NOVARTIS

Clinical Development

JWT629/Hydroxychloroquine/Plaquenil®

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

Statistical Analysis Plan (SAP)

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		References to the analysis of the primary endpoint once all participants have completed the Day 15 visit were deleted as this analysis was cancelled.		1.1 Study design 2.1 Data analysis general information 2.11 Interim analysis
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		The definition of clinically significant changes in ECG parameters was aligned with the definition provided in the protocol.		2.8.4.1.1 Clinically significant changes in ECG parameters
		The defintion of CTCAE grades for laboratory parameters was aligned with the defintion provided in the version 5.0 of the CTCAE grade guidance.		5.3.1 Laboratory parameters derivation

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List of abbreviations

AE	Adverse event
ATC	Anatomical Therapeutic Classification
AUC	Area Under the Curve
bid	bis in diem/twice a day
CSR	Clinical Study report
CRS	Compound Case Retrieval Strategy
CTC	Common Toxicity Criteria
CTCAE	Common Terminology Criteria for Adverse Events
DMC	Data Monitoring Committee
FAS	Full Analysis Set
FPFV	First participant first visit
eCRF	Electronic Case Report Form
hs-CRP	high-sensitivity C-reactive Protein
IVR	Interactive Voice Response
IRT	Interactive Response Technology
IWR	Interactive Web Response
LFT	Liver function test
MedDRA	Medical Dictionary for Drug Regulatory Affairs
NMQs	Novartis MedDRA queries
o.d.	Once Daily
LLOQ	Lower Limit of Quantification
PCR	Polymerase Chain reaction
PFS	Progression-Free Survival
PK	Pharmacokinetics
PPS	Per-Protocol Set
PRO	Patient-reported Outcomes
PT	Preferred term
qd	Qua'que di'e / once a day
QoL	Quality of Life
RAP	Report and Analysis Process
RAS	Randomized Analysis Set
SAF	Safety Analysis Set
SAP	Statistical Analysis Plan
SARS-CoV	severe acute respiratory syndrome coronavirus
SMQ	Standardized MedDRA Query
SOC	System Organ Class
SoC	Standard of Care
SpO2	Supplemental Oxygen
TFLs	Tables, Figures, Listings
WHO	World Health Organization

1 Introduction

The purpose of the Statistical Analysis Plan (SAP) is to describe the implementation of statistical analysis planned in the clinical study protocol. The clinical study report (CSR) of the JWT629A12301 study will be produced from this SAP.

On the 19th of June, 2020 a decision was made to halt the JWT629A12301 study for feasibility reasons. Hence only an abbreviated CSR will be created for this study. Analysis covered in the original SAP were reduced and/or simplified accordingly

The content of this SAP is based on the original clinical trial protocol of the JWT629A12301 study (Release date: 08-APR-2020).

1.1 Study design

This study is a multi-center, randomized, double-blind, 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: a screening period of up to four days to obtain the informed consent and assess participant's eligibility; a 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 (Figure 1-1).

Approximately 444 participants were to be randomized into either of three arms with a 1:1:1 ratio. When the decision was made to halt the study, a total of 20 participants had been randomized (including one mis-randomized participant).

