	525.2	[460.9, 600.3]
	Day 10	1128.6	[1059.4, 1197.8]
Cmin (ng/mL)	Day 1	382.15	[342.4, 417.8]
	Day 10	1012.5	[944.4, 1087.3]
AUC (ng/mL*hr)	Day 1	10603	[9484, 11696]
	Day 10	25690	[24080, 27413]

4.3 Rationale for choice of control drugs (comparator/placebo) or combination drugs

All participants will receive best standard of care for the treatment of COVID-19 disease and therefore placebo is only used to control the blind for the arms.

4.4 Purpose and timing of interim analyses/design adaptations

No formal interim analysis is planned for this trial. The primary endpoint analysis will be performed after all participants have completed Day 15 or discontinued prior to Day 15. A final analysis will be performed after all participants have completed their last follow-up visit at Day 40 (or discontinued prior to Day 40).

4.5 Risks and benefits

Appropriate eligibility criteria and clinical safety monitoring criteria are included in this protocol. The risk to participants in this trial may be minimized by compliance with the eligibility criteria and study procedures, as well as close clinical monitoring. Refer to the Hydroxychloroquine USPI (2018)/applicable labelling information.

There are currently no drugs approved for the treatment of patients with COVID-19, and there is a high medical need to control the global pandemic. Given the results of studies outlined above, HCQ as monotherapy or in combination with azithromycin, along with standard of care (SoC) treatment, offers a prospect of benefit in patients with moderate to severe COVID-19 disease more effectively than current SoC alone. Safety data have previously been generated on the use of HCQ and azithromycin in other indications. Therefore, a placebo-controlled study in combination with SoC is justified to address the high unmet need in the target patient population.

The safety profile of HCQ is described in the USPI/ applicable labelling information and also re-iterated in the FDA HCQ fact sheet for health care providers Emergency Use Authorization (EUA) dated 3/28/2020. Long term use has been associated with ocular toxicity and caution in administration to patients with hepatic/renal disease are well known. Investigators should also be aware that other precautions should be taken as per label (e.g. participants with glucose -6-phophate dehydrogenase (G-6-PD) deficiency) and anticipate any potential drug interactions. For azithromycin, equal diligence should be in place for participants with impaired liver function (primary elimination via liver) and impaired renal function. There are clinical safety hepatic and renal monitoring guidance in place and should be easily monitored in the hospital

setting. Participants should also be closely monitored for signs and symptoms of hypoglycemia, particularly those who are diabetic and taking anti-diabetic medications. More relevant to the short term administration of HCQ and azithromycin is drug-induced QT interval prolongation and potential pro-arrhythmic effects. To that end, in addition to relevant cardiac exclusion criteria, participants will also need to follow cardiac safety monitoring, with clear guidance on when to discontinue study medications with regard to QTcF changes. In the setting of active COVID-19 disease in the study population, the benefits of short-term treatment in a hospital setting should, in principle outweigh the known potential risks.

Women of child-bearing potential and sexually active males must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study, and agree that in order to participate in the study they must adhere to the contraception requirements outlined in the exclusion criteria. If there is any question that the participant will not reliably comply, they should not be entered or continue in the study.

5 Study Population

The study population will consist of approximately 444 male and female adult participants with moderate to severe COVID-19 disease receiving standard of care to be randomized into hydroxychloroquine, hydroxychloroquine plus azithromycin, or placebo in 1:1:1 ratio (148 participants / arm).

5.1 Inclusion criteria

Participants eligible for inclusion in this study must meet **all** of the following criteria prior to randomization:

1. Informed consent must be obtained prior to participation in the study
2. Adult patient ≥ 18 years old
3. Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV)-2 infection confirmed by polymerase chain reaction (PCR) test or rapid test from respiratory tract specimen (e.g. nasopharyngeal swab) within 4 days prior to randomization
4. Currently hospitalized or requiring hospitalization due to COVID-19 disease

5.2 Exclusion criteria

Participants meeting any of the following criteria are not eligible for inclusion in this study.

1. Use of other investigational drugs within 5 half-lives or 30 days of enrollment whichever is longer
2. Participation in any other clinical trial of an experimental treatment for COVID-19 within 5 half-lives or 30 days of enrollment whichever is longer
3. Expectation of concurrent treatment with other agents with actual or potential direct acting antiviral activity against SARS-CoV-2 during study drug dosing period, including but not limited to oseltamivir and protease inhibitors
4. History of hypersensitivity to any of the study treatments or its excipients or to drugs of similar chemical classes.

5. Requires, in the judgement of the investigator, admission to the intensive care unit (ICU) or mechanical ventilatory support (invasive or non-invasive) prior to the initiation of study drug

   (There might be a participant who cannot be admitted to the ICU, even if the participant's condition is severe enough, due to administrative reasons under the current circumstances. This case is also considered under admission to the ICU judged by the investigator)
6. Evidence of cytokine storm syndrome or multi-organ system failure
7. Confirmed co-infection with influenza
8. Creatinine clearance < 45 mL/min or requiring acute renal replacement therapy
9. History or current diagnosis of ECG abnormalities indicating significant risk of safety for participants participating in the study such as:
   - Concomitant clinically significant cardiac arrhythmias, e.g. sustained ventricular tachycardia, and clinically significant second or third degree AV
   - History of familial long QT syndrome or known family history of Torsades de Pointe
   - QTcF > 480 msec (at screening and/or Day 1 at pre-dose) based on the local ECG data
   - Uncorrected electrolyte abnormalities, such as hypokalemia, hypomagnesemia and hypocalcemia
   - Use of agents known to prolong the QT interval within 5 half-lives before screening
10. Any other condition (e.g. known liver disease) which, in the opinion of the investigator, would put the safety of the participant at risk, impede compliance or hinder completion of the study
11. Pregnant or nursing (lactating) women
12. Women of child-bearing potential, defined as all women physiologically capable of becoming pregnant, **unless** they are using basic methods of contraception during dosing of study treatment. Basic contraception methods include:
    - Total abstinence (when this is in line with the preferred and usual lifestyle of the participant. Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
    - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy), total hysterectomy, or tubal ligation at least six weeks before taking investigational drug. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
    - Male sterilization (at least 6 months prior to screening). For female participants on the study, the vasectomized male partner should be the sole partner for that participant
    - Barrier methods of contraception: Condom or Occlusive cap (e.g. diaphragm or cervical/vault caps).
    - Use of oral, (estrogen and progesterone), injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone

contraception or placement of an intrauterine device (IUD) or intrauterine system (IUS).

In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.

Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy), total hysterectomy or bilateral tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of child bearing potential.

If local regulations deviate from the contraception methods listed above to prevent pregnancy, local regulations apply and will be described in the ICF.

6 Treatment

6.1 Study treatment

6.1.1 Investigational and control drugs

The study treatment consists of:

- Investigational drug
  - Hydroxychloroquine (HCQ): doses of 200 mg or placebo
  - Azithromycin (AZI): dose of 250 mg or placebo

Table 6-1 Investigational and control drug

Investigational/ Control Drug	Pharmaceutical Dosage Form	Route of Administration	Supply Type	Sponsor (global or local)
HCQ 200 mg	Tablet	Oral use	Open label	Sponsor global
HCQ Placebo	Tablet	Oral use	Open label	Sponsor global
AZI 250 mg	Tablet	Oral use	Open label	Sponsor global
AZI Placebo	Tablet	Oral use	Open label	Sponsor global

6.1.2 Treatment arms/group

Participants will be assigned at Day 1 to one of the following 3 treatment arms in a ratio of 1:1:1. The treatment arms include:

Arm 1: hydroxychloroquine (HCQ) plus azithromycin (AZI) placebo

- HCQ: 600mg o.d. as loading dose (Day 1) followed by 200 mg t.i.d. The time between the 600mg loading dose and first 200mg dose should be 8-hours (not to exceed 12 hours)
- AZI placebo o.d. The loading dose of AZI placebo (Day 1) should be taken 4 hours after loading dose of HCQ

Arm 2: hydroxychloroquine (HCQ) plus azithromycin (AZI)

- HCQ: 600 mg o.d. as a loading dose (Day 1) followed by 200 mg t.i.d.. The time between the 600mg loading dose and first 200mg dose should be 8-hours (not to exceed 12 hours)
- AZI: 500 mg as a loading dose (Day 1) followed by 250 mg o.d. Day 2 – Day 5. The 500mg loading dose of AZI (Day 1) should be taken 4 hours after loading dose of HCQ

Arm 3: hydroxychloroquine (HCQ) placebo plus azithromycin (AZI) placebo

- HCQ placebo o.d. (Day 1) followed by HCQ placebo t.i.d. The time between the first and the second dose should be 8 hours (not to exceed 12 hours) to match other treatment arms.
- AZI placebo o.d. The loading dose of AZI placebo (Day 1) should be taken 4 hours after loading dose of HCQ placebo

6.1.3 Treatment duration

The total treatment duration of hydroxychloroquine is 10 days. The approach to include a loading dose on Day 1 is preferred in order to rapidly reach higher target tissue drug concentrations. The total treatment duration of azithromycin will be 5 days.

In case a participant is discharged prior to Day 10, they may complete study treatment as planned, at home, until Day 10 if QTcF $\leq$ 480 ms at the time of discharge based on the local ECG data. Otherwise, treatment will be discontinued at the time of discharge.

