ANTI-INFLAMMATORY CLARITHROMYCIN TO IMPROVE SARS-CoV-2 (COVID-19) INFECTION EARLY: THE ACHIEVE OPEN-LABEL NON-RANDOMIZED CLINICAL TRIAL

STUDY PROTOCOL

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DISCLOSURE OF PRINCIPAL INVESTIGATOR

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The herein protocol became known to myself by the Study Sponsor. I understand that the protocol remains as yet unpublished; I certify that all disclosed information to myself for this protocol will remain strictly confidential.

The Principal Investigator,

Print Name

Signature Date

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LIST OF ABBREVIATIONS

AE: adverse event

ATS: American Thoracic Society

CAP: community-acquired pneumonia

ECG: electrocardiogram

EOT: end of treatment

FiO_2: fraction of inspired oxygen

hBD-2: human β-defensin-2

IL: interleukin

LPS: lipopolysaccharide

PBMCs: peripheral blood mononuclear cells

P_{O2}: partial oxygen tension

SAE: serious adverse event

TOC: test of cure

TNFα: tumor necrosis factor-alpha

VAP: ventilator-associated pneumonia

SYNOPSIS

Aim	Recent information appearing from different countries suggest that treatment of Covid-19 with hydroxychloroquine or with a combination of hydroxychloroquine and azithromycin has either an indifferent effect on viral replication or substantial cardiotoxicity. This is a clinical trial aiming to prove that addition of oral clarithromycin to treatment regimen of Covid-19 is associated with early clinical improvement and attenuation of the high inflammatory burden of the host. The study will not comprise a placebo-comparator group since this is considered inappropriate in an era of a pandemic with substantial global mortality.
Design	Prospective, multicenter, open-label, non-randomized, single-arm trial
Inclusion criteria	• Age ≥18 years • Male of female gender • Written informed consent provided by the patients or by a first-degree relative in case of patients unable to consent • In case of women, unwillingness to remain pregnant during the study period achieved either by their partner using condom or by themselves using oral contraceptives. • Confirmed infection by SARS-CoV-2 virus • Infection of the upper respiratory tract or of the lower respiratory tract
Exclusion criteria	• Age below 18 years • Denial of written informed consent • Intake of any macrolide for the current episode of infection under study • Intake of hydroxychloroquine or chloroquine phosphate. • Presence of severe respiratory failure • Oral or intravenous intake of corticosteroids defined as any more than 0.4mg/kg daily intake of equivalent prednisone for the last 15 days • Neutropenia defined as an absolute neutrophil count below 1,000/mm^3 • Presence of any contraindications for the study drugs as stated in local label information • QTc interval at rest ECG ≥500 msec or history of known congenital long QT syndrome • Pregnancy or lactation

Study groups	Treatment will last for seven days. Every patient will receive one tablet of 500 mg of clarithromycin every 12 hours. It is explicitly stated that all other treatment is allowed with the only exclusion the parallel intake of a) any other drug of the macrolide class of antibiotics; and/or b) hydroxychloroquine or chloroquine phosphate. Drugs contraindicated with the intake of clarithromycin are also not allowed, as they are described in the local label information.
Primary study endpoint	This is defined on day 8 (EOT visit). This is a composite score since it is defined differently for patients with upper respiratory tract infection or lower respiratory tract infection by SARS-CoV-2. • For patients with an upper respiratory tract infection this is defined as no need for hospital admission in case of earlier discharge or as lack of progression into lower respiratory tract infection (as defined in APPENDIX II). • For patients with a lower respiratory tract infection this is defined as at least 50% decrease of the score of respiratory symptoms from the baseline. This score is the sum of scoring for the symptoms of cough, dyspnea, purulent sputum expectoration and pleuritic chest pain. Patients who develop by day 8 severe respiratory failure do not meet the study primary endpoint
Secondary study endpoints	• Comparison of the primary endpoint with historical comparators • Evaluation of the conditions composing the primary study endpoint on day 4 (visit 5) from start of treatment • Development of severe respiratory failure (TOC) • Hospital readmission until day 14 (TOC) defined as either need of re-hospitalization for discharged patients or any need for hospitalization of out-patients. • Change of viral load from baseline in respiratory secretions on days 4 and 8 • Change of function of monocytes, Th1 and Th2 (see sections of Laboratory procedures) at the EOT visit; this is also analyzed separately for patients with upper and with lower respiratory tract infection • Change of the serum levels of IL-6, IL-8 and hBD-2 defined as above (see sections of Laboratory procedures) at the EOT visit; this is also analyzed separately for patients with upper and with lower respiratory tract infection • Change of the IL-10/TNFα ratio defined as above (see sections of Laboratory