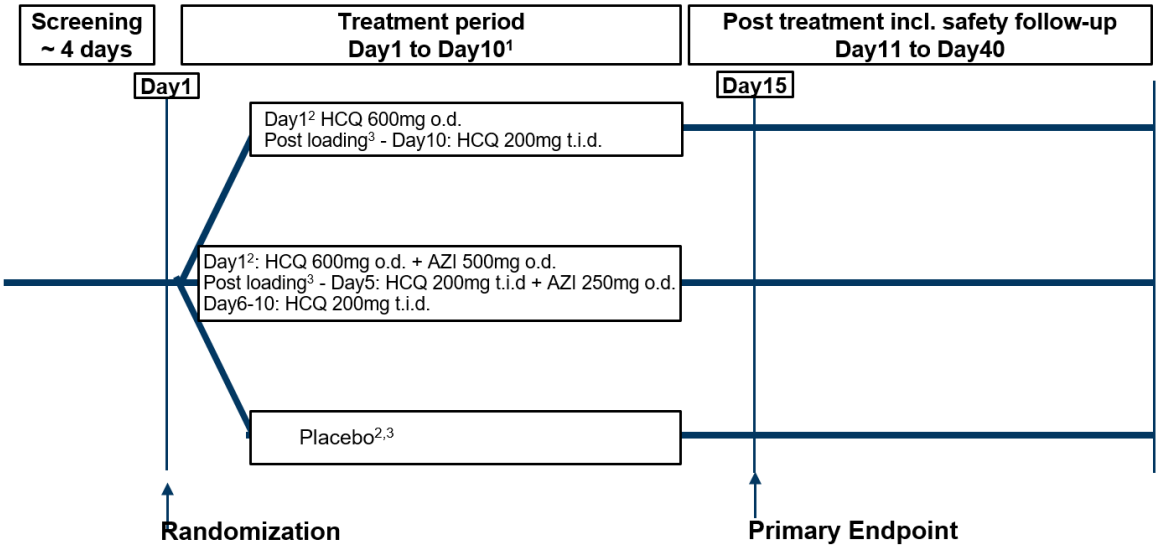
Study will be conducted in the United States.

No formal interim analysis is planned for this trial.

The CSR will be finalized after the final database lock, once the 20 randomized participants have completed Day 40 or discontinued study prior to Day 40.

Considering the limited number of participants randomized, only serious adverse events were reviewed during safety monitoring using a data monitoring committee (DMC).

Figure 1-1 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

1.2 Study objectives and endpoints

Study objectives and related endpoints are described in Table 1-1 below.

Table 1-1 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

Objectives	Endpoints
	• 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 the lower limit of quantification LLOQ SARS-COV-2 based on polymerase chain reaction (PCR) test by Day 10
• 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
[redacted]	[redacted]

2 Statistical methods

2.1 Data analysis general information

Novartis statistical and programming team will perform the CSR analysis as planned in this document.

Statistical Analysis System (SAS) software version 9.4 will be used to perform statistical analysis.

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.

2.1.1 General definitions

2.1.1.1 Terminology – Study drug

In this document the following terminology is used

- **Study drug or study medication or study treatment** always refers to randomized double-blind study drug
- **Standard of care:** It is considered that all participants will receive best standard of care as background therapy.

2.1.1.2 Study days

Study day 1 and Date of first administration of study drug/treatment

Study Day 1 (or Day 1 or reference start date) is defined as the first day of administration of randomized study medication (i.e. the date of first dose of the study drug). For participants with missing first dose date (for example mis-randomized participants), study day 1 will be defined based on the randomization date.

All other study days will be labeled relative to Day 1.

For events with dates on or after Day 1, study day for the event is calculated as (event date – first dose date + 1). For events with dates before Day 1, study day for the event is calculated as (event date – first dose date).

Duration of an event is calculated as (event end date – event start date +1).

Day post-study drug discontinuation

Day post-study drug discontinuation for a particular event is calculated as (event date – study drug discontinuation date). The date of study drug discontinuation will be the date of the last dose of study drug.

Day post-study drug discontinuation will be included in listings to facilitate identification of events/data occurring/collected post study drug discontinuation and to provide information on how long after study drug discontinuation the event/data occurred/was collected. Day 0 and negative days will not be used.

2.1.1.3 Baseline

The derived baseline is defined as the last assessment obtained prior to start of treatment (i.e. prior to study Day 1). In the situation where the screening visit was conducted on study day 1, the derived baseline will be defined as the assessment performed at the screening visit.

For ECG parameters

Baseline is defined as the Day 1 pre-dose value. If unavailable, the assessment made at last visit (screening visit or unplanned) before first dose date will be used. A screening visit

conducted on study day 1 will be considered to have been performed prior to first dose administration.

2.1.1.4 Date of Last contact

For participant who dies, the date of last contact will be the date of death. For other participants the date of last contact will be derived as the last visit assessment date.

2.1.1.5 Analysis cut-off

Unless otherwise specified all data should be used in analysis.