6.2 Other treatment(s)

6.2.1 Concomitant therapy

All relevant medications, procedures, and significant non-drug therapies (e.g. blood transfusions) administered after the participant was enrolled into the study must be recorded on the appropriate Case Report Forms (CRFs).

6.2.1.1 Standard of care for COVID-19 disease

All participants will receive best standard of care as background therapy. Although there are no specific therapies approved for the treatment of COVID-19, participants with moderate and severe disease are expected to receive supportive care as dictated by local treatment guidelines. Depending on the disease severity, supportive care may include the use of oxygen supplementation, antibiotic prophylaxis and other concomitant medications for comorbidities, ventilator support, and intensive care management for disease progression.

The study permits any of standard of care for COVID-19 disease except the medications listed in the prohibited medication in Table 6-2.

6.2.2 Rescue medication

Rescue therapy may be used at the discretion of the Investigator if there is evidence of clinical deterioration of COVID-19 disease and intervention with a rescue therapy is required beyond the standard of care measures.

6.2.3 Prohibited medication

Table 6-2 Prohibited medication

Medication	Prohibition period
Any drug known to prolong QTc interval (See https://crediblemeds.org/ for details as well as protocol supplementary guidance)	Within 5 half-lives before screening and throughout the study
Antiviral agents e.g. remdesivir, oseltamivir, interferon, lopinavir/ ritonavir or other protease inhibitors, chloroquine, nitazoxanide, convalescent COVID19 serum or anti-SARS-COV-2 immunoglobulins	Up to Day 15 or until discharge whichever earlier Except in the case these are needed to be used as rescue therapy (see Section 6.2.2)
Newly approved COVID-19 therapies (if any available since issuing the protocol)	Within 5 half-lives or 30 days of screening whichever is longer, and up to Day 15 or until discharge whichever earlier. Except in the case these are needed to be used as rescue therapy (see Section 6.2.2)

6.3 Participant numbering, treatment assignment, randomization

6.3.1 Participant numbering

Each participant is identified in the study by a Participant Number (Participant No.), that is assigned when the participant is enrolled for screening and is retained for the participant throughout his/her participation in the trial. A new Participant No. will be assigned at every subsequent enrollment if the participant is re-screened. The Participant No. consists of the Center Number (Center No.) (as assigned by Novartis to the investigative site) with a sequential participant number suffixed to it, so that each participant's participation is numbered uniquely across the entire database. Upon signing the informed consent form, the participant is assigned to the next sequential Participant No. available.

Participant numbers are assigned when the site creates the first entry for the participant in the CRF, therefore CRF entry must be created prior to contacting the Interactive Response Technology system.

6.3.2 Treatment assignment, randomization

At Day 1, all eligible participants will be randomized via Interactive Response Technology (IRT) to one of the treatment arms. The unblinded pharmacist will contact the IRT after confirmation from the investigator or his/her delegate that the participant fulfills all the inclusion/exclusion criteria. The IRT will assign a randomization number to the participant, which will be used to link the participant to a treatment arm and the unblinded pharmacist will be provided with the treatment arm assigned to the participant.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from participants and investigator staff. A participant randomization list will be produced by the IRT provider using a validated system

that automates the random assignment of participant numbers to randomization numbers. These randomization numbers are linked to the different treatment arms.

The randomization scheme for participants will be reviewed and approved by a member of the Randomization Office.

The unblinded pharmacist MUST NOT communicate the information of treatment arm to anyone who is involved to the study (site personnel including the investigator, participant, sponsor). If accidentally communicated to anyone, Novartis local monitor should be notified and the study treatment should be discontinued.

6.4 Treatment blinding

The study will be double-blind as both Investigator and participants will be blinded to the study medication from the time of randomization until the final database is locked after the last follow-up visit at Day 40.

Open label supply of investigational treatments (HCQ and AZI) and similar appearance placebo will be provided at site to the unblinded site pharmacist.

Unblinding will occur in the case of participant emergencies and will only be undertaken by the investigator (See Section 6.5.2). The unblinded pharmacist is not involved in emergency unblinding.

Designated Novartis clinical trial team members will be unblinded following data extraction for the primary endpoint analysis (Day 15) to perform the analysis.

Other Novartis team members, Investigators and participants will remain blinded to individual treatment allocation until final database lock. In addition, for the purposes of the Data Monitoring Committee (DMC) analysis, there will be unblinded Independent Statisticians and Programmers in charge of DMC reporting activities.

6.5 Additional treatment guidance

6.5.1 Treatment compliance

The unblinded pharmacist must record all study treatment dispensed in the Drug Accountability Log, which must not be shared with blinded members of the site staff.

The site staff must record the date and time of dosing for each medication in the source documents for the participant.

In the case that a participant is discharged prior to Day 10, they should be instructed on the dosing requirements and contacted at Day 10 to confirm compliance. The participant must also be instructed to contact he investigator if he/she is unable for any reason to take the study treatment as prescribed.

Compliance will be assessed by the investigator and/or study personnel at each visit using the information provided by the participant. This information should be captured in the source documents.

6.5.2 Emergency breaking of assigned treatment code

Emergency code breaks must only be undertaken when it is required to in order to treat the participant safely. Blinding codes may also be broken after a participant discontinues treatment due to disease progression if deemed essential to allow the investigator to select the participant's next treatment regimen, and after discussion and agreement with the sponsor. Most often, study treatment discontinuation and knowledge of the possible treatment assignments are sufficient to treat a study participant who presents with an emergency condition. Emergency treatment code breaks are performed using the IRT. When the investigator contacts the system to break a treatment code for a participant, he/she must provide the requested participant identifying information and confirm the necessity to break the treatment code for the participant. The investigator will then receive details of the investigational drug treatment for the specified participant and a fax or email confirming this information. The system will automatically inform the Novartis monitor for the site and the study team that the code has been broken.

It is the investigator's responsibility to ensure that there is a dependable procedure in place to allow access to the IRT/code break cards at any time in case of emergency. The investigator will provide:

- protocol number
- name
- participant number

In addition, oral and written information must be provided to the participant on how to contact his/her backup in cases of emergency, or when he/she is unavailable, to ensure that un-blinding can be performed at any time.

6.6 Preparation and dispensation

Each study site will be supplied with study drug in packaging as described under investigational and control drugs section.

As per the treatment assigned to the participant, the unblinded pharmacist will select the study treatment to be dispensed to the participant.

6.6.1 Handling of study treatment and additional treatment

6.6.1.1 Handling of study treatment

In order to ensure treatment blinding study treatment must be received, stored in a secure location and dispensed only by an unblinded pharmacist. All study treatment must be stored according to the instructions specified on the labels.

Clinical supplies are to be dispensed only in accordance with the protocol. Technical complaints are to be reported to the respective Novartis Country Organization Quality Assurance.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the study treatment but no information about the participant except for the medication number.

An accurate record of the shipment and dispensing of study treatment should be maintained in a drug accountability log. Monitoring of drug accountability will be performed by monitors during site visits or remotely and at the completion of the trial.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused study treatment, packaging, drug labels, and a copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

7 Informed consent procedures

Eligible participants may only be included in the study after providing (witnessed, where required by law or regulation), IRB/IEC-approved informed consent.

If applicable, in cases where the participant's representative(s) gives consent (if allowed according to local requirements), the participant must be informed about the study to the extent possible given his/her understanding. If the participant is capable of doing so, he/she must indicate agreement by personally signing and dating the written informed consent document.

Informed consent must be obtained before conducting any study-specific procedures (e.g. all of the procedures described in the protocol). The process of obtaining informed consent must be documented in the participant source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guidelines and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed by Novartis before submission to the IRB/IEC.

Information about common side effects already known about the investigational drugs can be found in the USPI/applicable labelling information. This information will be included in the participant informed consent and should be discussed with the participant during the study as needed. Any new information regarding the safety profile of the investigational drugs that is identified between labelling updates will be communicated as appropriate, for example, via an investigator notification or an aggregate safety finding. New information might require an update to the informed consent and then must be discussed with the participant.

The following informed consents are included in this study:

- Main study consent, which also includes:
  - A subsection that requires a separate signature for the ‘Optional Consent for Additional Research’ to allow future research on data/samples collected during this study
- As applicable, Pregnancy Outcomes Reporting Consent for female subjects or the female partners of any male subjects who took study treatment

Women of child bearing potential must be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirements.

Male participants must be informed that if a female partner becomes pregnant while he is enrolled in the study, contact with the female partner will be attempted to request her consent to collect pregnancy outcome information.

A copy of the approved version of all consent forms must be provided to Novartis after IRB/IEC approval.

8 Visit schedule and assessments

The Assessment Schedule (Table 8-1) lists all of the assessments when they are performed. All data obtained from these assessments must be supported in the participant's source documentation.

Participants should be seen for all visits/assessments as outlined in the assessment schedule (Table 8-1) or as close to the designated day/time as possible. Missed or rescheduled visits should not lead to automatic discontinuation.