	procedures) at the EOT visit; this is also analyzed separately for patients with upper and with lower respiratory tract infection
Power of the study	Since the study does not have a comparative arm no official power calculation is done. However, the number of enrolled patients is calculated in an indirect approach. According to this, it is anticipated that the primary endpoint is reached among 40% of untreated patients. To increase this to 65% with 90% power at the 5% level of significance, 90 patients should be enrolled.
Interim analysis	An interim analysis after the EOT visit of the first 20 patients will be done. At that analysis, the primary endpoint of the 20 patients treated with clarithromycin will be compared with two groups of historical comparators: i) patients with Covid-19 treated with hydroxychroroquine/chloroquine; and b) patients with Covid-19 treated with the combination of hydroxychroroquine/chloroquine and azithromycin. If the achievement rate of the primary endpoint is not different, then the study will continue towards the total enrolment of 90 patients.
Duration of the study	2 years

BACKGROUND

Humanity is experiencing since December 2019 a new pandemic by the novel SARS Coronavirus-19 (SARS-CoV-2). As of March 25 2020 418,099 documented case were reported worldwide; 18,608 patients died[1]. The analysis of the clinical characteristics of these patients showed that the natural course of this disease, know with the acronym Covid-19, is several times unpredictable. Most patients who develop pneumonia do not have worrying symptoms although their chest X-ray or chest computed tomography may be positive for diffuse infiltrates. Suddenly a certain proportion of these patients deteriorate into severe respiratory failure; this usually takes place between the 5th and the 10th day of illness and arrives without any preceding symptom[2,3]. Published evidence suggests that this is due to the sudden arrival of an acute pro-inflammatory reaction of the host[4]. With this in mind, it is reasonable to make the assumption than the early treatment with an agent that can efficiently modulate the host response and prevent sudden hyper-inflammatory reaction may prevent the development of severe respiratory failure[5].

The new guidelines published by the American Thoracic Society in 2019 clearly suggest that the management of community-acquired pneumonia (CAP) should rely on the combination of β-lactam antibiotics with macrolides[6]. This position statement is pretty much influenced by the retrospective analyses of observational studies and of their meta-analyses in showing that the addition of a macrolide improves survival from severe CAP[7-12]. Since we leave in an era of antimicrobial resistance, it is profound that survival benefit is linked to the anti-inflammatory properties of the macrolide class of antibiotics. These properties are not only limited to the attenuation of the production of pro-inflammatory mediators but they involve the enhancement of pathogen clearance[13].

With this in mind, a small open-label trial among patients with Covid-19 showed better viral containment as assessed by the persistence of the virus in respiratory secretions, when patients were treated with a combination of azithromycin and hydroxychloroquine[14]. However, the clinical benefit coming from this study has not yet been published. Contrary to azithromycin, clinical evidence suggests that clarithromycin is associated with substantial clinical benefit among critically ill patients. Two randomized clinical studies in a total of 800 patients with sepsis have shown 28-day survival benefit among the most severe cases[15, 16]. One of these

studies enrolled patients with sepsis and ventilator-associated pneumonia; among 100 patients allocated to placebo treatment 40% survived until day 90; this was 57% among clarithromycin-treated patients[17].

In recent publication coming from the research network of the Hellenic Sepsis Study Group (HSSG) 130 patients with CAP were treated with a combination of β-lactam and clarithromycin. They were compared with 130 patients treated with a combination of β-lactam and azithromycin. Groups were well-matched for severity and comorbidities; 28-day mortality was 20.8% and 33.8% respectively[18].

Based on the above analysis, it seems likely that treatment of patients with Covid-19 with oral clarithromycin will substantially increase their anti-inflammatory properties and decrease the chances for development of severe respiratory failure.