2.1.1.6 Treatment-emergent data

Treatment-emergent data will be defined as data collected after the start of the study treatment until respective cut-off dates

2.1.1.7 By-visit summary

By-visit summary will be provided for the following safety endpoints: ECG, vital signs and Lab (Hemathology, Chemistry, Inflammatory markers). *Nominal visits* (i.e. the scheduled visits collected in the database) will be used to summarize these endpoints.

For efficacy endpoints: the score achieved on the 9-item ordinal scale by Day 15 or by Day 28 will be reported. Accordingly, nominal visits will not be used. For this analysis, in case more than one assessment were performed on the same day, schedule assessment will be preferentially used.

Viral clearance will be reported by Day 6 and by Day 10; nominal visits will not be used to summarize these endpoint.

2.1.1.7.1 Rule for re-mapping visits which are not time-point specific

The early discharge visit and unplanned assessments, which are not time point specific, will be remapped to one of the scheduled time-point based on rules provided in Table 2-1, Table 2-2 and Table 2-3. The remapped visit will only be used in analysis, in case the corresponding schedule visit is missing.

Table 2-1 Remapping rule for vital signs

Visit	Visit window (study days)	Target Day
Baseline*	See Section 2.1.1.3	
Day 1	1	1
Day 2	2, 3	2
Day 4	4, 5	4
Day 6	6, 7	6
Day 8	8, 9	8
Day 10	10,11	10
Day 40	12 to 40	40

* Note: A screening assessment performed on study day 1, will be mapped to the baseline visit.

Table 2-2 Remapping rule for Lab (Hematology, Chemistry, Inflammatory markers)

Visit	Visit window (study days)	Target Day
Baseline*	See Section 2.1.1.3	
Day 1	1	1
Day 4	2 to 6	4
Day 10	7 to 12	10
Day 15	13 to 17	15
Day 40	18 to 40	40

* Note: A screening assessment performed on study day 1, will be mapped to the baseline visit.

Table 2-3 Remapping rule for ECG

Visit	Visit window (study days)	Target Day
Baseline*	See Section 2.1.1.3	
Day 1§	1	1
Day 2	2, 3	2
Day 4	4, 5	4
Day 6	6, 7	6
Day 10	8 to 12	10
Day 40	13 to 40	40

* Note: A screening assessment performed on study day 1, will be mapped to the baseline visit.

§ only applies to unplanned assessment performed on Day 1. For assessment performed at “Day 1- pre-dose” or at “Day 1 4 hours post-dose”, remapped visit (AVISIT) will be labelled “Day 1 pre-dose” or “Day 1 4 hours post-dose”.

2.1.1.7.2 Handling of multiple assessments within visit windows

In case multiple assessments of a participant may fall in a particular window, all results will be displayed in listings, but for summary statistics, only the value closest to the actual target day will be used. If two assessments are separated by the same number of days from the target day, the earlier assessment will be used. If an unplanned or unscheduled assessment (e.g. discharge visit) were conducted on the target day but a schedule assessment for this assessment is also available, the schedule assessment will be used.

2.1.1.8 Participants

Every effort should be made to use the term participant instead of the term patient or subject in this SAP and in the CSR deliverable of the JWT629A12301 trial.

2.1.1.9 Missing and partial dates

The general approach to handling missing dates is described in Section 5.1.

2.2 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.

2.3 Participants disposition, demographics and other baseline characteristics

2.3.1 Participants disposition

Participant's disposition will be assessed at screening, at end of treatment and at end of study.

The number of participants screened will be presented. In addition, the reasons for screen failures will be provided.

The number and percentage of participants in the SAF who completed double-blind study drug and who discontinued from double-blind study drug prematurely (including the reason for discontinuation) will be summarized.

The number and percentage of participants in the FAS who completed study and who discontinued from study prematurely (including the reason for discontinuation) will be summarized.

For each protocol deviation (PD), the number and percentage of participants for whom the PD applies will be tabulated. Summary by protocol deviation category will be provided in addition to summary by protocol deviation category and deviation term.

