Protocol Title: A randomized, open-label, active controlled, parallel group, multicenter phase 3 study to evaluate efficacy and tolerability of Casirivimab plus Imdevimab and Sotrovimab in patients with mild to moderate COVID-19 (**AntiCov**).

EudraCT: 2021-004035-88

Compounds: Casirivimab; Imdevimab; Sotrovimab

Study Phase: III

Short Title: AntiCov

Coordinating Investigator: Prof. Luca Richeldi

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADR	Adverse Drug Reaction
AIFA	Agenzia Italiana del Farmaco
AE	Adverse Event
ALT	Alanine AminoTransferase
aPTT	activated Partial Thromboplastin Time
AST	Aspartate AminoTransferase
ATC	Anatomical Therapeutic Chemical classification
BMI	Body Mass Index
CFR	Case Fatality Rate
CIs	Confidence Intervals
CRP	C-Reactive Protein
eCRF	Electronic Case Report Form
EC	Ethic committee
EDC	Electronic data capture
ESR	Erythrocyte Sedimentation Rate
FAS	Full Analysis Set
GGT	Gamma-glutamyl transferase
HB	Haemoglobin concentration
HCT	Hematocrit red blood cell volume
HR	Heart rate
ICH GCP	International Conference on Harmonisation-Good Clinical Practice
ICU	Intensive care unit
INR	International normalised ratio
IV	Intra Venous
K-M	Kaplan-Meier method
LDH	Lactate dehydrogenase
MCHC	Mean corpuscular haemoglobin concentration
MCV	Mean corpuscular volume
MHC	Mean corpuscular hemoglobin
NCI CTCAE	National Cancer Institute Common Terminology Criteria for Adverse Events

NSAIDs	Non-steroidal anti-inflammatory drugs
PaO_2/FiO_2	Ratio of arterial oxygen partial pressure to fractional inspired oxygen
PDF	Portable document format
PI	Principal Investigator
PPAS	Per-Protocol Analysis Set
PT	Prothrombin time
RBC	Red blood cell count
SADR	Serious Adverse Drug Reaction
SAE	Serious Adverse Event
SAF	Safety Analysis Set
SAP	Statistical analysis plan
SD	Standard deviation
SOC	Standard of Care
SpO_2	Peripheral Oxygen saturation
SUSAR	Suspected serious unexpected adverse reaction
TEAE	Treatment Emergent Adverse Event
UOC	Complex Operating Unit

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1. INTRODUCTION

1.1 Background and rationale

The Severe Acute Respiratory Syndrome COronavirus 2 (SARS-CoV-2) was first identified in December 2019 in Wuhan, China and is the etiological agent of the COronaVIrus Disease 2019 (COVID-19)[1]. COVID-19 symptoms are diverse and non-specific such as cough, fever, malaise, myalgia, gastrointestinal symptoms, ageusia, and anosmia. In some patients the disease course may lead to a critical care condition requiring ventilatory support and admission to an intensive care unit (ICU). Italy has been particularly affected by COVID-19 [2] and, according to the data of Protezione Civile on March 31, 2020, the average interregional case fatality rate (CFR) and ICU admission rate were 7.5% and 21.4%, respectively [3].

A recent trial evaluated the safety and efficacy of the combination of monoclonal antibodies bamlanivimab and etesevimab in outpatients with mild to moderate COVID-19. Treatment with bamlanivimab plus etesevimab, compared with placebo, was associated with a statistically significant reduction in SARS-CoV-2 viral load at day 11 [4]. The *post-hoc* analyses conducted in patients at high-risk of developing severe COVID-19 showed that hospitalizations rates were higher in the placebo group and no hospitalizations were observed in the active treatment group. Adverse events reported were mild, mostly nausea and diarrhea [5]. Moreover, a trial involving non-hospitalized patients with mild to moderate COVID-19 found similar results with the REGN-COV2 antibody cocktail (Casirivimab plus Imdevimab) [6]. In an interim analysis, REGN-COV2 was well tolerated with few and mainly low-grade adverse effects (vomiting and nausea) [7]. Preliminary data on an interim analysis from the COMET-ICE trial in outpatients with mild to moderate COVID-19 receiving 500 mg of Sotrovimab or placebo showed fewer cases of COVID-19 progression in terms of hospitalization for more than 24 hours or death by day 29 in the Sotrovimab group, compared to placebo [8]. The most common adverse effects were described as mild (rash and diarrhea) [9].

Given the latest data emerging from the very recent literature on the Bamlanivimab plus etesevimab association suggesting caution with its use in patients infected by the SARS-CoV-2 gamma variant because of the high risk of disease progression [10–12], Agenzia Italiana del Farmaco (AIFA) has stated that the antiviral activity of Bamlanivimab plus etesevimab is strongly inhibited against beta (B.1.351) and gamma (P.1) variants, unlike the other available monoclonal

antibodies (casirivimab plus imdevimab and sotrovimab). Therefore, it is suggested to use the Casirivimab plus imdevimab association and sotrovimab, effective against all variants, in the areas where beta and gamma variants circulation is present, or to precede the start of any therapy by genotyping/sequencing [13].

Monoclonal antibodies are currently recommended in patients with COVID-19 at high risk of progressing to severe disease by identifying the following conditions as risk factors: advanced age, obesity, cardiovascular disease (including hypertension), chronic lung disease (including asthma), type 1 or type 2 diabetes mellitus, chronic kidney disease (including patients on dialysis), chronic liver disease, immunosuppressed (cancer treatment, bone marrow or organ transplantation, immune deficiencies, HIV (if poorly controlled or evidence of AIDS), sickle cell anaemia, thalassaemia, and prolonged use of immune-weakening medications.

In the context of these findings, and since no studies directly compared casirivimab plus imdevimab with sotrovimab, we want to explore efficacy and tolerability of currently available monoclonal antibodies in two study cohorts defined as high-risk and low-risk populations based on patients' medical condition (i.e., medical history, comorbidities, medications) for COVID-19 treatment.

