BANDO AIFA ANTICORPI MONOCLONALI
PROPOSTA STUDIO INMI-SIMIT SULLA EFFICACIA DI ANTICORPI MONOCLONALI IN COVID-19 IN ITALIA

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TITOLO DELLO STUDIO: Adaptative, Phase IV Randomized, Open-label, Multicenter Study to Determine the Safety and Efficacy of different **MON**oclonal Antibodies (MoAbs) to SARS-CoV-2 for the **E**arly **T**reatment of COVID-19 in Non-hospitalized Adults (**MONET Study**)
SPONSOR/PROMOTORI: **Istituto Nazionale per le Malattie Infettive Lazzaro Spallanzani IRCCS, Roma e Società Italiana di Malattie Infettive e Tropicali (SIMIT)**
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TITLE: Adaptative, phase 4, Randomized, Open-label, Multicenter Study to Determine the Safety and Efficacy of different **MON**oclonal Antibodies (MoAbs) to SARS-CoV-2 for the **E**arly **T**reatment of COVID-19 in Non-hospitalized Adults

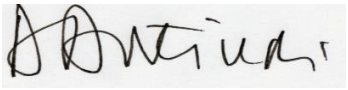
STUDY CODE: MONET Study

EudraCt number: 2021-004188-28

PROTOCOL VERSION: 7.0

DATE: 16/11/2021

PROTOCOL APPROVALS

Principal Investigator Dr Andrea Antinori Istituto Nazionale per le Malattie Infettive (INMI) "Lazzaro Spallanzani" IRCCS Via Portuense, 292, 00149 Roma RM	 _____ Data : 16-NOV-2021

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Study design

Adaptive phase 4 (i.e. post approval), multi-arm, multi-stage, open label, multicenter, individually randomized clinical trial for adult subjects (aged ≥18 years) with molecularly confirmed mild to moderate SARS-CoV-2 infection, no need for immediate hospitalization and significant risk factor for severe/critical COVID-19.

Sotrovimab (VIR-7831) 500 mg, casirivimab and imdevimab (REGN10933 and REGN10987), bamlanivimab and etesevimab (LY-CoV555 and LY-CoV016) will be given all intravenously (IV) over one-hour infusion.

Randomization will take place at an intervention to control ratio of 1:1:1. The adaptive design of the study is aimed to meet the most topical needs of translational medical research programs implemented during a massive epidemic emergency due to newly emergent pathogens, such as SARS-CoV-2.

Adaptation is carefully considered an investigational procedure for modifying study parameters while the trial is ongoing, based on a review of the interim data analyses.

The study will be conducted in 40 clinical centers across Italy.

Study population

Participants will be outpatient adults with documented positive SARS-CoV-2 test and mild-to moderate symptoms of COVID-19, who do not require supplemental oxygen therapy for COVID-19 and who are at high risk of progression to severe COVID-19 as defined by Center for Disease Control and prevention (CDC). Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19 are:

- Aged ≥65 years
- Obesity (BMI >30) or weight >95% percentile adjusted for age and sex
- Diabetes mellitus, type 1 and type 2
- Heart conditions (such as
    - heart failure,
    - coronary artery disease
    - cardiomyopathies
    - congenital heart disease
    - hypertension
- Cerebrovascular disease
- Chronic lung diseases
    - COPD chronic obstructive pulmonary disease
    - moderate-to-severe asthma
    - interstitial lung disease
    - cystic fibrosis
    - pulmonary hypertension
    - Pulmonary embolism
    - Bronchopulmonary dysplasia
    - Bronchiectasis

- Chronic liver diseases limited to:
  - Cirrhosis
  - Non-alcoholic fatty liver disease
  - Alcoholic liver disease
  - Autoimmune hepatitis
- Smoking, current and former
- Chronic kidney disease
- Hemoglobinopathies
  - Sickle cell disease
  - Thalassemia
- Immunocompromised state
  - Primary immunodeficiencies
  - secondary immunodeficiencies
  - HIV (human immunodeficiency virus)
  - Use of corticosteroids or other immunosuppressive medications
- Solid organ or blood stem cell transplantation
- Cancer, previous or current;
- Mental health disorders limited to:
  - Mood disorders, including depression
  - Schizophrenia spectrum disorders
- Tuberculosis
- Down syndrome
- Neurodevelopmental disorders
  - cerebral palsy or other conditions that confer medical complexity
  - genetic or metabolic syndromes
  - severe congenital anomalies
- Neurologic conditions, including dementia and Alzheimer disease
- Substance use disorders
- Medical-related technological dependence as
  - tracheostomy
  - gastrostomy, or
  - positive pressure ventilation that is not related to COVID-19)
- Pregnancy and recent pregnancy (lactating).