2.3.2 Background and demographic characteristics

Participant demographic and baseline characteristics will include:

- Age
- Age categories (≤ 65 , > 65 years)
- Sex
- Race
- Ethnicity
- Height
- Weight

- BMI

Background disease characteristics will include:

- Oxygen saturation at baseline (≤94%; > 94%)
- Requiring supplemental oxygen at baseline (No/Yes)
- Supplemental Oxygen Flow rate (L/min) (see also section 2.4.2.3)
- Number of days from onset of symptoms to first dose of study drug
- Number days from hospital admission to first dose of study drug
- Chest imaging (x-ray or CT scan) status at baseline (Normal/Abnormal/not available)
- Pre-morbid oxygen requirement (No/Yes)
- [redacted]
- Tachypnea (i.e. respiratory rate > 24 bpm) at baseline (No/Yes)

Comorbidities will include:

- Number of comorbidities (0,1 >1) , where comorbidities include the following list of solicited terms: Cerebrovascular disease, Chronic heart disease, Hypertension, Asthma, COPD, Chronic kidney disease, Malignant neoplasm, Diabetes.

[redacted]

Demographic and other baseline data will be summarized descriptively by treatment group for all study participants in the FAS.

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.

2.3.3 Medical history and current medical condition

Any medical history, including protocol-solicited medical history and current medical conditions will be coded using the Medical Dictionary for Regulatory Activities (MedDra).

As indicated in section 2.3.2, number and percentages of comorbities will be analyzed.

2.4 Treatments (study treatment, rescue medication, concomitant therapies, compliance)

2.4.1 Study treatment / compliance

Duration of exposure to double-blind study drug will be defined as time from first dose of treatment to last dose of study drug.

The analysis of exposure to double-blind study drug will be based on the SAF. The duration of exposure to study treatment will be summarized by component of study treatment (i.e. HCQ/Placebo and AZI/Placebo). The number and percentage of participants by cumulative exposure levels (e.g. ≥ 1 day; ≥ 2 days; ≥ 5 days; ≥ 8 days; 10 days) will also be reported.

2.4.2 Prior, concomitant and post therapies

Analyses described in this section will be performed on the safety set.

2.4.2.1 Concomitant medication

Records on the Prior and Concomitant Medications eCRF page will be coded using the WHO drug dictionary. All medications will be classified as prior or concomitant medication as follows:

- Prior medications are defined as drugs taken and stopped prior to start of the study medication on Day 1.
- Concomitant medications are defined as drugs taken at least once after the start of the study medication on Day 1

Medications will be categorized into one (and only one) of the two classes based on recorded or imputed start and end dates. When incomplete or missing, dates will be imputed according to Novartis standards (Section 5.1.3).

Concomitant medications will be summarized by treatment group, drug class (ATC level 1) and preferred term.

2.4.2.2 Surgical and medical procedures

Records on the surgical and medical procedures eCRF page will be coded using the MedDRA dictionary. All procedures will be classified as prior or concomitant procedure, in the same way as done for concomitant medications.

Imputation rules for start and end dates will follow the same rule as for the concomitant medications (Section 5.1.4).

Analysis of medical procedures that are specific to the Covid-19 indication are covered in Section 2.7 of this SAP. Imputation rules describes in Section 5.1.4 should not apply in this case. Other surgical and medical procedures will not be summarized.

2.4.2.3 Supplemental oxygen therapy

Supplemental oxygen therapy was solicited at the Screening, Day 1, Day 2, Day 4, Day 6, Day 8, Early Discharge/Day 10, at follow-up Day 15 visit and at EOS/Day 40. This assessment included a measure of Oxgen Flow rate in L/min.

Oxygen flow rate (L/min) at baseline will be analyzed using descriptive summary statistics. For patient who did not receive supplemental oxygen therapy at baseline, Oxgen Flow rate (L/m) will derived as 0. This parameter will be reported along with other background disease characteristics (see section 2.3.2).

2.5 Analysis of the primary objective

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.

2.5.1 Definition of the primary estimand

The primary clinical question of interest is: What is the effect of 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 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. The primary efficacy analysis will be based on the Full analysis set (FAS), following the intention-to-treat principle.

Endpoint: clinical response by Day 15. For participants *with a pre-morbid oxygen* requirement, clinical response is defined 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, clinical response is defined 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.