2. STUDY OBJECTIVES

2.1 Primary objective

- Explore the efficacy of monoclonal antibodies (casirivimab plus imdevimab and sotrovimab) and standard of care in COVID-19 patients by evaluating disease progression, measured as hospitalization, or oxygen desaturation ≥4%, or peripheral oxygen saturation ≤92%, during the 30-day follow-up period.
- Explore the efficacy of monoclonal antibodies (casirivimab plus imdevimab and sotrovimab) in COVID-19 patients by evaluating disease progression, measured as hospitalization, or oxygen desaturation ≥4%, or peripheral oxygen saturation ≤92%, during the 30-day follow-up period in high-risk patients.

2.2 Secondary objectives

- Assess the impact of monoclonal antibodies on safety and tolerability during the 30-day follow-up period.
- Assess the impact of monoclonal antibodies on survival during the 30-day follow-up period.
- Assess the impact of monoclonal antibodies on workplace/school productivity loss, in terms of days off from work (sick leave)/school, during the 30-day follow-up period.

2.3 Primary endpoint

- Disease progression, defined as: hospitalization, or oxygen desaturation ≥4% or peripheral oxygen saturation ≤92% during the 30-day follow-up period.

2.4 Secondary endpoints

- Incidence and severity of adverse events, with severity determined according to the 5-point severity scale (National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 [NCI CTCAE, v.5.0]) during the 30-day follow-up period.
- Proportion of patients admitted to the Emergency Department for COVID-19 disease during the 30-day follow-up period.
- All-cause mortality due to COVID-19 disease.
- Number of days off from work (sick leave)/school, during the 30-day follow-up period.

3. STUDY DESIGN

This is a randomized, open-label, parallel group, multicenter, phase IIIb/IV study to assess safety and efficacy of the monoclonal antibodies casirivimab plus imdevimab and sotrovimab in high-risk patients with mild to moderate COVID-19, and to assess safety and efficacy of casirivimab plus imdevimab, sotrovimab and standard of care in low-risk patients with mild to moderate COVID-19.

3.1 Study population

Patients with SARS-CoV-2 infection will be eligible for the study. Patients will be included after signature of the informed consent form and screening for inclusion and exclusion criteria (see

sections 3.2 and 3.3) and divided into two cohorts (high-risk and low-risk populations as defined by risk stratification criteria). Patients will be encouraged to ask any questions regarding the study aims and procedures, to be answered straightforwardly by the investigators.

3.2 Inclusion criteria

Participants are eligible to be included in the study if all the following criteria apply:

For both cohorts (high-risk and low-risk populations):

1. Signed informed consent form.
2. Men or non-pregnant women ≥12 years of age at the time of randomization.
3. Agree to the collection of nasopharyngeal swabs.
4. Currently not hospitalized.
5. Have one or more mild or moderate COVID-19 symptoms such as fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, or shortness of breath.
6. Must have sample collection for first positive SARS-CoV-2 viral infection.

3.3 Risk stratification criteria

High-risk for severe COVID-19 population will be stratified based on the following conditions:

- age ≥65 years, BMI ≥30 kg/m^2, chronic kidney disease, chronic lung diseases (including chronic obstructive pulmonary disease, moderate-to-severe asthma, interstitial lung disease, cystic fibrosis, pulmonary hypertension), diabetes, heart disease (including heart failure, coronary artery disease, cardiomyopathies, blood hypertension), immunocompromised state, liver disease, stroke or cerebrovascular disease.

Subjects that meet inclusion criteria but not satisfy the high-risk conditions, will be stratified in the low-risk group.

3.4 Exclusion criteria

Participants are excluded from the study if any of the following criteria apply (for both study populations):

1. SpO_2 ≤92% on room air at sea level or PaO_2/FiO_2 <300.
2. Respiratory rate ≥30 per minute.

3. Heart rate ≥125 per minute.
4. Hospitalized for COVID-19.
5. Respiratory failure secondary to COVID-19.
6. Known allergies to any of the components used in the formulation of the study drugs.
7. Hemodynamic instability.
8. Suspected or proven serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking study drugs.
9. Any comorbidity requiring surgery within 7 days, or that is considered life-threatening within 29 days.
10. Any serious concomitant systemic disease, condition, or disorder that, in the opinion of the investigator, should preclude participation in the study.
11. History of a positive SARS-CoV-2 serology.
12. Have received an investigational intervention for SARS-CoV-2 prophylaxis within 30 days before dosing (anti-COVID-19 vaccines are allowed).
13. Have received treatment with a SARS-CoV-2 specific monoclonal antibody.
14. Have a history of convalescent COVID-19 plasma treatment.
15. Have participated, within the last 30 days, in a clinical study involving an investigational intervention. If the previous investigational intervention has a long half-life, 5 half-lives or 30 days, whichever is longer, should have passed.
16. Concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study.
17. Pregnant or breast feeding.

3.5 Patients' withdrawals

In rare instances, it may be necessary for a participant to permanently discontinue study intervention. If the IV infusion is definitively discontinued, the participant will remain in the study for follow-up.

A participant may withdraw from the study:

- at any time at his/her own request;
- at the request of his/her designee (i.e., parents or legal guardian);

- at the discretion of the investigator for safety, behavioral, compliance, or administrative reasons;
- if the participant, for any reason, requires treatment with another therapeutic agent that has been demonstrated to be effective for treatment of the study indication, discontinuation from the study occurs prior to introduction of the new agent.

Discontinuations are expected to be rare. At the time of discontinuing from the study, if possible, an early discontinuation visit should be conducted.

If the participant withdraws consent for disclosure of future information, the investigators may retain and continue to use any data collected before such a withdrawal of consent.