Table 8-1 Assessment schedule

Period	Screening	Treatment						Post treatment		
Visit Name	Screening	Day 1	Day 2	Day 4	Day 6	Day 8	Day 10/ early discharge	Day 15 / early withdrawal Primary Endpoint	End of study follow up	Unscheduled[1] (report assessments as applicable)
Days	-3 to 0	1	2	4	6	8	10	15	40	-
Informed consent	X									
Inclusion / Exclusion criteria	X	X								
Demography	X									
Medical history/current medical conditions	X									
Chest imaging	X[3]							X[3]		
Randomization		X								
Drug dispensation and administration		X								
Pregnancy test (serum and urine dipstick)	X									
Physical Examination, vital signs and body measurements[2]	X	X	X	X	X	X	X			X
SARS-COV-2 test	X[4]	X			X		X			X
Electrocardiogram (ECG)	X	X[5]	X	X	X[6]		X[6]			X
[redacted]										
Laboratory assessments (hematology, chemistry, urinalysis, [redacted])[7]	X			X			X	X[3]		
Biomarker plasma and serum		X					X	X		
Prior and concomitant medications	X									
Adverse Events	X									
Study completion information		X								

X Assessment to be recorded in the clinical database or received electronically from a vendor, [1] All assessments for unscheduled visits are optional, [2]Height and weight collected at screening only, [3] If available record findings, [4] If results of a previously performed test within 4 days prior to planned randomization are available this does not need to be repeated for screening [5] pre-dose and 4 hours post dose, [6] If required in the opinion of the Investigator. [7]Hematology: Hct, Hgb, PLT, RBC, WBC, differential WBC count; Chemistry: ALP, ALT, AST, Ca, Mg, K, creatinine, direct and total bilirubin, BUN, glucose, troponin (I or C), CPK, [redacted]

8.1 Screening

Screening

The screening period will be a maximum of 4 days, and is used to check the participant's eligibility after obtaining informed consent and prior to the randomization on Day 1. The assessments required at screening are summarized in Table 8-1. If all eligibility criteria are confirmed screening and randomization may occur on the same day.

8.1.1 Information to be collected on screening failures

Participants who consented and are subsequently found to be ineligible prior to randomization will be considered a screen failure. The reason for screen failure should be recorded on the appropriate Case Report Form. The demographic information, informed consent, and Inclusion/Exclusion pages must also be completed for screen failure participants. No other data will be entered into the clinical database for participants who are screen failures, unless the participant experienced a serious adverse event during the screening phase (see SAE section for reporting details). If the participant fails to be randomized, the IRT must be notified within 2 days of the screen fail that the participant was not randomized.

Participants who are randomized and fail to start treatment, e.g. participants randomized in error, will be considered an early terminator. The reason for early termination should be recorded on the appropriate Case Report Form.

8.2 Participant demographics/other baseline characteristics

All baseline assessments must be performed prior to first study treatment administration. These may be in the screening period (e.g. demographics) or at the randomization visit, depending on the assessment.

8.2.1 SARS-COV-2 testing

Respiratory tract specimen (e.g. nasopharyngeal swab, mid-nasal swab) will be taken for SARS-COV-2 PCR or rapid test and analyzed locally whether negative (or below LLOQ) or not to determine eligibility. If results of a previously performed test within 4 days prior to planned randomization date are available this does not need to be repeated for screening.

8.2.2 Demographic information

Demographic data to be collected at screening on all participants include: year of birth or age, gender, race, ethnicity and child-bearing potential (for females only).

Any relevant medical history including date of onset of COVID-19 disease symptoms, date of diagnosis of COVID-19 disease protocol solicited medical history, and/or current medical conditions before obtaining informed consent will be recorded in the Medical History CRF. Significant findings that are observed after the participant has provided informed consent and that meet the definition of an AE must also be recorded in the AE CRF. Whenever possible, diagnoses and not symptoms will be recorded.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgment, the test abnormality occurred prior to the informed consent signature.

8.2.3 Prior and concomitant medications

Relevant prior and concomitant medications will be captured at the screening visit, and updated at the baseline visit. Any changes to the ongoing medications or any new concomitant medications will be recorded in CRF on an ongoing basis throughout study participation.

[redacted]

8.2.5 Other baseline characteristics

Baseline characteristic data to be collected for all participants listed below:

- ECG, vital signs, height and body weight
- [redacted]
- date and matrix (nasopharyngeal, oropharyngeal, other) of SARS-COV-2 test
- physical examination (to be recorded in source documents only)
- chest imaging (date and method of assessment – x-ray or CT scan, normal or abnormal – any clinically relevant findings to be reported in medical history)
- Any other testing required for inclusion/exclusion criteria

8.3 Efficacy

8.3.1 COVID-19 Participant status

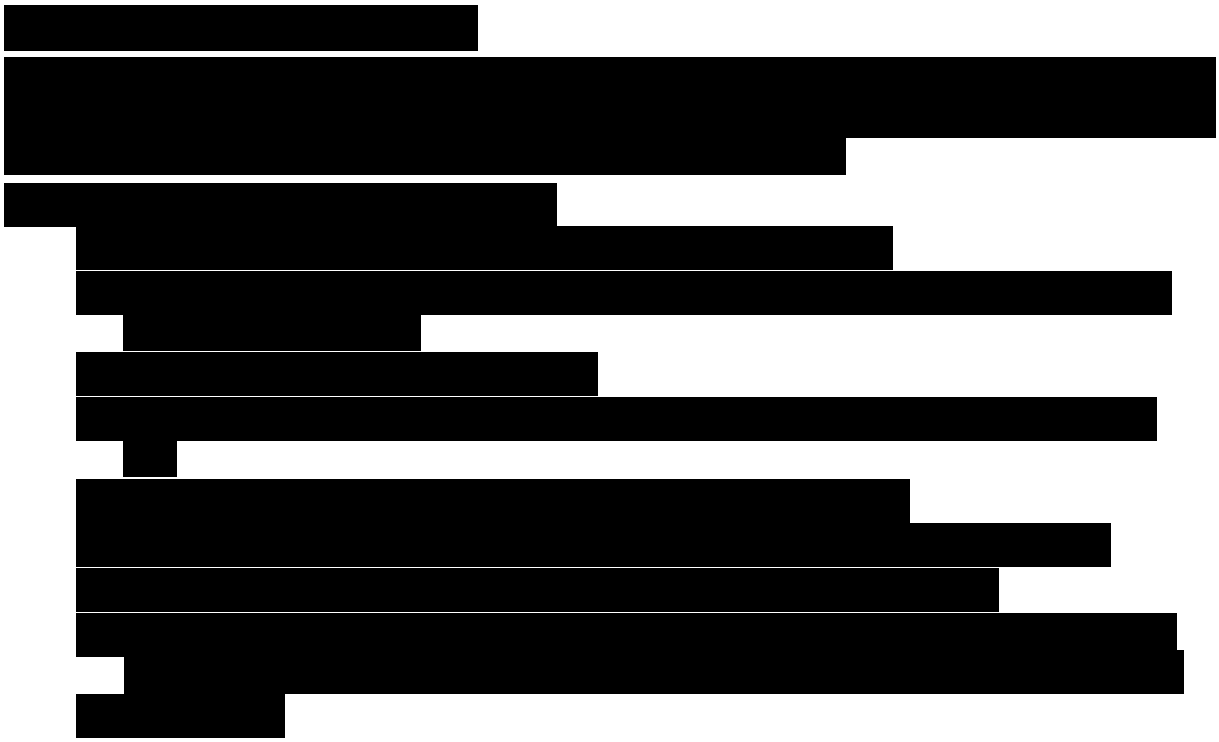
The following details on the participants' status will be collected in the at Baseline and hospital discharge at a minimum, in addition any change in status must be reported in the CRF:

- Hospitalization (including dates of admission and discharge* or ready for discharge)
- ICU stay (including dates of admission** and discharge***)
- Pre-morbid supplemental oxygen requirements and its volume if yes (start and stop dates, volume: L)
- Mechanical ventilation requirements (start and stop dates)
- Participant survival status (i.e. death)
- [redacted]

* If a participant is unable to be discharged due to administrative reasons, then the date that the participant, in the opinion of the investigator, is ready to be discharged (i.e. ready for discharge as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤ 2L supplemental oxygen) should be reported in the hospitalization status for date of discharge.

** In the case that a participant cannot be admitted to the ICU, even if the participant's condition is severe enough in the opinion of the investigator (e.g. due to administrative reasons under the current circumstances), this is also considered under admission and date of ICU admission should be reported

***If a participant is unable to be discharged from ICU due to administrative reasons, then the date that the participant, in the opinion of the investigator, is ready to be discharged should be reported in the ICU status for date of discharge.



8.3.2 SARS-COV-2 testing

At each SARS-COV-2 testing time point post screening detailed in Table 8-1 a respiratory tract specimen (nasopharyngeal swab) will be taken for SARS-COV-2 PCR testing. This sample will be analyzed at a specialist virology lab to determine whether negative (or below LLOQ) or not. An additional sample may be collected and sent to the central lab for future quantitative analysis. Additional details on sample collection and shipping are provided in the laboratory manual.

In order to maintain consistency, every effort should be made to use the same sample site (i.e. nostril) for all post baseline assessments in individual participants.

8.3.3 Appropriateness of efficacy assessments

Efficacy assessments are assessments of standard supportive care required to treat COVID-19 disease. Events that are clearly consistent with the expected pattern of progression of the underlying disease should not be recorded as adverse events (with the exception of death due to COVID-19 disease progression). These data will be captured as efficacy assessment data only.