As stated above, the efficacy of the treatment combination of hydroxychloroquine with azithromycin is based on results coming from only six patients[14]. Since the publication of these data other, yet unpublished, reports have appeared in the internet challenging the treatment efficacy of this combination. These results show that treatment with hydroxychloroquine either single or in combination with azithromycin have either an indifferent effect on viral replication or even a deleterious effect on the patient due to cardiotoxicity[19, 20]. With this in mind it is obvious that macrolide treatment in Covid-19 patients many of which have coronary heart disease and chronic heart failure as comorbidities[21] should be administered without hydroxychloroquine.

AIM OF THE STUDY

This is a clinical trial aiming to prove that the addition of oral clarithromycin to treatment regimen of Covid-19 is associated with early clinical improvement and attenuation of the high inflammatory burden of the host. The study will not comprise a placebo-comparator group since this is considered inappropriate in an era of a pandemic with substantial global mortality.

STUDY PROTOCOL

Study design

This is a prospective, open-label, single-arm trial to prove the efficacy of oral clarithromycin to attenuate the high inflammatory burden of patients with Covid-19. The study will be conducted according to the Helsinki declaration. Patients will be enrolled after written informed consent provided by themselves or by first degree relatives in case of patients not able to consent. The study protocol will be approved from the Ethics Committees of the participating hospitals, by the National Organization for Medicines of Greece and by the National Ethics Committee of Greece. The study will be registered at www.clinicaltrials.gov before inclusion of the first patient.

Inclusion criteria

Enrolled patients should meet ALL the below inclusion criteria:

- Age ≥18 years
- Male of female gender
- Written informed consent provided by the patients or by a first-degree relative in case of patients unable to consent
- In case of women, unwillingness to remain pregnant during the study period achieved either by their partner using condom or by themselves using oral contraceptives.
- Confirmed infection by SARS-CoV-2 virus
- Infection of the upper respiratory tract (as defined in Appendix I) or of the lower respiratory tract (as defined in Appendix II)

Exclusion criteria

Patients who meet ANY of the following cannot be enrolled in the study

- Age below 18 years
- Denial of written informed consent
- Presence of severe respiratory failure as defined in Appendix IV
- Intake of any macrolide for the current episode of infection under study

- Intake of hydroxychloroquine or chloroquine phosphate.
- Oral or intravenous intake of corticosteroids defined as any more than 0.4mg/kg daily intake of equivalent prednisone for the last 3 days
- Neutropenia defined as an absolute neutrophil count below 1,000/mm^3
- Presence of any contraindications for the study drugs as stated in local label information[22]
- QTc interval at rest ECG ≥500 msec or history of known congenital long QT syndrome
- Pregnancy or lactation

Screening procedures

Every patient eligible for the study should sign an informed consent form either by himself or by his first degree relative. Then the following should be evaluated:

- Presence of any of the exclusion criteria
- Rest ECG
- Acute symptoms of infection
- Physical examination including vital signs
- Past medical history
- Chest X-ray or chest computed tomography
- Lymphocyte absolute count (to be used for inclusion criteria)
- Arterial blood gases (to be used for inclusion criteria)

Once it is certain that a patient does not meet any of the exclusion criteria and that he meets all inclusion criteria, he may be enrolled in the study.

Intervention

Boxes containing cartridges of 14 oral tablets of 500mg of clarithromycin will be delivered to each site. Each box will have a separate number that corresponds to the each enrolled patients. Treatment will last for seven days. Every patient will receive one tablet of 500 mg of clarithromycin every 12 hours. It is explicitly stated that all other treatment is allowed with the only exclusion the parallel intake of a) any other drug of the macrolide class of antibiotics; and/or b) hydroxychloroquine or

chloroquine phosphate. Drugs contraindicated with the intake of clarithromycin are also not allowed, as they are described in the local label information[22].