4. CONCOMITANT MEDICATIONS

For any concomitant morbidity participants should be treated according to standard of care. Concomitant treatment with convalescent COVID-19 plasma is not allowed. Any medication, investigational agent, or vaccine that the participant is receiving at the time of enrollment or receives during the study must be recorded along with reason for use, dates of administration including start and end dates, and dosage information including dose and frequency for concomitant therapy of special interest. Corticosteroid use is permitted at any time during the study. Other concomitant medication may be considered on a case-by-case basis in the opinion of the investigator. Anti-COVID-19 vaccines are not expected to be received during the study. However, if any patient receives anti-COVID-19 vaccine, this should be recorded in the eCRF and the patient should continue in the study.

5. STUDY MEDICATION

The study medication intended for the high-risk study population are listed below:

- Casirivimab 1200 mg + imdevimab 1200 mg (manufactured by Regeneron-Roche)
- Sotrovimab 500 mg (manufactured by GlaxoSmithKline)

The study medication intended for the low-risk study population are listed below:

- Casirivimab 1200 mg + imdevimab 1200 mg (manufactured by Regeneron-Roche)
- Sotrovimab 500 mg (manufactured by GlaxoSmithKline)

- Standard of Care*

*Standard of Care (SOC) is defined according to "Raccomandazioni AIFA sui farmaci per la gestione domiciliare del COVID-19. Versione 2, aggiornata al 26/04/2021" [10], including symptomatic treatments such as paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) in case of symptoms such as fever and myalgia. Other symptomatic drugs are allowed, as in the opinion of the investigators.

6. STUDY PROCEDURE AND ASSESSMENTS

Study procedures and their timing are summarized in the schedule of activities (Table 1). In Figure 1 is summarized the overall study design.

Enrolment, screening, randomization and treatment infusions will take place at the coordinating Centre (Fondazione Policlinico Universitario A. Gemelli, IRCCS, Roma).

Enrolment and screening visits will also take place at the other participating Centres:

- Unità Operativa Complessa di Pronto Soccorso, Ospedale San Pietro, Fatebenefratelli, Roma;
- Unità Operativa Complessa di Pronto Soccorso e breve osservazione, Azienda Ospedaliera San Giovanni Addolorata, Roma;
- Unità Operativa Complessa Medicina D'Urgenza e Pronto Soccorso, Ospedale Pertini, Roma.

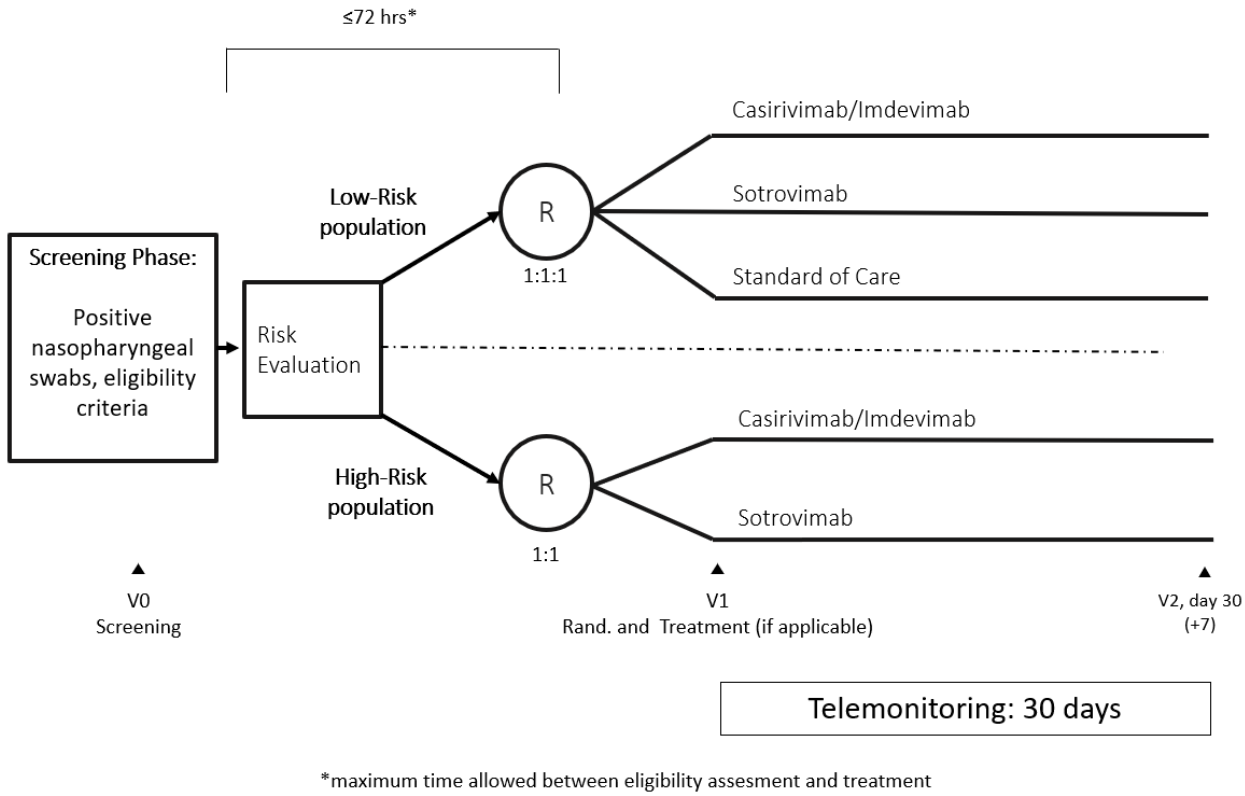

Figure 1. Study design

6.1 Study schedule

The investigational plan is summarized in the following schedule of activities.

Table 1. Schedule of activities.