Intercurrent events: 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.

Summary measure: Odds-ratio comparing experimental treatments of interest to placebo.

[redacted]

2.5.2 Statistical hypothesis, model, and method of analysis

The number (%) of participants who achieved clinical response will be summarized by Day 15 will be summarized. Analysis will be performed on the FAS.

2.5.3 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.

2.5.4 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.

Consideration with regards to handling death was provided in the derivation of the components of the clinical response.

In case of premature discontinuation from study, ongoing/missing end date of pulmonary support will not be imputed, i.e. pulmonary support should not be considered ended in this case.

2.5.5 Sensitivity analysis for the primary estimand

No sensitivity analysis are planned.

2.5.6 Supplementary analysis

No supplementary analysis are planned.

2.5.7 Supportive analyses

Clinical response by Day 28.

The number (%) of participants who achieved clinical response by Day 28 will be summarized by Day 28. Analysis will be performed on the FAS.

2.6 Analysis of the secondary objectives controlled for multiplicity

2.6.1 Secondary endpoint controlled for multiplicity

The secondary efficacy endpoint of the percentage of participants with negative or below LLOQ - SARS-COV-2 based on PCR by Day 10 will determined based on the PCR test that is performed at Day 6 and Day 10/Day of discharge. Data available in the literature would indicate that when viral clearance is achieved, participants will not reverse their viral clearance during the 15-day period.

2.6.2 Statistical hypothesis, model, and method of analysis

The number (%) of participants who achived viral clearance by Day 6 and by Day 10 will be summarized. Analysis will be performed on the FAS.

2.6.3 Handling of missing values/censoring/discontinuations

Viral clearance will be based on available PCR results by Day 10, which means that the last available PCR results available at Day 10 or an earlier visit will be used to determine viral clearance status. Patients who do not have PCR results post first dose of treatment will be considered as not having reached viral clearance.

2.7 Analysis of other secondary efficacy objective(s)

2.7.1 Other secondary endpoints

Time to return to pre-morbid oxygen requirement

The number (percentage) of participants who returned to pre-morbid oxygen requirement by Day 15 and by Day 28 will be summarized. Return to pre-morbid oxygen requirement is defined as no need of mechanical ventilation in any participants and no need of supplemental oxygen in any participants without pre-morbid oxygen requirement. Analysis will be performed on the FAS.

Time to discharge (or ready for discharge)

The number (percentage) of participants ready to be discharged by Day 15 and by Day 28 will be summarized. Analysis will be performed on the FAS.

2.8 Safety analyses

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

There is no formal safety hypotheses in this study. All safety analyses will be descriptive.

The safety analysis will include all treatment-emergent data, i.e., data collected after the start of the study treatment.

2.8.1 Adverse events (AEs)

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.

Adverse events reported will be sorted alphabetically by primary system organ class and then in descending frequency according to its incidence in the HCQ+AZI. For ties in incidence rate of HCQ group, sort adverse event by incidence rate of HCQ. 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. If a particular AE 'severity' is missing, this variable will be listed as missing and treated as missing in summaries. If a participant reported more than one adverse event with the same preferred term, the adverse event with the greatest severity will be presented. If a participant reported more than one adverse event within the same primary system organ class, the participant will be counted only once with the greatest severity at the system organ class level, where applicable.

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

Algorithms for date imputations are be provided in Section 5.1.2.

For serious adverse events (SAEs) occurred during screening a listing will be prepared for all participants screened including screening failures.
The MedDRA version used for reporting the study will be described in a footnote.

2.8.1.1 AE reporting for CT.gov and EudraCT

For the legal requirements of clinicaltrials.gov and EudraCT, two required tables on treatment emergent adverse events which are not serious adverse events with an incidence greater than 2% and on treatment emergent serious adverse events and SAE suspected to be related to study treatment will be provided by system organ class and preferred term on the safety set population.