Study visits

Visit 1

This is the visit of the first day (0 hours) of treatment. The following procedures will be done on that day in rank of order:

- Scoring of the respiratory symptoms in case of enrolment for lower respiratory tract infection. This includes separate scoring for cough, sputum production, dyspnea and pleuritic chest pain by the patient. Each symptom may be scored as absent (0 points), mild (1 point), moderate (2 points) or intense (3 points) (see Appendix III)
- Recording of co-morbidities, co-administered drugs and past-history
- Collection of 15 ml of blood. Blood will be drawn either from venipuncture of an antecubital vein or directly from a central vein catheter under sterile conditions and distributed as follows: a) 5ml into one sterile and pyrogen-free tube for serum isolation and measurement of pro- and anti-inflammatory mediators; and b) 10 ml into one EDTA-coated tube for isolation of peripheral blood mononuclear cells (PBMCs) and cytokine stimulation. This has to be shipped on the same day to the central lab.
- Administration of study drug two times during the day

Visit 2

This is the visit of the second day (post 24 hours) of treatment. The following procedures will be done on that day in rank of order:

- Scoring of the respiratory symptoms in case of enrolment for lower respiratory tract infection (Appendix III).
- New hospital admission in case of earlier hospital discharge
- Presentation of severe respiratory failure (see Appendix IV for definitions)
- Administration of study drug two times during the day
- In case of earlier hospital discharge, this visit is done either through phone call or through the internet

Visit 3

This is the visit of the third day (post 48 hours) of treatment. The following procedures will be done on that day in rank of order:

- Scoring of the respiratory symptoms in case of enrolment for lower respiratory tract infection (Appendix III).
- New hospital admission in case of earlier hospital discharge
- Presentation of severe respiratory failure (see Appendix IV for definitions)
- Administration of study drug two times during the day
- In case of earlier hospital discharge, this visit is done either through phone call or through the internet

Visit 4

This is the visit of the fourth (post 72 hours) day of treatment. The following procedures will be done on that day in rank of order:

- Scoring of the respiratory symptoms in case of enrolment for lower respiratory tract infection (Appendix III).
- New hospital admission in case of earlier hospital discharge
- Presentation of severe respiratory failure (see Appendix IV for definitions)
- Administration of study drug two times during the day
- Collection of sample from the upper airway for RT-PCR for SARS-CoV-2
- In case of earlier hospital discharge, this visit is done either through phone call or through the internet

Visit 5

This is the visit of the fifth (post 96 hours) day of treatment. The following procedures will be done on that day in rank of order:

- Scoring of the respiratory symptoms in case of enrolment for lower respiratory tract infection (Appendix III).
- New hospital admission in case of earlier hospital discharge
- Presentation of severe respiratory failure (see Appendix IV for definitions)
- Administration of study drug two times during this day
- In case of earlier hospital discharge, this visit is done either through phone call or through the internet

Visit 6

This is the visit of the sixth (post 120 hours) day of treatment. The following procedures will be done on that day in rank of order:

- Scoring of the respiratory symptoms in case of enrolment for lower respiratory tract infection (Appendix III).
- New hospital admission in case of earlier hospital discharge
- Presentation of severe respiratory failure (see Appendix IV for definitions)
- Administration of study drug two times during this day
- In case of earlier hospital discharge, this visit is done either through phone call or through the internet

Visit 7

This is the visit of the seventh (post 124 hours) day of treatment. The following procedures will be done on that day in rank of order:

- Scoring of the respiratory symptoms in case of enrolment for lower respiratory tract infection (Appendix III).
- New hospital admission in case of earlier hospital discharge
- Presentation of severe respiratory failure (see Appendix IV for definitions)
- Administration of study drug two times during this day
- In case of earlier hospital discharge, this visit is done either through phone call or through the internet

Visit 8: EOT

This is the end of treatment (EOT) visit that is taking place on the next day (day 8) from end of treatment. The following procedures will be done on that day in rank of order:

- Scoring of the respiratory symptoms in case of enrolment for lower respiratory tract infection (Appendix III).
- New hospital admission in case of earlier hospital discharge
- Rest ECG
- Presentation of severe respiratory failure (see Appendix IV for definitions)

- 15 ml of blood will be collected either from venipuncture of an antecubital vein or directly from a central vein catheter under sterile conditions and distributed as follows: a) 5ml into one sterile and pyrogen-free tube for serum isolation and measurement of pro- and anti-inflammatory mediators; and c) 10 ml into one EDTA-coated tube for isolation of PBMCs and cytokine stimulation. This has to be shipped on the same day to the central lab.
- Collection of sample from the upper airway for RT-PCR testing for SARS-CoV-2
- In case of earlier hospital discharge, this visit is done either through phone call or through the internet. In that case blood drawing and sample collection are not done

Visit 9: TOC

This is the test of cure (TOC) visit that is taking place 7 ± 1 day after the EOT visit. This visit can be done either by phone or on site. It can be done by phone if the patient is discharged from hospital or on site if the patient remains hospitalized. The following procedures will be done on that day in rank of order:

- Scoring of the respiratory symptoms in case of enrolment for lower respiratory tract infection (Appendix III).
- New hospital admission in case of earlier hospital discharge
- Presentation of severe respiratory failure (see Appendix IV for definitions)

An overview of study visits is presented in Appendix V.