Inclusion criteria:

- Age ≥ 18 years
- Signed informed consent provided by the patient, or by the patient's legally authorized representative(s), as applicable
- Virological diagnosis of SARS-CoV-2 infection (SARS-CoV-2 infection confirmed by 3rd generation antigenic or RT-PCR test);
- Have one or more mild or moderate COVID-19 symptoms: fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, or shortness of breath with exertion for no more than 10 days
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Exclusion criteria:

- Have oxygen saturation (SpO2) less than or equal to (≤)93 percent (%) on room air and persisting for more than 7 days
- Have any serious concomitant systemic disease, condition or disorder that, in the opinion of the investigator, should preclude participation in this study
- Enrolment in another concurrent clinical interventional study within 30 days
- Existence of any life-threatening co-morbidity or any other medical condition, which, in the opinion of the investigator, makes the patient unsuitable for the study
- Has known allergy or hypersensitivity to components of study drug

EXPERIMENTAL THERAPY

Arm A: participants will receive one single infusion of Sotrovimab (VIR-7831) 500 mg via a single one-hour intravenous infusion (IV);

Arm B: participants will receive one single infusion of REGN-COV2 casirivimab 1200 mg and imdevimab 1200 mg (REGN10933 and REGN10987), via a single one-hour intravenous infusion (IV);

Arm C: participants will receive one single infusion of the combination of bamlanivimab 700 mg and etesevimab 1400 mg (LY-CoV555 and LY-CoV016) via a single one-hour intravenous infusion (IV);

Primary Objective

To assess the efficacy of MoAbs in term reduction of occurrence of death, hospitalization and severe COVD-19 by day 29 after randomization.

Key Secondary objectives:

- To assess the effect of MoAbs in the prevention of hospitalization for COVID-19 by day 90 after randomization
- To assess the effect of MoAbs to reduce SARS-CoV-2 detection or levels of RNA in nasal swabs
- To assess the effect of MoAbs on symptom resolution

Other secondary objectives

- To evaluate differences in symptom duration between the MoAbs and SoC through day 29
- To evaluate differences in long-term symptoms and duration between the MoAbs after viral clearance
- To investigate the humoral response to non-Spike SARS-CoV-2 antigens
- To investigate the T-cell response to S and N viral antigens in a subgroup of enrolled patients

- To explore if baseline and follow-up hematology, chemistry, coagulation, viral, and inflammatory biomarkers are associated with clinical and virologic outcomes in relation to any MoAbs in the study protocol
- Viral genotypic analysis over time and phenotypic characterization of treatment-emergent mutations. Treatment-emergent variants at clinical failure, defined as fulfilling the primary endpoint, will be determined by comparing the sequencing results from baseline sample with the sample at failure;

Study Endpoints

Primary endpoint

Survival without experiencing clinical failure at day 29 after randomization. Clinical failure is assessed by a composite endpoint including: A) death for any cause; B) progression to severe COVID 19; C) scoring 5 or more in the WHO severity scale. Severe COVID-19 is defined by pneumonia (fever, cough, tachypnea, or dyspnea) AND lung infiltrates >50% OR hypoxemia (SpO2 < 92% in room air and/or severe respiratory distress).