ACTIVITIES	SCREENING	RANDOMIZATION	FOLLOW-UP	
Study Visit (V)	***V0***	***V1***	***Telemonitoring***	***V2***
Study Days (D)	***D-1***	***D-1 to D-3***	***Daily for the next 30 days***	***D-31 to D-34 (+ 7 days)***
Informed consent	X			
Demographics	X			
Medical history	X			
Physical examination	X			
Vital signs[1]	X	X		
Vital signs reduced[2]			X	
Height	X			

Weight	X			
Vaccination status	X			X
Concomitant medications	X	X	X	X
Comorbidities	X			
Nasopharyngeal swab PCR for SARS-CoV-2 viral infection	X			
Collection of haematology data[4] (non-mandatory)	X			
Collection of clinical chemistry and coagulation data[5] (non-mandatory)	X			
Arterial Blood Gas[6] (non-mandatory)	X			
Urine pregnancy test (mandatory)	X			
Review of in/exclusion criteria - Stratification	X	X		
Randomization		X		
Administer study intervention[7] (IV infusion or SOC)		X		
Telemonitoring devices (training and allocation)		X		
Adverse events		X	X	X
Vital status		X	X	X
Return of telemonitoring devices				X

[1]Blood pressure, heart rate, oxygen saturation: SpO_2 or PaO_2/FiO_2 Respiratory rate, body temperature.

[2]Heart rate, oxygen saturation

[3]SARS-CoV-2 nasopharyngeal swab.

[4]According to routine care; before IV infusion; Hemoglobin concentration (HB), Red blood cell count (RBC), Platelet count, Hematocrit red blood cell volume (HCT), MCV, MCH, MCHC, Leucocytes, Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils, Reticulocytes, ESR or erythrocyte sedimentation rate (in Italian: VES)

[5]According to routine care; before IV infusion; ALT, AST, Creatinine, GGT, Total Bilirubin, Urea, D-Dimer, PT, aPTT, INR, LDH, C-reactive protein (CRP), Procalcitonin.

[6] According to routine care; before IV infusion

[7]Study intervention must be administered within 72 hours from the time of first positive SARS-CoV-2 nasopharyngeal swab collection. Participants will be monitored for at least 60 minutes after completion of the infusion.

6.2 Assessment visit

A signed and dated informed consent must be obtained before any study-specific assessments are performed (refer to section 11).

Assessments that are part of routine care are not considered study-specific and may be used at screening to determine eligibility. These data will be registered in eCRF if performed.

Patients will perform nasopharyngeal swab PCR test for SARS-CoV-2 viral infection; these samples will be retained by the coordinating Centre, to perform SARS-CoV-2 variants genome sequencing.

All subjects will be screened for eligibility before randomization. Only eligible subjects will be randomized into the study. All screening procedures must be performed within 72 hours of documentation of SARS-CoV-2 infection.

6.3 Randomization

Three hundred (300) patients defined as Low-risk COVID-19 worsening will be randomized in an open-label fashion at a 1:1:1 ratio to the treatment groups casirivimab 1200 mg and imdevimab 1200 mg (Group A), sotrovimab 500 mg (Group B) or standard of care (Group C). Each treatment group will include 100 patients.

One hundred sixty (160) patients with the presence of risk factors of severe COVID-19 worsening, defined as high-risk, will be randomized in an open-label fashion at a 1:1 ratio to the treatment groups casirivimab 1200 mg and imdevimab 1200 mg (Group D) or sotrovimab 500 mg (Group E). Each treatment group will include 80 patients.

Two separate randomization lists will be produced: one for cohort of patients not at risk of severe illness for COVID-19 and one for cohort of patients at risk of severe illness of COVID-19.

The Randomization Biostatistician sets up the procedure for generating the randomization lists by using the SAS System software.

In order to ensure the reproducibility of the randomization lists, as from request of ICH Topic E9, the random number seeds and the procedure will be saved together with the randomization material. The randomization system GENIUS IWRS will be produced and implemented by the CRO and the platform will be part of the eCRF.

6.4 Treatment visit

Low-Risk participants will be randomized to receive a single IV infusion of either casirivimab plus imdevimab, sotrovimab or will be randomized to standard of care.

High-risk participants will be randomized to receive a single IV infusion of either casirivimab plus imdevimab or sotrovimab.

6.4.1 Treatment groups

Experimental medications for the low-risk population and high-risk population are the following:

- Casirivimab plus imdevimab: the recommended dose is casirivimab 1200 mg and imdevimab 1200 mg administered as a single intravenous infusion over 60 minutes.
- Sotrovimab: the recommended dose is 500 mg administered as a single intravenous infusion over 30 minutes.

Patients should be monitored during the IV infusion and for at least 60 minutes after infusion is finished. The site will have resuscitation equipment, emergency drugs and appropriately training staff.

6.4.2 Standard of Care for Low-Risk population

Standard of care (SOC) is defined according to “Raccomandazioni AIFA sui farmaci per la gestione domiciliare del COVID-19. Versione 2, aggiornata al 26/04/2021” [10], including symptomatic treatments such as paracetamol or non-steroidal anti-inflammatory drugs (NSAIDs) in case of symptoms such as fever and myalgia. Other symptomatic drugs are allowed, as in the opinion of the investigators.

6.5 Patient monitoring

After receiving the treatment, patients will leave the Centre and will be provided with daily medical and nursing assistance by a dedicated telemonitoring system. Participants must download the "Genius ROSA" telemedicine app (validated and certified as a Class IIa medical device) on their smartphone or tablet, equipped with a telephone line / internet connection.

Each patient will receive a pulse oximeter with bluetooth connection able to communicate with the “Genius ROSA” app for recording of the measured parameters. The "Genius ROSA" app is associated with a digital platform, allowing the investigators to access the data recorded by the patients, and to automatically transmit the corresponding values to the eCRF.

The medical and nursing study team (UOC Pneumologia, Fondazione Policlinico Universitario A. Gemelli IRCCS) will monitor study participants.

The tasks of this team will include:

1. register and activate patient’s profile on the “Genius ROSA” platform;
2. customize the monitoring plan and support patients and caregivers in the use of the app;
3. check the correct use of the pulse oximeter;
4. read and interpret data and alerts, made available through the platform.

The remote monitoring device consists of a wireless pulse oximeter (Wellue Viatom PC-60FW or other equivalent) for measuring peripheral arterial oxygen saturation (SpO_2) and heart rate (HR) and the secure transmission of data directly to the App "Genius ROSA". Participants will be instructed in the correct use of the telemonitoring device, and the pulse oximeter - smartphone coupling. This is explained in the Manual provided to the patient.