LABORATORY PROCEDURES

Isolation of PBMCs

PBMCs will be isolated after gradient centrifugation of whole blood over Ficoll. After serial washing, counting and exclusion of dead cells, they will be stimulated for 24 hours with SARS-CoV-2 purified antigens for the production of TNFα, IL-6 interferon (IFN)-α and IFN-γ. The change of cytokine production over visits 1 and 8 will be considered as an index of the effect of clarithromycin on the function of:

- Circulating monocytes using production of TNFα.
- Circulating Th1 cells using production of IFNγ

- Circulating both monocytes and Th2 cells using production of IL-6
- Antiviral responses using production of IFNα

Biomarkers

Measured biomarkers in serum will be:

- IL-6 and IL-8 as biomarkers of non-specific markers of pro-inflammatory activity
- Huma β-defensin-2 (hBD-2) as specific marker of neutrophil activation
- TNFα and IL-10 where decreases of the IL-10/TNFα ratio from baseline visit 1 will be considered a shift towards pro-inflammatory responses
- Serum samples may also be used for exploratory analysis, if needed.

STUDY ENDPOINTS

Primary study endpoint

This is defined on day 8 (EOT visit). This is a composite score since it is defined differently for patients with upper respiratory tract infection or lower respiratory tract infection by SARS-CoV-2.

- For patients with an upper respiratory tract infection this is defined as no need for hospital admission in case of earlier discharge or as lack of progression into lower respiratory tract infection (as defined in APPENDIX II).
- For patients with a lower respiratory tract infection this is defined as at least 50% decrease of the score of respiratory symptoms from the baseline. This score is the sum of scoring for the symptoms of cough, dyspnea, purulent sputum expectoration and pleuritic chest pain.

Patients who develop by day 8 severe respiratory failure do not meet the study primary endpoint

Secondary study endpoints

- Comparison of the primary endpoint with historical comparators
- Evaluation of the conditions composing the primary study endpoint on day 4 (visit 5) from start of treatment
- Development of severe respiratory failure (TOC visit)

- Hospital readmission until day 14 (TOC) defined as either need of re-hospitalization for discharged patients or any need for hospitalization of out-patients.
- Change of viral load from baseline in respiratory secretions on days 4 and 7
- Change of function of monocytes, Th1 and Th2 (see sections of Laboratory procedures) at the EOT; this is also analyzed separately for patients with upper and with lower respiratory tract infection
- Change of the serum levels of IL-6, IL-8 and hBD-2 defined as above (see sections of Laboratory procedures) at the EOT visit; this is also analyzed separately for patients with upper and with lower respiratory tract infection
- Change of the IL-10/TNFα ratio defined as above (see sections of Laboratory procedures) at the EOT visit; this is also analyzed separately for patients with upper and with lower respiratory tract infection
- Change of the concentrations of IL-1 and IL-6 at rhinopharynx (see sections of Laboratory procedures) on days 4 and EOT; this is also analyzed separately for patients with upper and with lower respiratory tract infection

POWER OF THE STUDY

Since the study does not have a comparative arm no official power calculation is done. However, the number of enrolled patients is calculated in an indirect approach. According to this, it is anticipated that the primary endpoint is reached among 40% of untreated patients. To increase this to 65% with 90% power at the 5% level of significance, 90 patients should be enrolled.

STATISTICAL ANALYSIS

Results will be calculated as percentage and 95% confidence intervals. Comparisons with historical comparators will be analyzed by the Fischer exact test.