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Secondary endpoints:

- Proportion of participants who experience hospitalization or Emergency Room (ER) visit within day 29 and within 90 days;
- Proportion of participants experiencing severe COVID-19 by day 29 after randomization;
- Variation of SARS-CoV-2 viral load measured by semi-quantitative RT-PCR between day of randomization and day 7 , 14 and 29;
- Proportion of participant with undetectable SARS-CoV-2 RNA at day 7, 14 and 29 after randomization;
- Variation of symptoms score from day of randomization to days 7, 14, and 29 after randomization;
- Proportion of participants demonstrating symptom resolution (i.e. scoring 0 in the WHO scale) at Days 7, 14 and 29 after randomization;
- Proportion of participants with any adverse event (grade ≤ 2 according to CTCAE) at day 7, 29 after randomization;
- Proportion of participants with severe adverse events (grade ≥ 3 according to CTCAE) at day 7, 29 after randomization;
- Variation of Hematology, chemistry, coagulation, and inflammatory markers between the day of randomization and day 7, 29 after randomization;
- Proportion of SARS-CoV-2 spike mutation gene (including D614G, N501Y, N501Y.V2, L452Y, L452R, E484K/Q, Y453F, N439K, P681R, T478K and K417N) among participant experiencing the primary endpoint;
- Proportion of SARS-CoV-2 spike mutation gene (including D614G, N501Y, N501Y.V2, L452Y, L452R, E484K/Q, Y453F,N439K, P681R, T478K and K417N) among participant with a detectable SARS-COV-2 viral load at day 29 after randomization.

Other endpoints:

- Time to return to usual (pre-COVID-19) health through Day 29;
- Duration of fever through Day 29 defined as the last day in the participant-reported symptom diary on which a temperature greater than 37.8°C was recorded or a potentially antipyretic drug, such as acetaminophen or ibuprofen, was taken;
- The proportion of patients who report long-COVID-19 symptoms from day 29 to day 90 according to arm treatment;
- The proportion of participants who have a post-treatment sero-response defined as a rise in IgG titers from day of dosing baseline value to the N antigen of SARS-CoV-2 through Day 29 and 90.
- Combinations of demographic, clinical, biological factors associated with efficacy of treatments

Sub-study IMMUNE-MONET (N=20 participants)

For each arm of the study (Sotrovimab 500 mg [Arm A] vs casirivimab 1200 mg and imdevimab 1200 mg [Arm B] vs SOC [Arm C]), 20 patients will be enrolled for the immunological sub-study called Immune-Monet. Each enrolled subject will provide blood samples for the study of serum and peripheral blood mononuclear cells (PBMCs) at enrollment and at days 7, 14 and 28, quantifiable in 1 serum tube and 6 EDTA tubes.

Primary endpoint

- Quantification of lymphocytes (total and subpopulations) circulating in peripheral blood at the various study timepoints.

Secondary endpoints

- Quantification (total and subpopulations), morphological and phenotypic description of the monocytes circulating in the peripheral blood at the various study timepoints;
- Quantification of the following cytokines: CCL3 / MIP-1α, CXCL10 / IP-10, IL-1α, IL-1β, IL-2, IL-6, IL-7, IL-10, IL-12 p70 and TGF-β , in serum samples at the various study timepoints;
- Transcriptomic analysis of T cell receptors at the various study timepoints;
- Transcriptomic analysis of B cell receptors at the various study timepoints;
- Measurement of the expression of NLRP3 inflammasome, caspase 1,3,4,5 and intracellular pro-inflammatory cytokines (PBMCs).

Sub-Study PK of COVID-19 Mab (N=150 participants)

MAb in serum or plasma will be measured using a validated, fit for purpose Liquid Chromatography-Mass/ Mass Spectrophotometry (LC-MS/MS) method with a lower limit of quantification of 10 to 25 mg/L. The LC-MS/MS method will be based on the analysis of a unique peptide generated by enzymatic digestion of each monoclonal antibody, so as to allow for each

monoclonal antibody to be individually quantitated from the human or plasma serum samples collected during the study. The sampling for pharmacokinetics will take place at each useful timing (es. at each visit) to better define the pharmacokinetic profile of each monoclonal drug.

STUDY ASSESSMENTS AND PROCEDURES

Screening (Day -1/Day 1)

At screening the investigators or medically qualified designee have to check the eligibility of patient for the study and obtain informed consent.