If for the same participant, several consecutive AEs (irrespective of study treatment causality, seriousness and severity) occurred with the same SOC and PT:

- a single occurrence will be counted if there is ≤ 1 day gap between the end date of the preceding AE and the start date of the consecutive AE
- more than one occurrence will be counted if there is > 1 day gap between the end date of the preceding AE and the start date of the consecutive AE

For occurrence, the presence of at least one SAE/SAE suspected to be related to study treatment / non SAE has to be checked in a block e.g., among AE's in a ≤ 1 day gap block, if at least one SAE is occurring, then one occurrence is calculated for that SAE.

The number of deaths resulting from SAEs suspected to be related to study treatment and SAEs irrespective of study treatment relationship will be provided by SOC and PT.

2.8.2 Deaths

The primary causes of death may be attributable to complication of COVID-19 disease or any other reasons.

Deaths will be listed.

2.8.3 Laboratory data

Laboratory samples will be taken at screening, Day 4, Day 10 and at the Day 15 visit. Laboratory tests will be conducted by a local lab. For hematology, biochemistry and urinalysis parameters, sites will be asked to only provide results in case the lab results was abnormal (i.e. normal lab results may not be collected on the local CRF page).

All results of inflammatory markers will be collected in the CRF where possible.

2.8.3.1 Standard data summaries

[redacted]

For the list of parameters provided in Section 5.3.1, the number (percentage) of participants with at least one newly occurring or worsening lab abnormality during study will presented by laboratory test and CTCAE grade value. For a given test, the lab results with maximum severity will be reported.

Laboratory results marked as grade 3 or grade 4 will be listed by treatment group, participant, and visit.

2.8.3.2 Serum pregnancy test

Results from serum pregnancy test will not be collected on the CRF.

2.8.3.3 Liver transaminase elevation

Considering the limited number of participants in the trial, newly occurring or worsening liver enzyme abnormalities will not be summarized.

2.8.4 Other safety data

2.8.4.1 ECG and cardiac imaging data

ECGs are scheduled at screening, Day 1 (pre-dose and 4 hours post dose), Day 2, Day 4, Day 6 (if required in the opinion of the investigator) and at Day 10 (if required in the opinion of the investigator). In case of safety concerns, additional ECGs must be performed to confirm the safety. A copy of the local tracing will be sent to a central ECG reader.

Only "QTcF interval, aggregate" will be recorded on the local ECG crf page. The interpretation of the ECG (normal, abnormal) will also be collected on the local ECG crf page.

2.8.4.1.1 Clinically significant changes in ECG parameters

The number and percentage of participants meeting the Fridericia QTcF interval criteria defined below at any time post-baseline will be summarized by treatment group (new means that the criteria were not met at baseline or was missing at baseline:

Fridericia QTc interval: new > 480 msec, new > 500 msec, change from baseline 30 - 60 msec, change from baseline > 60 msec, New > 500 msec and change from baseline > 60 msec

Summary of clinically significant changes in ECG will be based on ECG recorded locally .

2.8.4.1.2 Overall interpretation of the ECGs – ECG findings

Recording of ECG findings (e.g. prolonged QTc, Torsade de Pointes, Ventricular Tachycardia,..) will be send to Novartis by the central ECG vendor.

ECG findings will be summarized by treatment group and visit/time-points.

2.8.4.1.3 Summary statistics of ECG parameters (i.e. measurements)

Summary statistics of ECG parameters will be presented by treatment and visit/time. This analysis will be based on ECG parameters assessed centrally.

2.8.4.2 Vital signs

Vital signs measurement include: weight (kg), temperature (C), pulse rate (beats/min), systolic blood pressure (mmHg), diastolic blood pressure (mmHg), oxygen saturation (%) and respiratory rate (breaths/min).

Vital signs measurement will be analyzed using descriptive summary statistics for the change from baseline by treatment group and visit/time.

2.8.4.3 Chest imaging

In case of available records findings, chest imaging will be recorded in the CRF, at screening and at Day 15/early withdrawal.

Chest imaging (X-ray or and CT scan) data will summarized at baseline (Section 2.3.2).

2.9 Biomarkers

Analysis of other biomarkers will not be conducted.

2.10 Interim analysis

No formal interim analysis is planned for this trial.

3 Sample size calculation

3.1 Primary endpoint

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 3-1.

Table 3-1 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
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

3.2 Secondary endpoint

Data available from recent studies published by Gautret et al., 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.