The study team will illustrate how to use the wireless pulse oximeter, how to connect the app with the device, verify that the data entered in the app has been sent to the platform, respond to alerts or messages sent, manage the video consultation function, and manage possible system errors. The parameters monitored will be specifically the peripheral arterial oxygen saturation (SpO_2) and heart rate (HR). The patient will proceed with the measurement daily (twice a day) during pre-established time windows (8:00 - 10:00 and 18:00 - 20:00). Data submitted by patients via the app will be viewed and evaluated by a team member. The team will be contactable by each patient at an e-mail address and a dedicated telephone number provided during enrollment.

The "Genius ROSA" app provides alerts relating to the parameters measured by patients during follow-up. Clinically significant changes in SpO_2 and / or heart rate will trigger alerts that will be sent to investigators. In the case of alerts from the system, a member of the study team (medical or nursing staff) responsible for daily monitoring will inform the medical staff to identify the most appropriate interventions, including updating the alerts, schedule a telematic clinical consultations, alert the emergency room of the coordinating Centre and send a referral letter to the emergency room triage. The description of the alerts is defined in the platform manual.

Follow-up visits can be carried out electronically to verify and update the risk profile of the participants, the personalized program and the correct functioning of the devices. The duration of the follow-up is set at 30 days. Finally, a final visit is foreseen which will allow the patient's state of health to be assessed and the devices supplied to be returned on V2, to be performed within 7 days after the 30th day of telemonitoring follow-up.

7. EVALUATION OF ADVERSE EVENTS AND SAFETY INFORMATION

7. 1 Definitions

For this study, an adverse event (AE) is defined as any untoward medical occurrence in a patient which does not necessarily have a causal relationship with medicinal product.

An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory finding), symptom, or disease not necessarily temporally associated with the use of a medicinal product.

An Adverse Drug Reaction (ADR) is “a response to a medicinal product which is noxious and unintended” [DIR 2001/83/EC Art 1 (11)]. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. An adverse reaction is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Use outside the marketing authorization includes off-label use, overdose, misuse, abuse and medication errors.

A Serious Adverse Event (SAE) / Serious Adverse Drug Reaction (SADR) is any untoward medical occurrence or effect that at any dose falls in one or more of the following categories:

- Resulting in death: death is not an AE but an outcome. It is the cause of death that should be regarded as the AE. The only exception to this rule is “sudden death” where no cause has been established; in this latter instance, “sudden death” should be regarded as the AE and “fatal” as its reason for being serious.
- Being life-threatening: life-threatening refers to a reaction in which the patient was at risk of death at the time of the reaction (e.g., aplastic anemia, acute renal failure, and anaphylaxis). The term does not refer to a reaction which hypothetically might have caused death if it were more severe.
- Requiring in-patient hospitalization: hospitalization refers to a situation whereby an AE is associated with unplanned overnight admission into hospital, usually for purpose of investigating and/or treating the AE. Hospitalization for the treatment of a medical condition that occurs on an “elective” or “scheduled” basis or for a pre-existing condition that did not worsen during the study should not necessarily be regarded as an AE. Complications that occur during the hospitalization are AEs. If a complication prolongs hospitalization, the event is a serious AE.
- Resulting in persistent or significant disability or incapacity: the term significant disability should be viewed as any situation whereby an AE has a clinically important effect on the patient’s physical or psychological well-being to the extent that the patient is unable to function normally.
- Being a congenital anomaly or birth defect.
- Being a medically significant AE: this criterion allows for any situations in which medical and scientific judgement should be exercised in deciding whether other situations should be considered serious, such as important medical events that might not be immediately life-threatening or result in death or hospitalization, but might jeopardize the patient or might require intervention to prevent one of the above outcomes.

Examples of such events include 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 drug dependency or drug abuse.

A Non-Serious AE/Non-Serious ADR is an AE or ADR that does not meet the criteria listed above for a SAE/serious ADR.

A suspected serious unexpected adverse reaction (SUSAR) is defined as an adverse reaction that is both unexpected (not consistent with the applicable product information) and meets the definition of a Serious Adverse Reaction.

7.2 Intensity of Adverse Event/Adverse Reaction

Each AE/ADR must be rated using 5-point severity scale (National Cancer Institute Common Terminology Criteria for Adverse Events, Version 5.0 [NCI CTCAE, v.5.0.].

7.3 Causality Collection

The investigator should assess causal relationship between study intervention and each AE, and answer 'yes' or 'no' to the question 'Do you consider that there is a reasonable possibility that the event may have been caused by the investigational product?'

For SAEs, causal relationship should also be assessed for other medication and study procedures. Note that for SAEs that could be associated with any study procedure the causal relationship is implied as 'yes.'

7.4 Conditions that should not be reported as serious adverse events

The conditions listed below, that may require hospitalization of a patient, are not considered to be SAE and shall not be reported as such, but only need to be recorded in the eCRF:

- Hospitalization for routine treatment or monitoring of the studied indication, not associated with any deterioration in condition.
- Abnormal lab values or test results that do not induce clinical signs and/or symptoms and require intervention/therapy, i.e., are clinically significant.

7.5 Outcome

Each AE must be rated by choosing among:

- Recovered/resolved.
- Recovering/resolving.
- Not recovered/not resolved.

- Recovered with sequelae/resolved with sequelae.
- Fatal.
- Unknown.

7.6 Recording adverse events

All AEs occurring during the study must be documented in the AE page of the eCRF. It is responsibility of the investigator to collect all AEs including laboratory finding or other abnormal assessment derived by spontaneous, unsolicited reports of patients, by observation and by routine open questionings. Additionally, cases of suspected drug interaction, pregnancy, breast-feeding exposure, and lack of efficacy should be also collected and reported (7.8).

The recording period for collecting AEs is the period since the informed consent signature until the patient's end of observation.