The following procedures will be performed:

- Demographic characteristics
- Focused medical history and current medication
- Physical examination and vital signs (blood pressure, heart rate, respiratory rate, temperature)
- Urine pregnancy test at screening (for women of childbearing potential)
- Routine blood tests (blood count, creatinine, BUN, sodium, potassium, ALT, AST, LDH, fibrinogen, D-dimers, ferritin, PCR)
- SARS-CoV2 serology
- T-cell response to S and N (in a subgroup of patients)
- PCR SARS-CoV2 on nasopharyngeal swab by quantitative reverse transcriptase–polymerase chain reaction and for genotypic sequencing
- Nasopharyngeal swab will be stored for genotypic sequencing in failed patient to explore treatment-emergent variants
- Pocket/wallet card with site staff contact information will be delivered

Baseline (Day 1)

Screening, randomization and baseline visit may be performed on the same day and no other procedures need to be repeated.

On baseline visit, eligible participants will be randomized (1:1:1) to receive:

- **Treatment Group A (experimental arm):** participants in the experimental arm A will receive one single infusion of Sotrovimab (VIR-7831) 500 mg via a single one-hour intravenous infusion (IV);
- **Treatment Group B (experimental arm):** participants in the experimental arm B will receive one single infusion of REGN-COV2 casirivimab 1200 mg and imdevimab 1200 mg (REGN10933 and REGN10987), via a single one-hour intravenous infusion (IV);
- **Treatment group C (control arm)**: participants will receive one single infusion of the combination of bamlanivimab 700 mg and etesevimab 1400 mg (LY-CoV555 and LY-CoV016) via a single one-hour intravenous infusion (IV);

After randomization, the following evaluations will be performed on baseline:

- Physical examination and vital signs (blood pressure, heart rate, respiratory rate, temperature)
- Instructions on what to do if participants have worsening symptoms/become hospitalized

- Study Symptom Diary will be supplied to the patient and will be trained by the site staff on how to complete the diary
- Concomitant medications
- IMP administration
- Review of adverse events.

Daily Study Assessment (Day 7, 14, 29 And Day 90)

During follow-up visits (after Day 1) through Day 29, peripheral oxygenation saturation measures < 96% should be reviewed by an investigator and referral for medical attention made at the discretion of the investigator. The participant should be assessed for severe COVID-19, characterized by a minimum of either pneumonia (fever, cough, tachypnoea, or dyspnoea, AND lung infiltrates) AND hypoxemia (SpO2 < 92% in room air and/or severe respiratory distress) and a score of 5 or higher in the WHO Clinical Progression Scale in Appendix A. If the patient develops severe COVID-19 as defined above, genotypic sequencing of SARS-CoV2 on nasopharyngeal swab will be performed by protocol. When severe COVID-19 is suspected, diagnostic procedure including TC or Thoracic Ultrasound and evaluation of hypoxemia by arterial blood gas analysis will be evaluated by medical investigator according to current guidelines.

The following evaluations are to be completed at days 7, 14, 29 and 90:

- Physical examination and vital signs (blood pressure, heart rate, respiratory rate, temperature)
- Routine blood tests (blood count, creatinine, BUN, sodium, potassium, ALT, AST, LDH, fibrinogen, D-dimers, ferritin, PCR) at days 7 and 29
- SARS-CoV2 serology (IgA, IgG, IgM and neutralizing antibodies) at days 7, 29 and 90
- T-cell response to S and N antigens (in a subgroup of patients) at days 7, 29 and 90
- PCR SARS-Cov2 on nasopharyngeal swab by quantitative reverse transcriptase–polymerase chain reaction (RT-PCR) at days 7, 14 and 29; Genotypic sequencing will be performed at failure and at day 29 if SARS-Cov2 on nasopharyngeal swab is still detectable;
- Concomitant medications;
- Review of adverse events

Study intervention and the participant-reported symptom diary will be dispensed to the participant according to the study protocol either by a GP or by USCAR during the home visit or at the clinic in a dedicated area for COVID-19 positive patients, based on AIFA indication, regional organization and also on site's preferences and/or resources availability.

Discontinuation And Withdrawn Visit

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits.

Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the Day 29 visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements.

Survival status at Day 29 is required for all randomized participants and should still be reported for participants who withdraw from the study where permitted by local guidelines.

A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (e.g., telephone contact, a contact with a relative or treating physician, or Information from medical records).