4 Change to protocol specified analyses

None.

5 Appendix

5.1 Imputation rules

5.1.1 Study drug

Not applicable.

5.1.2 AE date imputation

Partial AE start and end dates will be imputed. If there is uncertainty whether an AE occurred treatment-emergent or not, imputation will be performed, such that AE will be considered as treatment-emergent. Rules for imputing AE end date or start date will be provided in Programming Dataset Specification (PDS) document in details.

5.1.3 Concomitant medication date imputation

Rules for imputing the CM end date or start date will be provided in Programming Dataset Specification (PDS) document in details.

5.1.4 Concomitant therapies and procedures date imputation

The missing dates will be imputed using the same rule as for the concomitant medication.

5.2 AEs coding/grading

The verbatim term recorded on CRF will be identified as adverse event and will be coded by primary system organ class and preferred term using Medical Dictionary for Regulatory Activities (MedDRA) version 23.0 and above.

5.3 Safety derivations

5.3.1 Laboratory parameters derivations

CTCAE grade for the laboratory parameters assess in the trial are provided in Table 5-1.

Table 5-1 CTCAE grades for laboratory parameters (CTCAE Version 5.0)

		Grade			
Abnormality	**Lab parameter**	**1**	**2**	**3**	**4**
Hematology					
Anemia	Hemoglobin (g/L)	<LLN - 100 g/L	<100 - 80 g/L	<80 g/L; transfusion indicated	Life-threatening consequences; urgent intervention indicated
Platelet count decreased	Platelets (thrombocytes) (10^9/L)	<LLN-75.0 x 10^9/L	<75.0 - 50.0 x 10^9/L	<50.0 - 25.0 x 10^9/L	<25.0 x 10^9/L
White blood cell decreased	Leukocytes (WBCs) (10^9/L)	<LLN - 3.0 x 10^9/L	<3.0 - 2.0 x10^9/L	<2.0 - 1.0 x 10^9/L	<1.0 x 10^9/L
Neutrophil count decreased	Absolute neutrophil count (10^9/L)	<LLN - 1.5 x10^9/L	<1.5 - 1.0 x10^9/L	<1.0 - 0.5 x10^9/L	<0.5 x10^9/L

		Grade			
Abnormality	**Lab parameter**	**1**	**2**	**3**	**4**
Lymphocyte count decreased	Absolute lymphocyte count (10^9/L)	<LLN x 0.8 - 10^9/L	<0.8 - 0.5 x 10^9/L	<0.5 - 0.2 x 10^9/L	<0.2 x 10^9/L
Lymphocyte count increased	Absolute lymphocyte count (10^9/L)		>4 – 20 x 10^9/L	> 20 x 10^9/L	
Chemistry					
Liver function					
Alanine aminotransferase increased	ALT (SGPT) (U/L)	ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnor
Aspartate aminotransferase increased	AST (SGOT) (U/L)	>ULN - 3.0 x ULN if baseline was normal; 1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 5.0 x ULN if baseline was normal; >3.0 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Blood bilirubin increased	Bilirubin (µmol/L)	>ULN - 1.5 x ULN if baseline was normal; > 1.0 - 1.5 x baseline if baseline was abnormal	>1.5 - 3.0 x ULN if baseline was normal; >1.5 - 3.0 x baseline if baseline was abnormal	>3.0 - 10.0 x ULN if baseline was normal; >3.0 - 10.0 x baseline if baseline was abnormal	>10.0 x ULN if baseline was normal; >10.0 x baseline if baseline was abnormal
GGT increased	Gamma-glutamyl transferase (GGT) (U/L)	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Alkaline phosphatase increased	Alkaline Phosphatase (U/L)	>ULN - 2.5 x ULN if baseline was normal; 2.0 - 2.5 x baseline if baseline was abnormal	>2.5 - 5.0 x ULN if baseline was normal; >2.5 - 5.0 x baseline if baseline was abnormal	>5.0 - 20.0 x ULN if baseline was normal; >5.0 - 20.0 x baseline if baseline was abnormal	>20.0 x ULN if baseline was normal; >20.0 x baseline if baseline was abnormal
Electrolytes					
Hypermagnesemia	Magnesium (Mg)	>ULN - 1.23 mmol/L	-	>1.23 - 3.30 mmol/L	>3.30 mmol/L; life-threatening consequences
Hypomagnesemia	Magnesium (Mg)	<LLN - 0.5 mmol/L	<0.5 - 0.4 mmol/L	<0.4 - 0.3 mmol/L	<0.3 mmol/L; life-threatening consequences
Hypokalemia	Potassium (K)	<LLN - 3.0 mmol/L	Symptomatic with <LLN - 3.0 mmol/L; intervention indicated	<3.0 - 2.5 mmol/L; hospitalization indicated	<2.5 mmol/L; life-threatening consequences