8.4 Safety and tolerability

Safety assessments are specified below with the assessment schedule detailing when each assessment is to be performed.

For details on AE collection and reporting, refer to AE section.

8.4.1 Physical examination

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to informed consent being obtained must be included in the Relevant Medical History/Current Medical Conditions CRF. Significant findings made after informed consent is given which meet the definition of an Adverse Event must be recorded on the Adverse Event screen of the participants CRF.

8.4.2 Vital signs and body measurements

Systolic and diastolic blood pressure (mmHg), pulse rate (bpm), will be recorded. Peripheral oxygen saturation (SpO2, %) should be also measured at the same time as vital signs, height in centimeters (cm) will be reported at screening visit only.

Weight in pounds (lbs) or kilograms (kg), and body temperature (including method of collection) in Centigrade (°C) or Fahrenheit (°F) will be recorded.

8.4.3 Laboratory evaluations

Laboratory test will be conducted as per Table 8-1 by local lab. Details on the parameters are listed below in Table 8-2.

Clinically significant abnormal results for hematology, chemistry and urinalysis will be reported in the laboratory results CRF and as an AE, otherwise all these results will be kept in the source documents and will not need to be recorded in CRF. [redacted]

Table 8-2 Laboratory parameters (local lab)

Test Category	Test Name
Hematology	Hematocrit, hemoglobin, platelets, red blood cells, white blood cells (WBC), absolute differential WBC count (basophils, eosinophils, lymphocytes, monocytes, neutrophils, bands, other)
Chemistry	Alkaline phosphatase, alanine transaminase (ALT), aspartate aminotransferase (AST), calcium, magnesium, potassium, creatinine, direct bilirubin, total bilirubin, blood urea nitrogen (BUN), glucose, troponin (I or C as available), CPK
Urinalysis (dipstick)	Specific gravity, pH, protein, glucose and blood
Pregnancy Test	Serum / Urine pregnancy test
[redacted]	[redacted]

8.4.4 Electrocardiogram (ECG)

ECGs (preferably 12-lead) must be recorded after 10 minutes rest in the supine position to ensure a stable baseline. The preferred sequence of cardiovascular data collection during study

visits is ECG collection first, followed by vital signs. The Fridericia QT correction formula (QTcF) should be used for clinical decisions.

On Day 1 an ECG must be performed pre-dose and at 4 hours post dose.

Single ECGs (preferably 12-lead) will be collected using the sites own ECG machines and key parameters and the original trace available within the source data. A copy of the local tracing will be sent to a central ECG reader for additional safety evaluations. Any identifier details must be redacted e.g. subject initials, date of birth prior to sending to the central reader.

If participants are monitored by continuous telemetry, an assessment should be reported in the CRF for one time point on days when ECG monitoring is required and a copy of ECG tracing for this time point sent to the central ECG reader. In case of clinically significant findings the unscheduled visit can be used to report findings and an adverse event form completed if applicable.

For any ECGs with potential participant safety concerns, two additional ECGs (preferably 12-lead) must be performed to confirm the safety finding. A local monitoring or review process should be in place for clinically significant ECG findings throughout the study. Clinically significant abnormalities must be recorded on the CRF as either medical history/current medical conditions or adverse events as appropriate.

Given the known QT prolonging effect and treatment regimen of both HCQ and AZI, measure ECG until Day 4, then if required by the investigator from Day 6.

Please also refer to the cardiac safety monitoring Section 10.2.1 for additional details.

8.4.5 Pregnancy test

All pre-menopausal women who are not surgically sterile will have urine pregnancy testing and serum pregnancy test at screening as per Table 8-1.

If the result of urine pregnancy test is positive, the patient must not be randomized and the result confirmed by the serum pregnancy test result. If the result of the serum pregnancy test is positive, the participant must be considered as a screen failure.

A positive pregnancy test during the study requires immediate discontinuation from study drug. The participant must be followed to understand the outcome of the pregnancy. Refer to Section 10.1.4 for details on pregnancy reporting.

8.4.6 Appropriateness of safety measurements

The safety assessments selected are appropriate for this protocol, which utilizes a marketed compound where the safety profile has been established. The assessments are relevant to the critical care setting and will enable determination of therapeutic response in this setting.

8.5 Additional assessments

8.5.1 Unscheduled assessments

In the case of clinically significant abnormalities, safety concerns required repeat testing or if additional assessments need to be performed, information should be reported in the relevant CRF page using the Unscheduled visit pages.

8.5.2 Assessments pre and post hospital discharge

In the case that a participant is discharged from hospital during the study, the following guidelines must be followed:

- If the participant is discharge prior to Day 10, assessments for Day 10/early discharge visit should be completed prior to discharge
- If the participant continues treatment up to Day 10 at home, guidelines in Section 6.1.3 should be followed. The site must contact the participant to assess compliance, and report any dose interruptions and stop dates of treatment, adverse events and relevant concomitant medications in the CRF
- Day 15 and Day 40 visits may be performed via phone call, an onsite visit is not mandated, at a minimum COVID-19 participant status, adverse events and relevant concomitant medications, and study completion status (as applicable) must be assessed.
- In the case that the participant is still hospitalized for either or both Day 15 and Day 40 visits additional assessments requested in Table 8-1 if assessed, as per local practices, may be reported in the relevant CRF pages.

8.5.3 Biomarkers

Serum and plasma will be stored for future biomarker analysis and will be covered by the secondary data use informed consent provided at time of screening.

Sample(s) will be collected at the time point(s) defined in the Assessment Schedule (Table 8-1) when possible.

Follow instructions for sample collection, numbering, processing, and shipment provided in the laboratory manual.

9 Study discontinuation and completion

9.1 Discontinuation and completion

9.1.1 Study treatment discontinuation and study discontinuation

Discontinuation of study treatment for a participant occurs when study treatment is stopped earlier than the protocol planned duration and can be initiated by either the participant or the investigator. The investigator must discontinue study treatment for a given participant if, he/she believes that continuation would negatively impact the participant's well-being.

If, for any reason, one of the study drugs should be stopped prior to day 5, then the both study drugs should be discontinued and the reason for discontinuation reported in the CRF.

Study treatment must be discontinued under the following circumstances:

- Participant/guardian decision
- Pregnancy
- Use of prohibited treatment as per recommendations in the prohibited treatment section
- Any situation in which study participation might result in a safety risk to the participant including cardiac events (please refer to Section 10.2 and Section 16 for additional safety monitoring criteria)
- Following emergency unblinding
- Unsatisfactory therapeutic effect
- Any laboratory abnormalities that in the judgment of the investigator, taking into consideration the participant's overall status, prevents the participant from continuing participation in the study

If discontinuation of study treatment occurs, the investigator should record the primary reason for the participant's premature discontinuation.

Participants who discontinue study treatment or who decide they do not wish to participate in the study further should NOT be considered withdrawn from the study UNLESS they withdraw their consent (see 'Withdrawal of Informed Consent' section). **Where possible, they should be assessed as per visit schedule in** Table 8-1.

After study treatment discontinuation, at a minimum, in abbreviated visits, the following data should be collected at clinic visits or via telephone/email contact:

- New / concomitant treatments
- Adverse Events / Serious Adverse Events

The investigator must also contact the IRT to register the participant's discontinuation from study treatment.

If discontinuation occurs because treatment code has been broken, please refer to Emergency breaking of treatment code section.

9.1.2 Withdrawal of informed consent

Participants may voluntarily withdraw consent to participate in the study for any reason at any time. Withdrawal of consent occurs only when a participant:

- Does not want to participate in the study anymore,

and

- Does not want any further visits or assessments

and

- Does not want any further study related contacts

In this situation, the investigator should make a reasonable effort to understand the primary reason for the participant's decision to withdraw his/her consent and record this information.

Where consent to the use of personal and coded data is not required, participant therefore cannot withdraw consent. They still retain the right to object to the further use of personal data.

Study treatment must be discontinued and no further assessments conducted, and the data that would have been collected at subsequent visits will be considered missing.

Further attempts to contact the participant are not allowed unless safety findings require communicating or follow-up.

All efforts should be made to complete the assessments prior to study discontinuation. A final evaluation at the time of the participant's study discontinuation should be made as detailed in the assessment table.

Novartis/Sponsor will continue to retain and use all research results (data) that have already been collected for the study evaluation.

9.1.3 Lost to follow-up

For participants whose status is unclear because they fail to appear for study visits without stating an intention to discontinue or withdraw, the investigator must show "due diligence" by documenting in the source documents steps taken to contact the participant, e.g. dates of telephone calls, registered letters, etc. A participant should not be considered as lost to follow-up until due diligence has been completed or until the end of the study.

9.1.4 Early study termination by the sponsor

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the participant should be seen as soon as possible and treated as a prematurely withdrawn participant. Adverse events and laboratory findings will be continually reviewed during the study. New enrollment and/or dosing for a treatment arm or study overall may be paused in case of safety concerns that are suspected to be related to study drug, including:

- > 2 participants with Torsade de Pointes or Ventricular Tachycardia **associated with** QTcF > 500 msec and QTcF prolongation > 60 msec

The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the participant's interests. The investigator will be responsible for informing the Institutional Review Board/Independent Ethics Committee (IRBs/IECs) of the early termination of the trial.