Lost To Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fail to return to the clinic for a required study visit:

The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.

Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.

Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.

Site personnel, or an independent third party, will attempt to collect the survival status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get the IMP. Public sources may be searched for survival status information. If survival status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up.

Participant-Reported Symptom Diary

During the first 29 days, participants will be asked to report their COVID-19 symptoms and temperature in diary (Appendix B). On Day 1, participants will be trained by the site staff on how to complete the diary. It is important that the participant responds to questions without being influenced by anyone else. Day 1 assessments must be completed before administering IMP. Participants will be asked to complete subsequent entries in the diary each evening on Day 1 through 29 (the entry on Day 29 may be completed with the site staff during the Day 29 visit, if the visit occurs on Day 29 versus another day in the Day 29 visit window). From day 29 to day 90 the diary must be filled in once a week.

The diary will ask participants to report on the following:

Temperature, Shortness of breath, Difficulty breathing, Chills, Cough, Fatigue, Muscle aches, Body aches, feeling hot or feverish, headache, nausea, vomiting and diarrhoea.

Diary Reminder And Staff Review Of Diary

Participant will be reminded every day through the end of the study to complete their diary. This reminder will be received through the electronic device. In the event an electronic device is not available when the participant is randomized, there will be a paper diary alternative with detailed

instructions for participants and site staff. The diary will be reviewed by study staff in person with each participant according to the study procedures.
The participant's answers on the diary will be transcribed into the eCRF.
Participants who report worsening symptoms from any cause during the study may be referred to their healthcare provider or closest emergency room. Such instances will be recorded at the time of the notification, and during follow-up to assess study endpoints, hospitalization or death.

Study design and STATISTICAL PLAN

This is an adaptive phase 4 (i.e. post approval), multi-arm, multi-stage, open label, multicenter, individually randomized clinical trial for adult subjects (aged ≥18 years) with molecularly confirmed mild to moderate SARS-CoV-2 infection.
This study will compare the efficacy of the three currently approved anti-SARS-CoV-2 Moab. The study is designed to randomize participants with 1:1:1 ratio to receive either: 1) sotrovimab (Xevudy) or 2) casirivimab/imdevimab (Regeneron) or 3) bamlanivimab/etesevimab (Lylli). The bamlanivimab/etesevimab will serve as the active control arm.
The adaptive design of the study will include:

A. 3 stage sequential design
B. Multi arm design (multiple comparison are adjusted according to Dunnet method)
C. Binding stopping rule for efficacy (alpha spending function according to O'Brien and Flemming)
D. Binding stopping rule for futility (beta spending function according to O'Brien and Flemming)
E. Open sample size recalculation (according to observed efficacy with 90% power for next stage)

The study is designed on the (superiority) hypothesis that at least one of test arms, either sotrovimab or casirivimab/imdevimab, improves frequency patients meeting the primary endpoint from the expected 85% in the control arm to ≥ 92.5% in at least one of the test arms (i.e. RD ≥ 7.5%). If the experimental hypothesis is true, the study has a one-tailed alpha-error of <0.025 and an overall power >90%.

Definition of the study sample

Average sample size 936 patients (from a minimum of 300 to maximum of 1239 patients)

Analysis of efficacy (primary outcome)

Interim analysis and final analysis will be carried out by taking into account the potential effect of each individual component of the adaptive design.

Analysis of secondary outcome

Analysis of secondary and explorative endpoints will be carried out by regression models. Outcomes expressed by binary variables will be assessed by logistic regression model, outcome expressed by continuous variables will be assessed by linear regression model. Polynomial mixed linear regression model with random intercept at participants level and random slope at the level of the time after randomization will be used to model kinetics of repeated continuous measures

Software for simulation and analysis

Study design, simulations, interim analysis and final analysis of primary outcome will be carried out by ICON ADDPLAN V 6.1. This is a proprietary statistical package that contains approved algorithm for dealing with the adaptive design according to EMA and FDA standards. The analysis of secondary outcomes will be carried out at the end of the trial and will be carried out by STATA V.15.