A diagnosis, if known, or clinical signs and symptoms if diagnosis is unknown, rather than the clinically significant abnormal laboratory finding, should be reported on AE eCRF page. If no diagnosis is known and clinical signs and symptoms are not present, then the abnormal finding should be recorded.

All SAEs ongoing at the end of observation will be reported as "ongoing" in the eCRF.

7.7 Reporting procedure for investigators

The investigator must report all ADR ad SAE to the CRO Safety Contact listed below within 24 hours of awareness by sending the completed AE form. SAE form can be recorded in AE page of the eCRF.

Additionally, the investigator should report to CRO Safety Contact conditions of use outside the marketing authorisation of the medicinal product (i.e., off-label or medication errors) or from occupational exposure, as well as cases of suspected drug interaction, pregnancy, breast-feeding exposure and lack of efficacy.

The CRO Safety contact must be contacted at the following e-mail address: anticov-safety@exomgroup.com .

Within 1 working day from the event knowledge, the CRO will report all the available information to Safety Contact of Fondazione Policlinico Universitario A. Gemelli IRCCS (email address: farmacovigilanza@policlinicogemelli.it), the Clinical Study Manager and the Medical Experts.

7.7 Reporting adverse drug reactions to Regulatory Authorities / Ethics Committees / IRB

Although the submission of the relevant cases collected during the study to the concerned CA is under the investigator's responsibility; the Promoter, Fondazione Policlinico Universitario A. Gemelli IRCCS, supported by the CRO, shall ensure that this activity is carried out within the timelines foreseen by the current applicable local law.

7.8 Pregnancy

In case of pregnancy, an additional form (Pregnancy Report Form) should be filled in by the Investigator. The completion of the form can be fulfilled by Pregnancy Form page in eCRF.

Upon learning of pregnancy, the Investigator shall report the information within 24 hours to the CRO safety contact by filling in the appropriate form. The CRO Safety Contact will then inform Safety Contact of Fondazione Policlinico Universitario A. Gemelli IRCCS within one working day of being notified.

The first two pages of the Pregnancy Report Form, available in eCRF, should be completed by the investigator with all the available information. The third page will be completed as soon as the investigator has knowledge of the pregnancy outcome. In instance where the pregnancy outcome meets the criteria for immediate classification of an ADR (e.g., spontaneous or therapeutic abortion, stillbirth, neonatal death, congenital anomaly, birth defect) the investigator should follow the procedure for reporting ADRs.

8. OVERDOSE

Cases of overdose (accidental) which may or may not result in serious adverse reactions are to be reported to Study Safety Contact, following the same procedure for SAE, within 24 hours from the Investigator's knowledge of its occurrence. The Medical Expert should be contacted to discuss corrective treatment, if necessary.

If patient receive by accident up to 2 times the recommended single antibody dose, the Investigator shall provide in the SAE form information about symptoms, corrective treatment, and outcome of overdose.

9. DATA MANAGEMENT

An electronic CRF (eCRF) will be filled-in by the Investigator and/or his/her representative designee. Access to electronic systems used for data collection will be granted to the study personnel only after appropriate training.

Front-end edit checks will run at the time of data collection and back-end edit checks will be used by the Data Manager to check for discrepancies and to ensure consistency and completeness of the data.

Medical history, adverse events and concomitant procedures will be coded using the MedDRA dictionary; medications will be coded using the WHO Drug Dictionary and Anatomical Therapeutic Chemical classification (ATC).

After the completion of data collection and cleaning, a data review meeting will be held to determine the occurrence of any protocol violation and to define the subject populations for the analysis. Once the database has been declared to be complete and accurate, it will be locked, and the planned statistical analysis will be performed.

10. STATISTICS

10.1 Sample Size

The sample size is discussed for the primary efficacy endpoint of the study defined as the percentage of patients clinically worsened at Day 30 after study drug administration.

The sample size is justified separately for low-risk and high-risk patients.

<u>Low-risk patients cohort:</u>

The sample size considerations for this cohort of patients are based upon estimation precision for the percentage of patients clinically worsened at Day 30.

There is no formal statistical hypothesis, hence all efficacy and safety endpoints results will be presented by 95% confidence intervals (CIs) and descriptively explained.

A sample size of approximately 100 patients per treatment group is planned for this cohort. A total of 300 low-risk patients will randomized in this cohort.

In the Standard of Care treatment group is expected a percentage of worsened patients equal to 5%. Therefore, a sample size of 100 patients produces a two-sided 95% confidence interval with a width equal to 9.6% when the treatment group percentage is 5%.

In the Casirivimab 1200 mg and Imdevimab 1200 mg group as well as in Sotrovimab 500 mg group is expected a percentage of worsened patients equal to 1.5%.

Therefore, a sample size of 100 patients for each treatment group produces a two-sided confidence interval with a width equal to 6.2% when the treatment group percentage is 1.5%.

The Clopper-Pearson's formula has been used for the computations.

High-risk patients cohort:

No statistical comparison between the two experimental treatment groups is foreseen.

The *One-Sample Proportion Test* is used to assess whether the treatment groups percentages (P1) are significantly different from a hypothesized value (P0). This is called the hypothesis of *inequality*.

A sample size of 80 patients per treatment group achieves 80% power to detect a difference (P1-P0) of 10% using a two-sided exact test with a significance level (alpha) of 5%. These results assume that the hypothesized population percentage under the null hypothesis (P0) is 15% and is 5% under the alternative hypothesis (P1). A total of 180 high-risk patients will be randomized in this cohort.

Overall, the study sample size will be equal to 460 patients.

10.2 Statistical Methods

The following describes the statistical analysis as it is foreseen at the time of planning the investigation. A detailed statistical analysis plan (SAP) will be issued after the study starts. The contents of the SAP will include the investigation's objectives, type of primary analysis, clear specification of all primary and secondary endpoints, full and detailed descriptions of the statistical methods for data analysis and will address special issues as definition of major protocol violators, missing values replacement procedure, power considerations, and exploratory analyses. The plan will be reviewed and may be updated before the study database lock.