9.2 Study completion and post-study treatment

Study completion is defined as when the last participant finishes their Study Completion visit and any repeat assessments associated with this visit have been documented and followed-up appropriately by the Investigator or, in the event of an early study termination decision, the date of that decision (e.g. Each participant will be required to complete the study in its entirety and thereafter no further study treatment will be made available to them).

All randomized and/or treated participants should have a safety follow-up call conducted 30 days after last administration of study treatment. The information collected is kept as source documentation. All SAEs reported during this time period must be reported as described in Section 10.1.3. Documentation of attempts to contact the participant should be recorded in the source documentation.

There is no planned post-study-treatment in this study.

10 Safety monitoring and reporting

10.1 Definition of adverse events and reporting requirements

10.1.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (e.g. any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a clinical investigation participant after providing informed consent for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The investigator has the responsibility for managing the safety of individual participant and identifying adverse events.

Novartis qualified medical personnel will be readily available to advise on trial related medical questions or problems.

The occurrence of adverse events must be sought by non-directive questioning of the participant at each visit during the study. Adverse events also may be detected when they are volunteered by the participant during or between visits or through physical examination findings, laboratory test findings, or other assessments.

Adverse events must be recorded under the signs, symptoms, or diagnosis associated with them, accompanied by the following information (as far as possible) (if the event is serious refer to Section 10.1.2):

1. The severity grade:
   - mild: usually transient in nature and generally not interfering with normal activities
   - moderate: sufficiently discomforting to interfere with normal activities
   - severe: prevents normal activities
2. Its relationship to the study treatment. If the event is due to lack of efficacy or progression of underlying illness (i.e. progression of the study indication) the assessment of causality will usually be 'Not suspected.' The rationale for this guidance is that the symptoms of a lack of efficacy or progression of underlying illness are not caused by the trial drug, they happen in spite of its administration and/or both lack of efficacy and progression of underlying disease can only be evaluated meaningfully by an analysis of cohorts, not on a single participant
3. Its duration (start and end dates) or if the event is ongoing, an outcome of not recovered/not resolved must be reported
4. Whether it constitutes a SAE (see Section 10.1.2 for definition of SAE) and which seriousness criteria have been met
5. Action taken regarding study treatment.

   All adverse events must be treated appropriately. Treatment may include one or more of the following:
   - Dose not changed
   - Dose Reduced/increased

- Drug interrupted/withdrawn

6. Its outcome (i.e. recovery status or whether it was fatal)

Conditions that were already present at the time of informed consent should be recorded in medical history of the participant.

Adverse events (including lab abnormalities that constitute AEs) should be described using a diagnosis whenever possible, rather than individual underlying signs and symptoms.

Adverse event monitoring should be continued for at least 30 days following the last dose of study treatment.

Once an adverse event is detected, it must be followed until its resolution or until it is judged to be permanent (e.g. continuing at the end of the study), and assessment must be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the interventions required to treat it, and the outcome.

Information about adverse drug reactions for the investigational drugs can be found in the USPI/applicable labelling information.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms
- they are considered clinically significant
- they require therapy

10.1.2 Serious adverse events

An SAE is defined as any adverse event [appearance of (or worsening of any pre-existing)] undesirable sign(s), symptom(s), or medical conditions(s) which meets any one of the following criteria:

- fatal
- life-threatening

Life-threatening in the context of a SAE refers to a reaction in which the participant was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if it were more severe (please refer to the ICH-E2D Guidelines).

- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
    - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
    - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
    - social reasons and respite care in the absence of any deterioration in the participant's general condition

  - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
- is medically significant, e.g. defined as an event that jeopardizes the participant or may require medical or surgical intervention to prevent one of the outcomes listed above

Medical and scientific judgment should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the participant or might require intervention to prevent one of the other outcomes listed above. Such events should be considered as "medically significant." Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization or development of dependency or abuse (please refer to the ICH-E2D Guidelines).

All new malignant neoplasms will be assessed as serious under "medically significant" if other seriousness criteria are not met and the malignant neoplasm is not a disease progression of the study indication.

Any suspected transmission via a medicinal product of an infectious agent is also considered a serious adverse reaction.

All reports of intentional misuse and abuse of the product are also considered serious adverse event irrespective if a clinical event has occurred.

10.1.3 SAE reporting

To ensure participant safety, every SAE, regardless of causality, occurring after the participant has provided informed consent and until 30 days after the last study visit must be reported to Novartis safety within 24 hours of learning of its occurrence. Detailed instructions regarding the submission process and requirements are to be found in the investigator folder provided to each site.

All follow-up information for the SAE including information on complications, progression of the initial SAE and recurrent episodes must be reported as follow-up to the original episode within 24 hours of the investigator receiving the follow-up information. An SAE occurring at a different time interval or otherwise considered completely unrelated to a previously reported one must be reported separately as a new event.

If the SAE is not previously documented in the Package Insert and is thought to be related to the study treatment, a CMO & PS Department associate may urgently require further information from the investigator for health authority reporting. Novartis /Sponsor may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same study treatment that this SAE has been reported.

Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with EU Guidance 2011/C 172/01 or as per national regulatory requirements in participating countries.

Any SAEs experienced after the 30 day safety follow up period should only be reported to Novartis Safety if the investigator suspects a causal relationship to study treatment.

10.1.4 Pregnancy reporting

Pregnancies

If a female trial participant becomes pregnant, the study treatment should be stopped, and the trial participant must be asked to read and sign pregnancy consent form to allow the Study Doctor ask about her pregnancy. To ensure participant safety, each pregnancy occurring after signing the informed consent must be reported to Novartis/Sponsor within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded and reported by the investigator to the Novartis/Sponsor Chief Medical Office and Patient Safety (CMO&PS). Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment any pregnancy outcome. Any SAE experienced during pregnancy must be reported.

Pregnancy outcomes should be collected for the female partners of any males who took study treatment in this study. Consent to report information regarding these pregnancy outcomes should be obtained from the mother.

10.1.5 Reporting of study treatment errors including misuse/abuse

Medication errors are unintentional errors in the prescribing, dispensing, administration or monitoring of a medicine while under the control of a healthcare professional, participant or consumer (EMA definition).

Misuse refers to situations where the medicinal product is intentionally and inappropriately used not in accordance with the protocol.

Abuse corresponds to the persistent or sporadic, intentional excessive use of a medicinal product, which is accompanied by harmful physical or psychological effects.

Study treatment errors and uses outside of what is foreseen in the protocol will be recorded on the appropriate CRF irrespective of whether or not associated with an AE/SAE and reported to Safety only if associated with an SAE. Misuse or abuse will be collected and reported in the safety database irrespective of it being associated with an AE/SAE within 24 hours of Investigator's awareness.

Table 10-1 Guidance for capturing the study treatment errors including misuse/abuse

Treatment error type	Document in Dosing CRF (Yes/No)	Document in AE eCRF	Complete SAE form
Unintentional study treatment error	Yes	Only if associated with an AE	Only if associated with an SAE
Misuse/Abuse	Yes	Yes	Yes, even if not associated with a SAE

For more information on AE and SAE definition and reporting requirements, please see the respective sections.

10.2 Additional Safety Monitoring

10.2.1 Cardiac safety monitoring

In case of QTcF > 500 msec and QTcF prolongation > 60 msec from baseline, please take the following steps:

- Temporarily interrupt study treatment
- Assess the quality of the ECG recording and the QT value and record two additional ECG tracings to confirm the values
- Determine the serum electrolyte levels (in particular hypokalemia, hypomagnesemia and/or hypocalcemia). If abnormal, correct abnormalities before resuming study treatment.
- Review concomitant medication use for other causes for QT prolongation (refer to qtdrugs.org for known QT prolonging drugs) and for drugs with the potential to increase the risk of drug exposure of study drugs
- Check the dosing schedule and treatment compliance
- Increase cardiac monitoring as indicated, (consider continuous telemetry monitoring) until the QTcF returns to ≤ 480 msec
- If QTcF is ≤ 480 msec prior to the next dose, continue dosing with another ECG collected 4 hrs post dose
- If QTcF remains > 480 msec prior to the next dose discontinue study treatment for the participant permanently

In case of persistent QTcF > 500 msec and QTcF prolongation > 60 msec from baseline and/or documented new onset arrhythmia (e.g. Torsade de Pointes, Ventricular Tachycardia) or syncope - discontinue treatment for the participant and request evaluation by a cardiologist.

Please refer to Appendix 1 for notable vital signs.

Local practices should be followed to ensure participant safety for Liver and Renal monitoring, in addition below are suggested guidelines for safety monitoring.

10.2.2 Liver safety monitoring

To ensure participant safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Please refer to Table 16-1 in Appendix 2 for complete definitions of liver laboratory triggers.

Once a participant is exposed to study treatment, it is suggested that every liver event defined in Table 16-1 should be followed up by the investigator or designated personnel at the trial site, as summarized below. Additional details on actions required in case of liver events are outlined in Table 16-2. Repeat liver chemistry tests (i.e. ALT, AST, TBL, ALP and G-GT) to confirm elevation.

These liver chemistry repeats should be performed using the local laboratory used by the site. Repeated laboratory test results must be reported as appropriate.