Duration of Recruitment

9 months

Anticipated Start Date / Anticipated End Date

1 December 2021

The end of study is defined as the date the last patient completes the last study assessment, withdraws from the study or is lost to follow-up.

Data analysis and Final Study Report

DECEMBER 2022

Regulations and ethical aspects

The clinical study will be performed under the regulations of the National Agency for Drug Development (AIFA) and of the Italian Ministry of Health. An Independent Data Monitoring Committee (IDMC) will advise the coordinating group of the study to provide oversight and monitoring of the conduct of clinical trials, to protect ethical interests and to ensure the safety of participants and the validity and integrity of study data. The IDMC will be made of 2 to 5 members, selected among trialists experts in Infectious disease, statisticians, hospital pharmacist and expert in Resuscitation. No member of the IDMC have direct involvement in the design or conducting of the study.

Feasibility and technical aspects

Study intervention and the participant-reported symptom diary will be dispensed to the participants, according to the study protocol, either by:

- Hospital-based outpatient clinics in a dedicated area of hospitals for COVID-19 positive patients;
- Territorial outpatient clinics with prepared ambulatory setting by general practitioners (GP) or territorial health agencies (ASL)
- At home visit by GP o USCAR, if admitted by AIFA indications and regional organization

Currently AIFA approved only MoAbs administration in an intra-hospital setting, so all the trial procedures, including drug administration and follow-up management will be performed according with AIFA statements and regulatory dispositions, and by organization at regional level. In order to expanding administration setting and to create an unprecedented network between

healthcare professionals intra- and extra-hospital, SIMIT and other scientific societies (the Italian Society of General Medicine and Primary Care -SIMG), could be involved in the study.
The possibility of early administration of a specific therapy represents an opportunity of fundamental importance in the management of non-hospitalized patients and implies the use of a territorial network that can identify COVID patients at the onset of the first symptoms of disease or in any case in the first hours of laboratory diagnosis.

Screening and deferred enrollment

To meet the criterion of testing and treating simultaneously in all cases where it is technically feasible, screening, enrollment, randomization, administration of therapy, and observation of immediate side effects must occur on the same day, in the care setting in which the patient is first observed. The only exception to this scheme, is given by the possibility to screen the patient by telephone by the GP, usually when the patient is still at home, and next sending to the reference center closest to the patient's home.

Screening, enrollment, randomization, administration and contextual observation

The administration of the drug in territorial POCs (post-acute COVID facilities and territorial residential facilities) can be managed by a specific team (territorial team), which will be responsible for the safe administration of the drug and carry out the observation period.
The following procedures should be performed at the referral center for administration:

- collection of demographic characteristics;
- collection of remote, proximate and pharmacological pathological history;
- execution of the objective examination and verification of vital parameters (blood pressure, heart rate, respiratory rate, temperature);
- performance of laboratory tests (as required by the study protocol, including pregnancy test for women of childbearing age);
- performance of serological test for SarsCoV2;
- performance of nasopharyngeal molecular swab for PCR and genotypic sequencing.

Follow up

The follow up activities will be carried out at the center of administration of therapy in collaboration with the General Practitioner of the patient and the GP belonging to the research network SIMG who made the enrollment. In case of administration at a residential facility, the follow up will be carried out by the team that provided the administration in collaboration with the patient's General Practitioner and the GP belonging to the research network SIMG who carried out the enrollment.

The following table summarizes the professional figures involved for each phase and for each POC:

CARE SETTING IN WHICH THE PATIENT IS FIRSTLY EVALUATED	**PROFESSIONALS / OPERATIONAL STRUCTURES INVOLVED BASED ON POINT OF CARE (POC) AND STUDY ASSESMENT**		
	SCREENING, ENROLLMENT	**RANDOMIZATION, ADMINISTRATION AND OBSERVATION**	**FOLLOW-UP**
hospital POC with Infectious Diseases Department	Infectious disease specialist, ER doctor	Infectious Diseases Department, Emergency room	Infectious Diseases Department or GP of the patient and/or GP from the SIMG network who enrolled the patient
hospital POC in a territorial network without Infectious Diseases Department	SIMG Network GP, ER doctor	Personal of COVID-19 Department or equivalent, reference to Infectious Diseases Department	Personal of COVID-19 Department or equivalent or Infectious Diseases Department (after contact) / GP of the patient and/or GP from the SIMG network who enrolled the patient
Territorial POC at dedicated post-acute COVID-19 department	SIMG network GP, USCA doctors	Staff of the post-acute COVID-19 Department, reference to Infectious Diseases Department	Staff of the post-acute COVID-19 department / GP of the patient and/or GP from the SIMG network who enrolled the patient
Residential territorial POC	SIMG network GP, USCA doctors	Territorial team or dedicated infectious disease team	Territorial team / GP of the patient and/or GP from the SIMG network who enrolled the patient