All statistical analyses and data processing will be performed using SAS® Software (release 9.4 or later) on a Windows 10 PRO operating system.

Descriptive statistics will be provided in summary tables according to the type of variable.

Continuous variables will be summarized by descriptive statistics (number of cases, mean, and standard deviation [SD], median, minimum, and maximum). Categorical variables will be summarized using counts of patients and percentages.

All p-value will be rounded to three decimal places. Unless otherwise specified, the significance level used for statistical testing will be 0.05 and two-sided tests will be used.

Statistical analysis will be performed separately for low and high-risk patients.

All data collected will be presented in by-patient data listings.

10.3 Analysis sets

The following populations are defined for this investigation:

10.3.1 Safety analysis set

The Safety Analysis Set (SAF) consists of all randomized patients who receive the study drug. This analysis set is used for the safety analysis.

10.3.2 Full analysis set

The Full Analysis Set (FAS) contains all patients in the SAF who have at least one post-baseline efficacy measurement. This analysis set is used for the analysis of primary and secondary efficacy endpoints.

10.3.3 Per-protocol analysis set

The Per-Protocol Analysis Set (PPAS) contains all patients in the FAS who meet all in- and exclusion criteria and have no major protocol violations that are considered to imperil the scientific integrity and interpretation of the study results. This analysis set will be used for sensitivity analyses of the primary efficacy endpoint only.

The decision whether a protocol violation is relevant or not for the classification of patients to subsets should be made case-by case in a data review meeting that will be held before performing the database lock.

Patients who are screened, but not randomized, will only be listed.

10.4 Missing data

Missing data will be replaced applying statistical approaches that will be detailed in the SAP.

10.5 Coding dictionaries

Adverse events, past and concomitant diseases will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 24.1 or higher. All verbatim terms will be assigned to a Preferred Term and will be classified by primary System Organ Class (SOC).

Previous and concomitant medications will be coded using the WHO-DRL Dictionary version 2017 or later and classified according to 3rd level ATC level subgroup.

10.6 Analysis of efficacy endpoints

No statistical comparisons among the treatment arms will be performed.

The analysis of the primary endpoint defined as the percentage of patients clinically worsened at Day 30 after study drug administration will be performed reporting the number and the percentage of patients worsened. The 95% confidence interval for the percentages will be also provided.

In the high-risk patients cohort the following statistical hypotheses will be tested for the two treatment groups:

$H0 : P = P0$ versus $H1: P = P1 \neq P0$

where P0 and P1 are the hypothesized value and the expected value in each treatment group, respectively.

The number of accesses to the emergency room during the follow-up period will be analysed by means of descriptive statistics.

The change from baseline over the study period in continuous endpoints (e.g., SpO2, etc.) will be analysed within each treatment group using an analysis of variance model for repeated measures with change from baseline to the entire study treatment period as dependent variable.

Time-dependent efficacy endpoints (i.e., overall survival at 30 days and time-to-hospitalization) will be investigated by means of the Kaplan-Meier (K-M) method.

K-M estimates of the median time-to-event and the corresponding 95% confidence interval will be presented along with the estimates for the 25^{th} and 75^{th} percentiles. The survivor function will be displayed graphically using a K-M curve. Patients not reaching the time-event will be censored at the date of last study visit assessment.

10.7 Analysis of safety

Analysis of safety will be performed on the SAF population. Statistics will be presented for each cohort and treatment group.

Any adverse event which started at or after the date of administration of the study treatment and until 30 days after the study drug administration will be considered a Treatment Emergent Adverse Event (TEAE).

TEAEs will be tabulated by System Organ Class (SOC) and Preferred Term after medical coding using the Medical Dictionary for Regulatory Activities (MedDRA).

An overview of TEAEs will be prepared showing the number of TEAEs and the number of patients with any TEAEs, treatment-related TEAEs, serious TEAEs, treatment-related serious TEAEs, severity of TEAEs and TEAEs leading to withdrawal. TEAEs relationship to study treatments will be investigated with frequency tables. Missing classifications concerning study drug relationship will also be considered as treatment-related.

Summary tables showing the number of patients with at least one TEAE and event count by SOC and PT will be prepared.

Results of vital signs parameters including also SpO2 will be summarized by treatment arm and visit by means of default descriptive statistics. Physical examination abnormalities will be reported by means of frequency tables.

For clinical laboratory parameters, where appropriate, the reported values will be converted into SI units and if needed boundary values for reference ranges will be converted as well. A summary table of the laboratory parameters value at baseline will be produced.

10.8 Multicentre study

This study will be conducted by multiple Investigators at multiple centres. Site-related differences will not be evaluated and presented in the statistical output as the study does not foresee a randomization stratified by Centre.

10.9 Interim analysis

No interim statistical analyses are planned for this investigation.

11. INFORMED CONSENT

Informed consent must be written in a language understandable to the patients. It is the responsibility of the Investigator to obtain written consent from each patient prior to inclusion in the study, by using the latest EC approved version of the document.

Adequate time shall be given to the patient to enquiry the PI about any clarification needed and to consider his or her decision to participate in the study.

Consent must be documented by the patient's dated signature. The signature confirms that the consent is based on information that has been understood. Moreover, the Investigator must sign and date the informed consent form.

Each patient's signed informed consent must be kept on file by the Investigator. The consent should be signed in two copies, in case the patient will be enrolled at Fondazione Policlinico Gemelli; or in three copies, in case the patient will be enrolled at a satellite site: one copy must be given to the patient, one copy should be filed at the satellite site, one copy should be provided to the coordinating Centre by the patient

In case the patient is and underage (aged between 12 and 17 years), is mandatory the signatures of both parents (if applicable) or the legal tutor.

Additionally, in this study, for those clinical sites interested in using it, the Informed Consent administration could be conducted through an electronically managed procedure, named "GENIUS ENGAGE". In details, the study investigator will open the appropriate Informed Consent form by the means of an electronic device, i.e., smartphone, tablet, personal computer (laptop and desktop) and will provide it to the patient for reading and understanding. Once the patient has carefully read it and listened the audio supportive material, he/she will sign it electronically or on paper.