- If the initial elevation is confirmed, close observation of the participant will be initiated, including consideration of treatment interruption if deemed appropriate.
- Discontinuation of the investigational drug (refer to the Discontinuation of study treatment section), if appropriate
- Causality assessment of the liver event
- Thorough follow-up of the liver event should include based on investigator's discretion:
  - serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease

All follow-up information and procedures performed must be recorded as appropriate in the CRF.

10.2.3 Renal safety monitoring

Once a participant is exposed to study treatment, the following two categories of abnormal renal laboratory alert values should be assessed during the study period:

- Serum creatinine increase ≥ 50% compared to baseline during normal hydration status
- Any one of the following:
  - Urine protein-creatinine ratio (PCR) ≥1g/g or ≥100 mg/mmol, OR
  - New onset dipstick proteinuria ≥ 3+, OR
  - New onset dipstick hematuria ≥ 3+ (after excluding menstruation, UTI, extreme exercise, or trauma)

Abnormal renal event findings must be confirmed after ≥24 hours but ≤ 5 days after first assessment.

Once a participant is exposed to study treatment, renal laboratory alerts or renal safety events should be monitored and followed up by the investigator or designated trial staff according to the local practice, guidance is summarized in Table 16-4 in Appendix 2.

10.2.4 Data Monitoring Committee

This study will include an internal data monitoring committee (DMC), which will function independently of all individuals associated with the conduct of this clinical trial, including the site investigators participating in the study. Specific details regarding composition, responsibilities, data monitoring and meeting frequency, documentation of DMC reports, minutes and recommendations will be described in a separate DMC charter.

11 Data Collection and Database management

11.1 Data collection

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

Designated investigator staff will enter the data required by the protocol and defined in the assessment schedule (Table 8-1) into the Electronic Case Report Forms (eCRF). The eCRFs have been built using fully validated secure web-enabled software that conforms to 21 CFR Part 11 requirements, Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs, allow modification and/or verification of the entered data by the investigator staff.

The investigator/designee is responsible for assuring that the data (recorded on CRFs) (entered into eCRF) is complete, accurate, and that entry and updates are performed in a timely manner. The Investigator must certify that the data entered are complete and accurate.

This study may also incorporate electronic technology (eSource DDE) to capture source documents and source data electronically, consistent with final (CDER 2013) FDA guidance regarding electronic source and Regulations related to the maintenance of adequate participant case histories (21 CFR 312.62(b)).

A Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE and/or eCRFs) with the investigators and their staff.

After final database lock, the investigator will receive copies of the participant data for archiving at the investigational site.

All data should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation, and verification.

11.2 Database management and quality control

Novartis personnel will review the data entered by investigational staff for completeness and accuracy. Electronic data queries stating the nature of the problem and requesting clarification will be created for discrepancies and missing values and sent to the investigational site via the EDC system. Designated investigator site staff are required to respond promptly to queries and to make any necessary changes to the data.

Concomitant treatments and prior medications entered into the database will be coded using the World Health Organization (WHO) Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) terminology.

Dates of screenings, randomizations, screen failures, as well as randomization codes and data about all study treatment (s) dispensed to the participant will be tracked using an Interactive Response Technology (IRT). The system will be supplied by a vendor, who will also manage the database. The data will be sent electronically to Novartis/Sponsor (or a designated CRO) at specific timelines.

Each occurrence of a code break via IRT will be reported to the clinical team and monitor. The code break functionality will remain available until study shut down or upon request of Novartis/Sponsor.

11.3 Site monitoring

Before study initiation, at an initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and data capture requirements (i.e. eSource DDE and/or CRFs) with the investigators and their staff. During the study, Novartis employs several methods of ensuring protocol and GCP compliance and the quality/integrity of the sites' data. The field monitor will check the completeness of participant records, the accuracy of data capture / data entry, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor in conducting these activities. Continuous monitoring of each site's data will be performed throughout the conduct of the study. Additionally, a central analytics organization may analyze data and identify risks and trends for site operational parameters, and provide reports to Novartis clinical teams to assist with trial oversight. The investigator must maintain source documents for each participant in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to the respective source documents. The investigator must also keep the original informed consent form agreed by the participant and/or legal representative (a copy is given to the participant).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the data capture and/or data entry. Novartis monitoring standards require verification for the presence of all informed consents, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the participants will be disclosed.

12 Data analysis and statistical methods

The primary analysis time point is Day 15. The analyses of efficacy and safety described in this protocol will occur when all participants in the study have completed their final study visit at Day 40.

Unless otherwise specified, descriptive summaries for categorical data will include frequencies and percentages, and continuous data will be presented with mean, standard deviation, median, minimum, and maximum. For selected parameters, 25th and 75th percentiles may also be presented.

Differences, relative ratios (RR) or odds ratios (OR) for the comparisons between the two treatment arms will be presented with 2-sided 95% confidence interval (CI). P-values will be presented only if a formal hypothesis test is performed.

Any data analysis carried out independently by the investigator should be submitted to Novartis before publication or presentation.

12.1 Analysis sets

The Randomized Analysis Set (RAS) consists of all randomized participants regardless of receiving study treatment.

The Full Analysis Set (FAS) comprises all participant to whom study treatment has been assigned by randomization excluding mis-randomized participants. Mis-randomized participants are defined as cases where IRT contact is made by the Investigator/qualified site staff either prematurely or inappropriately prior to confirmation of the participant's final randomization eligibility and treatment is not administered to the participant. According to the intent to treat principle, participants will be analyzed according to the treatment they have been assigned to during the randomization procedure.

The Safety Set (SAF) includes all participants who received at least one dose of study treatment. Participants will be analyzed according to the study treatment received, where treatment received is defined as the randomized/assigned treatment if the participant took at least one dose of that treatment or the first treatment received if the randomized/assigned treatment was never received.

The analysis of the primary objective and all other efficacy variables will be performed on the FAS. The Safety Set will be used in the analysis of all safety variables.

12.2 Participant demographics and other baseline characteristics

Demographic and other baseline data including disease characteristics will be listed and summarized descriptively by treatment group for all study participants in the FAS and safety set. Participant demographic and baseline characteristics will include: age, sex, race, ethnicity, height, weight, BMI, oxygen saturation (SpO2), duration of symptom onset to randomization, duration from hospital admission to randomization, SARS-COV-2-RNA/viral load PCR test result (negative/positive), COVID-19 abnormal chest x-ray at baseline consistent with COVID-19 (No/Yes), requiring oxygen at randomization (No/Yes), [redacted].

Categorical data will be presented as frequencies and percentages. For continuous data, mean, standard deviation, median, minimum, and maximum will be presented. For selected parameters, 25th and 75th percentiles will also be presented.

Protocol-solicited medical history will be summarized by treatment group.

12.3 Treatments

The Safety set will be used for the analyses below. Categorical data will be summarized as frequencies and percentages. For continuous data, mean, standard deviation, median, 25th and 75th percentiles, minimum, and maximum will be presented.

The duration of exposure in days to hydroxychloroquine, azithromycin, and placebo will be summarized by means of descriptive statistics using the safety set.

Concomitant medications and significant non-drug therapies prior to and after the start of the study treatment will be listed and summarized according to the Anatomical Therapeutic Chemical (ATC) classification system and preferred term, by treatment group.

12.4 Analysis of the primary endpoint(s)/estimand(s)

The primary analysis for this study will be conducted on the FAS using a treatment policy strategy.

12.4.1 Definition of primary estimand(s)

The primary objective of the study is to demonstrate in participants receiving best standard of care that the percentage who achieve clinical response with hydroxychloroquine or hydroxychloroquine plus azithromycin is superior to placebo by Day 15.

The primary efficacy estimand defined in Section 2.1 incorporates as its endpoint clinical response by Day 15 defined for participants with a pre-morbid oxygen requirement as: Discharge (or ready to discharge as evidenced by normal body temperature and respiratory rate, and stable oxygen saturation on ambient air or ≤ 2L supplemental oxygen) OR survival without need for mechanical ventilation. The clinical response endpoint for participants without a pre-morbid oxygen requirement is defined as: discharge (or ready for discharge) OR survival without need for mechanical ventilation or oxygen supplementation for the last 24 hours.

The components of clinical response will be derived from the disease status CRF that will be collected whenever there is a change in disease status (Section 8.3.1). Day 15 is the last study day where these criteria can be met. Study participants can meet the clinical response criteria prior to Day 15 if the criteria for discharge are met. Handling of missing data are provided in Section 12.4.4.

12.4.2 Statistical model, hypothesis, and method of analysis

The numbers and percentages of responders will be summarized by treatment group. The difference in observed response rates between active treatment groups and placebo arms will be presented along with 95% confidence intervals. The statistical hypothesis tested for clinical response is that there is no difference in the proportion of participants achieving clinical response at Day 15 with hydroxychoroquine or hydroxychloroquine plus azithromycin plus versus placebo.