		Grade			
Abnormality	**Lab parameter**	**1**	**2**	**3**	**4**
Hyperkalemia	Potassium (K)	>ULN - 5.5 mmol/L	>5.5 - 6.0 mmol/L; intervention initiated	>6.0 - 7.0 mmol/L; hospitalization indicated	>7.0 mmol/L; life-threatening consequences
Cardiac abnormalities					
Renal function Note: A semi-colon (;) indicates 'or' within the description of the grade.					
CPK increased	CPK (creatine phosphokinase)	>ULN - 2.5 x ULN	>2.5 x ULN - 5 x ULN	>5 x ULN - 10 x ULN	>10 x ULN
Creatinine increased	Creatinine (µmol/L)	>ULN - 1.5 x ULN	>1.5 - 3.0 x baseline; >1.5 - 3.0x ULN	>3.0 baseline; >3.0 - 6.0 x ULN	>6.0 x ULN
Metabolism					
Hypoglycemia	Glucose (mmol/L)	<LLN - 55 mg/dL; <LLN - 3.0 mmol/L	<55 - 40 mg/dL; <3.0 - 2.2 mmol/L	<40 - 30 mg/dL; <2.2 - 1.7 mmol/L	<30 mg/dL; <1.7 mmol/L; life-threatening consequences; seizures

Note: summary statistics for laboratory parameters will only be based on laboratory measurements. Therefore the definition of CTCAE grade in these summary may slightly differ from the above definition.

5.4 Statistical models

Statistical models will not be implemented.

5.5 Exclusion criteria of analysis sets

The RAS, FAS and SAF analysis set will be used in analysis. Rule for participant classification in analysis set is provided in Table 5-2.

Table 5-2 Participant classification

Analysis Set	PD ID that cause participants to be excluded	Non-PD criteria that causes participants to be excluded
ENR	NA	Not having informed consent; Not having screening epoch disposition page
RAS	NA	Not randomized
FAS		Not in RAS; Mistakenly randomized and no double-blind study drug taken
SAF	NA	No double-blind study drug taken

5.6 Type of pulmonary/ventilatory support and component of the 9-point ordinal scale for clinical status

Table 5-3 Type of pulmonary/Ventilatory support

Type of support	Non invasive or invasive pulmonary support	Invasive pulmonary support
Low flow nasal oxygen	Yes	No
High flow nasal oxygen	Yes	No
Oxygen via face mask	Yes	No
Non-invasive ventilation	Yes	No
Mechanical ventilation	Yes	Yes
Intubation	Yes	Yes
Tracheostomy	Yes	Yes
ECMO	Yes	Yes

Table 5-4 9-point ordinal scale for clinical status

Score	Item
0	No clinical or virological evidence of infection
1	Ambulatory (defined as not in hospital or in hospital and ready for discharge): No limitation on activities
2	Ambulatory: Limitation of activities
3	Hospitalized Mild Disease: no oxygen therapy (defined as SpO2 >= 94% on room air)
4	Hospitalized Mild Disease: oxygen by mask or nasal prongs
5	Hospitalized Severe Disease: non-invasive or high-flow oxygen
6	Hospitalized Severe Disease: Intubation and mechanical ventilation
7	Hospitalized Severe Disease: Ventilation plus additional organ support – pressors, Renal replacement therapy (RRT), Extracorporeal membrane oxygenation ECMO
8	Death

6 References

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