INTERIM ANALYSIS

An interim analysis after the EOT visit of the first 20 patients will be done. At that analysis, the primary endpoint of the 20 patients treated with clarithromycin will

be compared with two groups of historical comparator: i) patients with Covid-19 treated with hydroxychroroquine/chloroquine; and b) patients with Covid-19 treated with the combination of hydroxychroroquine/chloroquine and azithromycin. If the achievement rate of the primary endpoint is not different, then the study will continue towards the total enrolment of 90 patients.

ADVERSE EVENTS

Adverse events (AEs) and Serious Adverse Events (SAEs) will be collected from baseline until the last patient's evaluation. Investigators should monitor subjects for adverse events and are responsible for recording ALL adverse events and serious adverse events occurring to a patient during the trial. Mortality will not be reported as an SAE since this is the study secondary endpoint.

An adverse event is any undesirable medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. The time relationship is defined from the moment the AE occurs during therapeutic treatment until 30 days or 5 half-lives after treatment discontinuation. The adverse event may be a sign, a symptom, or an abnormal laboratory finding. Reporting to Health Authorities and Ethics Committees will be done by investigator according to the local requirements.

Serious adverse events. SAEs must be reported by the investigator to the health authorities and ethics committee according to the local requirements within 24 hours. If an adverse event meets any of the following criteria, it is considered SAE:

- **Life-threatening situation** The subject was at risk of death at the time of the adverse event/experience. It does not refer to the hypothetical risk of death if the AE were more severe or were to progress.
- **Inpatient hospitalization** or prolongation of existing hospitalization.
- **Persistent or significant disability/incapacity** Any AE having an outcome that is associated with a substantial disruption of the ability to carry out normal life functions, including the ability to work. This is not intended to include transient interruption of daily activities.
- **Congenital anomaly/birth defects** Any structural abnormality in subject's offspring that occurs after intrauterine exposure to treatment.

- **Important medical events/experiences** that may not result in death, be life-threatening, or require hospitalization may be considered a serious adverse event/experience when, based upon appropriate medical judgment, **they may jeopardize the subject and may require medical or surgical intervention to prevent one of the outcomes listed above,** i.e., death, a life-threatening adverse event/experience, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant disability/incapacity, or a congenital anomaly/birth defect. Examples of such medical events/experiences include allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasias or convulsions that do not result in inpatient hospitalization, or the development of drug dependency or drug abuse.
- **Spontaneous and elective abortions** experienced by study subject.

A non-serious adverse event is any untoward medical occurrence in a patient or subject who is administered a pharmaceutical product, and which does not necessarily have a causal relationship with this treatment. A non-serious adverse event is one that does not meet the definition of a serious adverse event given. **Non-serious adverse events** must be reported by the investigator to the health authorities and ethics committee according to the local requirements at the end of the trial.

Grading of severity

The severity of the adverse events shall be graded as:

- **Mild** the adverse event is transient and well tolerated by the patient
- **Moderate** the adverse events causes discomfort and affects the usual activities of the patient.
- **Severe** the adverse events affects the usual activities of the patient to an important degree and may cause disability or be life-threatening.

Relationship to the drug

The investigator will use the following definitions to assess the relationship of the adverse event to study drug:

- **Probably Related**: The adverse event has a strong time relationship to the drug or relapses if re-induced, and another etiology is improbable or clearly less probable.
- **Possibly Related**: The adverse event has a strong time relationship to the drug and an alternative aetiology is as probable or less probable.
- **Probably not Related**: The adverse event has a slight or no time relationship to the drug and/or there is a more probable alternative aetiology.
- **Unrelated**: The adverse event is due to an underlying or concomitant disease or to another pharmaceutical product and is not related to the drug (no time relationship and a much more probable alternative aetiology).

If an investigator's opinion of possibly related, probably not related or not related to study drug is given, an alternate etiology must be provided by the investigator. Please note that a severe adverse event/experience is not necessarily serious, as the term severe is a measure of intensity while a serious adverse event is determined based on the aforementioned regulatory criteria. Individual un-blinding thought to be necessary for the management of an adverse event will be documented in the subject Case Report Form.

QUALITY CONTROL AND ASSURANCE

Quality control and assurance checks are performed by sponsor in order to allow periodic review of adequacy of the study activities and practices and allow for revising such practices as needed so the data and process are maintained, the study meets the protocol and procedural requirements, and is reproducible.