Let p_j denote the proportion of clinical responders at Day 15 for treatment groups j, j = 0,1,2 where

- 0 corresponds to placebo
- 1 corresponds to hydroxychloroquine plus azithromycin
- 2 corresponds to hydroxychloroquine

The following statistical hypotheses will be tested to address the primary efficacy objective:

$$H_1: \frac{P1(1-P0)}{P0(1-P1)} = 1,\ H_{A1}: \frac{P1(1-P0)}{P0(1-P1)} \neq 1$$

$$H_2: \frac{P2(1-P0)}{P0(1-P2)} = 1,\ H_{A2}: \frac{P2(1-P0)}{P0(1-P2)} \neq 1$$

In other words,

H_1: hydroxychloroquine plus azithromycin is not different to placebo with respect to the likelihood of clinical response by Day 15

H_2: hydroxychloroquine is not different to placebo with respect to the likelihood of clinical response by Day 15

The primary efficacy endpoint of clinical response at Day 15 in the FAS will be evaluated using a logistic regression model with treatment group and whether or not supplemental oxygen is required at randomization as explanatory variables. Odds ratios will be computed for each of active treatment comparisons to placebo. Based on what data is available from the evolving COVID-19 literature, it is anticipated that hydroxychloroquine plus azithromycin will have a greater clinical response than hydroxychloroquine and thus each of the primary and secondary hypotheses will be tested first in a closed testing procedure in order to preserve familywise Type I error rate at 0.05 two-sided. Details of the closed testing procedure are provided in Section 12.5.

12.4.3 Handling of remaining intercurrent events of primary estimand

The primary analysis has incorporated all potential intercurrent events related to treatment or concomitant therapy as part of the treatment of interest attribute of the estimand and no other intercurrent events are necessary.

12.4.4 Handling of missing values not related to intercurrent event

Given that the participants in this clinical trial will be hospitalized for their participation, it is not expected that there will be any additional missing data in the primary analysis.

12.4.5 Sensitivity analyses for primary endpoint/estimand

The following sensitivity analyses will be performed for the primary estimand, to assess the robustness of the estimation in the presence of deviations from the assumptions specified in the primary analysis.

- In order to determine the robustness of the logistic regression model used for the primary analysis of clinical response at Day 15, a non-parametric regression model (Koch et al 1998) will also be evaluated using the same explanatory variables as the logistic regression model.

12.4.6 Supplementary analysis

No supplementary analysis are planned at this time.

12.4.7 Supportive analyses

The primary efficacy endpoint will be evaluated with respect to the following subgroups

- Age (18-65, > 65 years)
- SpO2 (≤94% > 94%)
- Requiring supplemental oxygen at the time of randomization (No/Yes)

The primary estimand will be applied here to each of these subgroups variables adding the subgroup variable and treatment group by subgroup interaction to the model to evaluate whether there is any association between the level of subgroup variable and treatment.

12.5 Analysis of secondary estimands

Viral clearance at Day 15

The secondary efficacy endpoint of the percentage of participants with negative or below LLOQ - SARS-COV-2 based on PCR by Day 15 will determined based on the PCR test that is performed at Day 6, Day 10, and Day 15/Day of discharge. Data available in the literature would indicate that when viral clearance is achieved, that participants will not reverse their viral clearance during the 15-day period. The endpoint will be evaluated in the FAS using a logistic regression model with treatment group and whether or not supplemental oxygen is required at randomization as explanatory variables. Odds ratios will be computed for each of active treatment comparisons to placebo. Based on what data is available from the evolving COVID-19 literature, it is anticipated that hydroxychloroquine plus azithromycin will have a greater viral response than hydroxychloroquine and thus will be tested first for the secondary endpoints in the closed testing procedure to preserve familywise Type I error rate at 0.05 two-sided.

The hypotheses in the closed testing procedure will be evaluated in the following order:

H_1: hydroxychloroquine plus azithromycin is not different to placebo with respect to the percentage of participants achieving clinical response by Day 15

H_2: hydroxychloroquine is not different to placebo with respect to percentage of participants achieving clinical response by Day 15

H_3: hydroxychloroquine plus azithromycin is not different to placebo with respect to the percentage of participants achieving viral clearance by Day 15

H_4: hydroxychloroquine is not different to placebo with respect to the percentage of participants achieving viral clearance by Day 15

Time to SARS-CoV-2 negativity/ Time to return to pre-morbid oxygen requirement /Time to discharge (or ready for discharge)

The event rates for these different endpoints will be estimated with Kaplan-Meier product-limit formula. Greenwood's formula will be used to estimate the variance of failure rates and to derive 95% Z-test based confidence intervals for the difference in event rates between active treatment groups and placebo.

12.5.1 Safety endpoints

For all safety analyses, the safety set will be used. All listings and tables will be presented by treatment group.

Safety summaries (tables, figures) include only data from the on-treatment period with the exception of baseline data which will also be summarized where appropriate (e.g. change from baseline summaries). In addition, a separate summary for death including on treatment and post treatment deaths will be provided. In particular, summary tables for adverse events (AEs) will summarize only on-treatment events, with a start date during the on-treatment period (treatment-emergent AEs).

The on-treatment period lasts from the date of first administration of study treatment to *30* days after the date of the last actual administration of any study treatment.

Adverse events

A treatment-emergent AE is defined as any AE that develops after initiation of the study treatments or any event already present that worsens following exposure to the study treatment.

All information obtained on adverse events will be displayed by treatment group and participant.

The number (and percentage) of participants with treatment-emergent adverse events (events started after the first dose of study medication or events present prior to start of double-blind treatment but increased in severity based on preferred term) will be summarized in the following ways:

- by treatment, primary system organ class and preferred term.
- by treatment, primary system organ class, preferred term and maximum severity.
- by treatment, Standardized MedDRA Query (SMQ) and preferred term.

Separate summaries will be provided for study medication related adverse events, death, serious adverse events, other significant adverse events leading to discontinuation.

A participant with multiple adverse events within a primary system organ class is only counted once towards the total of the primary system organ class.

Vital signs

All vital signs data will be listed by treatment group, participant, and visit/time and if ranges are available, abnormalities will be flagged. Summary statistics will be provided by treatment group and visit/time.

ECG

The overall interpretation of the ECGs will be summarized by treatment group and visit/time.

Any clinically significant changes in ECG parameters will be summarized by treatment group.

Summary statistics will be presented by treatment and visit/time, as appropriate.

Clinical laboratory evaluations

All laboratory data will be listed by treatment group, participant, and visit/time and if normal ranges are available abnormalities will be flagged. Summary statistics will be provided by treatment and visit/time. Shift tables using the low/normal/high/ (low and high) classification will be used to compare baseline to the worst on-treatment value.

12.5.2 Biomarkers

All biomarker data will be listed by treatment group, participant and visit. Summary statistics and graphical summaries (including spaghetti plots, boxplots and mean plots with SD) will be provided by treatment and visit. The number of values outside of the limits of quantification will be reported in each table. Values above the ULOQ will be imputed as ULOQ in graphical

summaries (with a special symbol) and for the calculation of the summary statistics. Values below the LLOQ will be imputed as LLOQ/2 for these analyses.

[redacted]

12.7 Interim analyses

No formal interim analysis is planned for this trial. The primary endpoint analysis will be performed after all participants have completed Day 15 or discontinued prior to Day 15. A final analysis will be performed after all participants have completed their last follow-up visit at Day 40 (or discontinued prior to Day 40).

12.8 Sample size calculation

12.8.1 Primary endpoint(s)

Assuming a true treatment difference in clinical response of 20% for hydroxychloroquine plus azithromycin plus SoC vs. placebo plus SoC, and an odds-ratio of at least 2.25, a sample size of 148 participants per treatment group (444 overall) provides at least 93% power that the primary analysis will be statistically significant at the two-sided 5% significance level. This holds for a variety of different assumptions with respect to treatment and clinical response rates.

These sample size assumptions were evaluated using East Version 6.4.

The sensitivity of different assumptions for clinical response rate for treatment and control groups and effect size on power are summarized in Table 12-1.

Table 12-1 Sensitivity of sample size to different response rates for 148 participants per group (N=444) and treatment differences for level of significance alpha = 0.05

HCQ/HCQ plus AZ Response Rate (%)	Standard of care response rate	Odds Ratio	Treatment difference (%)	Power (%)
50	35	1.86	15	74

HCQ/HCQ plus AZ Response Rate (%)	Standard of care response rate	Odds Ratio	Treatment difference (%)	Power (%)
50	30	2.33	20	94
50	25	3.00	25	99
60	45	1.83	15	73
60	40	2.25	20	93
60	35	2.79	25	99
70	55	1.91	15	76
70	50	2.33	20	94
70	45	2.85	25	99

12.8.2 Secondary endpoint(s)

Data available from recent studies published by Gautret (2020) would indicate that viral clearance for hydroxychloroquine plus azithromycin is high. In one study all participants receiving this combination therapy achieved viral clearance by Day 6. Participants receiving standard of care generally do not achieve a response rate higher than 50%. However, many of these studies are small and often not randomized. If one were to assume that hydroxychloroquine plus azithromycin has an 80% response rate by Day 15 and standard of care has a 50% response rate by Day 15, under this scenario, using the sample size justified for the primary efficacy endpoint, the 30% treatment difference corresponds to an odds-ratio of 4.0 and given 148 participants per treatment group. There will be more than 99% power to detect such a treatment difference.

13 Ethical considerations and administrative procedures

13.1 Regulatory and ethical compliance

This clinical study was designed and shall be implemented, executed and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US CFR 21), and with the ethical principles laid down in the Declaration of Helsinki.