In case of electronic signature, a portable document format (PDF) copy of the electronically signed Informed Consent will be generated for satellite center investigator's filing, for the patient and a third copy for central site administering the drug, to be archived with the medical records concerning treatment, visits and follow-up.

12. CONFIDENTIALITY AND DATA PROTECTION

By signing this protocol, the investigator agrees to keep all the information provided by the sponsor in strict confidentiality and to request the same confidentiality from his/her staff. Study documents provided by the sponsor (protocols and other materials) will be stored appropriately to ensure confidentiality. The information provided by the sponsor to the investigator cannot be disclosed to others without direct written authorization from the sponsor, except for the extent necessary to obtain the electronic informed consent from the subjects wishing to participate in the study.

Data on subjects collected in the source documents during the study will be transferred to the Sponsor in an anonymized way. If, as an exception, for safety or regulatory reasons identification of a subject becomes necessary, the sponsor and the investigator will be bound to keep this information confidential.

On the eCRF (and patient diaries), patients will be identified only by the assigned patient number. If patient names are included on copies of documents submitted to Sponsor or its delegate, the names will be obliterated or masked, and the assigned patient number added to the document. The Investigator should keep a separate log (Patient Master List) of patient's codes, names, and addresses.

13. SOURCE DOCUMENTS/DATA

13.1 Recording of source data

Data collection is the responsibility of the clinical study staff at the site under the supervision of the site investigator. The investigator is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents should be completed in a neat, legible manner to ensure accurate interpretation of data.

Data recorded in the eCRF derived from source documents should be consistent with the data recorded on the source documents.

13.2 Direct access to source document/data

The Investigators must permit study-related monitoring, audits, EC review or regulatory inspection, providing direct access to source data/documents.

14. STUDY MONITORING

Monitoring will be performed by Exom Group who has been designated by the Promoter. If for healthy or logistics reasons on-site monitoring visits will not be possible at the planned time intervals, such visits will be conducted in a virtual mode. A purpose-built source document workspace (Genius SITE VAULT) under the full and unique control of the site staff and completely separated from the study database is implemented and available. Site staff will upload certified electronic copies of the source documents and will allow the study monitor to conduct the verification of the source data against the eCRF data. Encription protocols as well audit trails assure full security and regulatory compliance.

The purpose of the monitoring visit is to verify that the rights and the wellbeing of the patient are protected, that the reported data are accurate, complete, and verifiable from source documents and that the conduct of the trial complies with the currently approved protocol and any amendments, with ICH GCP (E6-R2), and with regulatory requirements.

Monitoring will also include support to site for handling the electronic device for patients' self-monitoring, IMP accountability and reconciliation, as well as follow-up with site as to SAEs. The CRA will also follow-up resolution of clinical/safety queries. Specific monitoring activities will be detailed in the Monitoring Plan.

Prior to study start, the Investigator will be informed of the anticipated frequency of the monitoring visits. (S)He will also receive a notification prior to each monitoring visit during the study. It is expected that the Investigator and/or his/her sub-Investigator(s) and other appropriate staff, including the pharmacist(s) and responsible of the local laboratory, will be available on the day of the visit to discuss study conduct and to cooperate with the monitor to ensure that any problems detected during these monitoring visits are resolved.

Before any patient enters the study, a representative of Sponsor or its delegate, will meet with the PI and his or her staff to review the procedures to be followed during the study and to train them on recording the data in the eCRF using the electronic data capture (EDC) system. After the

first patient is enrolled, the Sponsor/CRO representative, a monitor, will periodically monitor the progress of the study by conducting on-site visits. This CRA will also be able to review query statuses remotely, possibly warranting more frequent communication with the PI and his or her staff. The PI will make available to the CRA the eCRF, source documents, signed consent forms, and all other study-related documents.

The PI and his or her staff will be responsible for reviewing eCRF, resolving data queries generated by the monitor via the system, providing missing or corrected data, approving all changes performed on his or her data, and endorsing the patient data within the eCRF. This approval method will include applying an electronic signature, a uniquely assigned username and password that together will represent a traditional handwritten signature.

15. INSURANCE AND INDEMNITY

Coverage for any damage resulting from the participation of the subjects in the clinical trial is warranted. an insurance cover will be issued in favors of the subjects participating in this clinical study. The insurance is following the local regulation and with the requirements of the Health Authorities.

16. PROMOTER

Promoter of the study is Fondazione Policlinico Universitario A. Gemelli IRCCS (Roma, Italy).

17. REFERENCES

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18. APPENDICES

Appendix 1 – Protocol Signature Page (protocol writers)

Protocol Title: A randomized, open-label, active controlled, parallel group, multicenter phase 3 study to evaluate efficacy and tolerability of Casirivimab plus Imdevimab and Sotrovimab in patients with mild to moderate COVID-19 (AntiCov).

The present research protocol was subject to critical review and has been approved in the present version by the persons who undersigned. The information contained is consistent with the moral, ethical, and scientific principles governing clinical as set out in the Declaration of Helsinki and the principles of ICH/GCP.

Signature:

Date: September 29th, 2021

Prof. Luca Richeldi, MD
Principal Investigator, Study Chairman
Fondazione Policlinico Gemelli IRCCS

Appendix 2 – Protocol Signature Page (principal investigator)

Protocol Title:

A randomized, open-label, active controlled, parallel group, multicenter phase 3 study to evaluate efficacy and tolerability of Casirivimab plus Imdevimab and Sotrovimab in patients with mild to moderate COVID-19 (AntiCov).

Declarations of the Principal Investigator:
I have read the present research protocol and agree to conduct the study according to the protocol.
I will enroll the first subject only after all ethical and regulatory requirements are fulfilled.
I pledge to obtain written consent for study participation from all subjects.
I pledge to retain all study-related documents and source data as described.

Principal Investigator (Head of the study center):

Name: _____

Study Center: _____

Signature: _____Date: _____