Before enrolling any subject in this study, sponsor personnel and the investigator have to review the protocol, the IB, the CRFs and instructions for their completion, the procedure for obtaining informed consent and the procedure for reporting AEs and SAEs.

A qualified representative of the sponsor will monitor the conduct of the study by visiting the site and by contacting the site by telephone and e-mail. During these site visits, all source documents are reviewed, and information recorded in the CRFs is verified against them.

Besides routine monitoring, quality assurance will be documented through independent auditing of the quality control activities and where applicable, by regulatory authorities through inspections.

ETHICAL CONSIDERATIONS

Prior to the initiation of this study, the study design will receive ethical, scientific, and where applicable, regulatory review. Investigators will conduct this study in accordance with the principles of the Declaration of Helsinki, GCP, and applicable regulatory requirements.

Regarding Informed Consent Form obtaining procedures, before any procedure specified in the protocol is performed, a subject must:

- Be informed of all pertinent aspects of the study and all elements of informed consent
- Be given time to ask questions and to consider the decision to participate
- Voluntarily agree to participate in the study
- Sign and date the updated and approved by IEC/REB ICF version.

PROTOCOL ADHERENCE AND AMENDMENTS

Investigators ascertain that they will apply due diligence to avoid protocol deviations. All significant protocol deviations will be recorded and reported in the clinical study report (CSR). Any change or addition to the protocol can only be made in a written protocol amendment that must be approved and signed by the sponsor, health authorities where required, and the IEC/REB.

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APPENDIX I Definition of upper respiratory tract infection

Acute presentation of at least two of the following signs or symptoms:

- Core temperature ≥ 37.5°C
- New onset of cough
- Chills or rigor
- Total absolute lymphocyte count less than 1,500/mm^3

APPENDIX II Definition of upper respiratory tract infection

Acute presentation of all categories of signs or symptoms is necessary

Category 1

Infiltrates compatible with lower respiratory tract infections in chest X-ray or in chest computed tomography

Category 2

At least 1 of the following

- New onset of cough or worsening cough
- Dyspnea
- Respiratory rales compatible with lung infection
- Total absolute lymphocyte count less than 1,500/mm^3

APPENDIX III Scoring of symptoms of lower respiratory tract infection

Symptom	Absent (score=0)	Mild (score=1)	Moderate (score=2)	Severe (score=3)
Cough	No cough or resolution (to pre-CAP levels)	Cough present but it does not interfere with subject's usual daily activities	Cough present, frequent and it does interfere with some of the subject's usual daily activities	Cough is present throughout the day and night; it limits most of the subjects' usual daily activities and sleep patterns
Chest pain	No chest pain or resolution of chest pain related to CAP	Chest pain present occasionally with deep breathing but it does not interfere with subject's usual daily activities	Chest pain is present with normal breaths and it does interfere with the subject's usual daily activities	Chest pain is present at rest and/or with shallow breathing; it limits most of the subject's usual daily activities
Shortness of breath (dyspnea)	No shortness of breath or resolution (to pre-CAP Baseline)	Shortness of breath with strenuous activities only but it does not interfere with subject's usual daily activities	Shortness of breath with usual activities and it does interfere with the subject's usual daily activities	Shortness of breath with minimal exertion or at rest; it limits most of the subject's usual daily activities
Sputum	No coughing up of phlegm/sputum or resolution (to pre-CAP Baseline)	Subject coughs up a small amount of phlegm/sputum	Subject coughs up a moderate amount of phlegm/sputum	Subject coughs up a large amount of phlegm/sputum

APPENDIX IV Definition of severe respiratory failure

Presence of all of the following:

- pO_2/FiO_2 less than 150
- Need for mechanical or non-mechanical ventilation (CPAP)

APPENDIX V Study visits

Visits days	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8 EOT**	**14 TOC**
Informed consent	x								
Scoring of symptoms	x	x	x	x	x	x	x	x	x
Nasopharyngeal swab	x			x				x	
Blood sampling	x							x	
Study drug administration	x	x	x	x	x	x	x		
New hospital admission		x	x	x	x	x	x	x	x
Severe respiratory failure		x	x	x	x	x	x	x	x
ECG at rest	x							x	
AE/SAE		x	x	x	x	x	x	x	x