13.2 Responsibilities of the investigator and IRB/IEC

Before initiating a trial, the investigator/institution must obtain approval/favorable opinion from the Institutional Review Board/Independent Ethics Committee (IRB/IEC) for the trial protocol, informed consent form, consent form updates, participant recruitment procedures (e.g., advertisements) and any other written information to be provided to participants. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis/Sponsor monitors, auditors, Novartis/Sponsor Quality Assurance representatives, designated agents of Novartis/Sponsor, IRBs/IECs, and regulatory authorities as required. If an

inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis/Sponsor immediately that this request has been made.

13.3 Publication of study protocol and results

The protocol will be registered in a publicly accessible database such as clinicaltrials.gov and as required in EudraCT. In addition, after study completion (defined as last participant last visit) and finalization of the study report the results of this trial will be submitted for publication and posted in a publicly accessible database of clinical trial results, such as the Novartis clinical trial results website and all required Health Authority websites (e.g. Clinicaltrials.gov, EudraCT etc.).

For details on the Novartis publication policy including authorship criteria, please refer to the Novartis publication policy training materials provided to you at the trial investigator meetings.

13.4 Quality Control and Quality Assurance

Novartis maintains a robust Quality Management System (QMS) that includes all activities involved in quality assurance and quality control, to ensure compliance with written Standard Operating Procedures as well as applicable global/local GCP regulations and ICH Guidelines.

Audits of investigator sites, vendors, and Novartis systems are performed by auditors, independent from those involved in conducting, monitoring or performing quality control of the clinical trial. The clinical audit process uses a knowledge/risk based approach.

Audits are conducted to assess GCP compliance with global and local regulatory requirements, protocols and internal SOPs, and are performed according to written Novartis processes.

14 Protocol adherence

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Additional assessments required to ensure safety of participants should be administered as deemed necessary on a case by case basis. Under no circumstances including incidental collection is an investigator allowed to collect additional data or conduct any additional procedures for any purpose involving any investigational drugs under the protocol, other than the purpose of the study. If despite this interdiction prohibition, data, information, observation would be incidentally collected, the investigator shall immediately disclose it to Novartis and not use it for any purpose other than the study, except for the appropriate monitoring on study participants.

Investigators ascertain they will apply due diligence to avoid protocol deviations. If an investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC and Health Authorities, where required, it cannot be implemented.

14.1 Protocol amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis/Sponsor, health authorities where required, and the IRB/IEC prior to implementation.

Only amendments that are required for participant safety may be implemented immediately provided the health authorities are subsequently notified by protocol amendment and the reviewing IRB/IEC is notified.

Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any participant included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed according to local regulations.

15 References

References are available upon request

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16 Appendices

16.1 Appendix 1: Clinically notable laboratory values and vital signs

Investigators are responsible for reviewing abnormal laboratory values for clinical significance, signing the laboratory reports to indicate their review, and reporting values considered clinically significant in the appropriate eCRF.

Any clinically significant abnormal laboratory value should be evaluated and followed-up by the investigator until normal or a cause for the abnormality is determined.

See Appendix 2 for specific liver event and laboratory test trigger definitions and follow-up requirements.

See Appendix 3 for specific renal alert criteria and actions.

Post-baseline vital signs will be flagged as notable abnormalities as follows:

1. Systolic/Diastolic blood pressure: ≥25% decrease or ≥25% increase from baseline

2. Pulse: ≥110 bpm with ≥15% change from baseline, or <50 bpm with ≥15% change from baseline

16.2 Appendix 2: Suggested Liver event and laboratory trigger definitions & follow-up requirements

Table 16-1 Liver event and laboratory trigger definitions

	Definition/ threshold
Liver laboratory triggers If ALT, AST and total bilirubin normal at baseline:	• ALT or AST > 5 × ULN • ALP > 2 × ULN (in the absence of known bone pathology) • Total bilirubin > 3 × ULN (in the absence of known Gilbert syndrome) • ALT or AST > 3 × ULN and INR > 1.5 • Potential Hy's Law cases (defined as ALT or AST > 3 × ULN and Total bilirubin > 2 × ULN [mainly conjugated fraction] without notable increase in ALP to > 2 × ULN) • Any clinical event of jaundice (or equivalent term) • ALT or AST > 3 × ULN accompanied by (general) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia • Any adverse event potentially indicative of a liver toxicity*
If ALT or AST abnormal at baseline:	• ALT or AST > 2x baseline or > 300 U/L (whichever occurs first)
*These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; non-infectious hepatitis; benign, malignant and unspecified liver neoplasms ALP: Alkaline phosphatase, ALT: Alanine aminotransferase, AST: Aspartate aminotransferase, ULN: upper limit of normal	

Table 16-2 Follow up requirements for liver laboratory triggers with liver symptoms

	ALT	**TBL**	**Liver Symptoms**	**Action**
ALT increase without bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN **If elevated at baseline:** ALT > 2 x baseline or > 300 U/L (whichever occurs first)	Normal For participants with Gilbert's syndrome: No change in baseline TBL	None	• **No change to study treatment** • Measure ALT, AST, ALP, GGT, TBIL, INR, albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms.
	If normal at baseline: ALT > 5 x ULN for more than two weeks	Normal For participants with Gilbert's syndrome: No	None	• **Interrupt study drug** • Measure ALT, AST, ALP, GGT, TBIL, INR,

	ALT	TBL	Liver Symptoms	Action
	If elevated at baseline: ALT > 3 x baseline and >10 x ULN	change in baseline TBL		albumin, CK, and GLDH in 48-72 hours. • Follow-up for symptoms. • Initiate close monitoring and workup for competing etiologies. • Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
	If normal at baseline: ALT > 8 x ULN	Normal	None	
ALT increase with bilirubin increase:				
	If normal at baseline: ALT > 3 x ULN	TBL > 2 x ULN For participants with Gilbert's syndrome: Doubling of direct bilirubin	None	
	If elevated at baseline: ALT > 2 x baseline			
	If normal at baseline: ALT > 3 x ULN	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	
	If elevated at baseline: ALT > 2 x baseline			

Table 16-3 Follow up requirements for liver laboratory triggers

Criteria	Actions required	Follow-up monitoring
Total Bilirubin (isolated)		
>1.5 – 3.0 ULN	• Maintain treatment • Repeat LFTs within 48-72 hours	Monitor LFTs weekly until resolution[a] to ≤ Grade 1 or to baseline
> 3 - 10 × ULN (in the absence of known Gilbert syndrome)	• Interrupt treatment • Repeat LFT within 48-72 hours • Establish causality • Record the AE and contributing factors (e.g. conmeds, med hx, lab) in the appropriate CRF	Monitor LFTs weekly until resolution[a] to ≤ Grade 1 or to baseline (ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT) Test for hemolysis (e.g. reticulocytes, haptoglobin, unconjugated [indirect] bilirubin)
> 10 x ULN	• Discontinue the study treatment immediately • Establish causality • Record the AE and contributing factors(e.g. conmeds, med hx, lab)in the appropriate CRF	ALT, AST, total bilirubin, Alb, PT/INR, ALP and GGT until resolution[a] (frequency at investigator discretion)

Criteria	Actions required	Follow-up monitoring
General symptoms		
Any AE potentially indicative of a liver toxicity*	• Consider study treatment interruption or discontinuation • Establish causality • Record the AE and contributing factors(e.g., conmeds, med hx, lab)in the appropriate CRF	Investigator discretion
[a]Resolution is defined as an outcome of one of the following: (1) return to baseline values, (2) stable values at three subsequent monitoring visits at least 2 weeks apart, (3) remain at elevated level after a maximum of 6 months, (4) liver transplantation, and (5) death. *(General) malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia		

Based on investigator's discretion investigation(s) for contributing factors for the liver event can include: Serology tests, imaging and pathology assessments, hepatologist's consultancy; obtaining more detailed history of symptoms and prior or concurrent diseases, history of concomitant drug use, exclusion of underlying liver disease.

16.3 Appendix 3: Suggested Specific Renal Alert Criteria and Actions and Event Follow-up

Table 16-4 Specific Renal Alert Criteria and Actions

Serum Event	
Serum creatinine increase 25 - 49% compared to baseline	Confirm 25% increase after 24-48h Follow up within 2-5 days
Acute kidney injury: serum creatinine increase ≥50% compared to baseline	Follow up within 24 -48h if possible Evaluate the need for study treatment interruption or discontinuation Consider specialized treatment
Urine Event	
New dipstick proteinuria ≥1+ Albumin- or Protein-creatinine ratio increase ≥2-fold Albumin-creatinine ratio (ACR) ≥30 mg/g or ≥3 mg/mmol; Protein-creatinine ratio (PCR) ≥150 mg/g or ≥15 mg/mmol	Confirm value after 24-48h Perform urine microscopy Evaluate the need for study treatment interruption / or discontinuation
New dipstick glycosuria ≥1+ not due to diabetes	Blood glucose (fasting) Perform serum creatinine, ACR
New dipstick hematuria ≥1+ not due to trauma	Urine sediment microscopy Perform serum creatinine, ACR
For all renal events:	
Document contributing factors in the CRF: co-medication, other co-morbid conditions, and additional diagnostic procedures performed Monitor subject regularly (frequency at investigator's discretion) until either: Event resolution: sCr within 10% of baseline or protein-creatinine ratio within 50% of baseline, or Event stabilization: sCr level with ± 10% variability over last 6 months or protein-creatinine ratio stabilization at a new level with ± 50% variability over last 6 months.	