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1. INTRODUCTION

1.1 Background

On January 9 2020, the "World Health Organization" (WHO) declared the identification, by Chinese Health authorities, of a novel coronavirus, further classified as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1].

The outbreak of SARS-CoV-2 was considered to have originally started via a zoonotic transmission and later on a human to human transmission was recognized; this virus initially emerged in the Chinese city of Wuhan in December 2019, led to a sharply spreading outbreak of human respiratory disease (COVID-19), both within Republic of China and in several other countries worldwide. On March 11 2020, WHO declared COVID-19 a pandemic [2].

To date, over 228 million cases were reported and more than 4.6 million deaths have been reported

to WHO. During the period of 13-19 September the numbers of weekly COVID-19 cases and deaths globally continued to decline, with over 3.6 million cases and just under 60 000 deaths reported [3]. SARS-CoV-2 is a positive-sense, single-stranded RNA virus belonging to the family of coronaviridae. SARS-CoV-2 targets cells through the viral structural spike (S) protein binding to the angiotensin converting enzyme 2 (ACE2) receptor. The serine protease type 2 transmembrane serine protease (TMPRSS2) in the host cell promotes viral uptake by cleaving ACE2 and activating the SARS-CoV-2 S protein. Early in the infection, viral copy numbers can be high in the lower respiratory tract.
The viral inflammatory response, consisting of both the innate and the adaptive immune response (comprising humoral and cell-mediated immunity), impairs lymphopoiesis and increases lymphocyte apoptosis. Moreover, in severe COVID-19, activation of coagulation and consumption of clotting factors occur. The manifestations of COVID-19 are characterized by an extremely heterogeneous spectrum of clinical severity ranging from a mild, self-limiting, upper respiratory tract infections with minimal symptoms to a diffuse viral pneumonia causing significant hypoxia with Acute Respiratory Distress Syndrome (ARDS) and sequelae including multiorgan failure and death [4-9]. Most SARS-CoV-2 infected persons are not hospitalized, and relatively little is known about the progression of symptoms, clinical outcomes, and severity predictors among outpatients [10,11]. Current pathophysiological understanding of the SARS-CoV-2 is based on an induced host immune response and no specific drugs have proven to be fully efficacious for SARS-CoV-2 infection.

1.2 Rational of the study

According with Italian data by ISS, the hospitalisation rate in the last 30 days, is about eight times higher for the unvaccinated than for the fully vaccinated subjects (190.9 vs 24.6 hospitalisations per 100,000 inhabitants) [12]. There is a need to rapidly evaluate treatments in the non-hospitalized setting, to prevent disease progression, and reduce serious complications of COVID-19 and most importantly, transmission.
Nowadays, effective interventions to prevent or treat COVID-19 remain few in number and clinical experience is limited; Anti-SARS-CoV-2 monoclonal antibodies that target the spike protein have been shown to have a clinical benefit in treating SARS-CoV-2 infection13]. Neutralizing antibodies, whether natural or monoclonal, can bind directly to portions of viruses that they use to attach to and enter cells, preventing them from initiating the infection cycle. Within the COVID-19, the primary target for such antibodies is the viral spike, the trimeric protein [15,16] that is responsible for the binding of the virus to the ACE2 receptor on the host cell [17-19]. MoAbs neutralize beta-coronaviruses by blocking the attachment of the S protein receptor-binding domain (RBD) to the receptor on host cells, ACE2 [20].
Many competition-binding, structural, and functional studies allowed clustering of the MoAbs, demonstrating potential panels of MoAbs targeting distinct epitopes on SARS-CoV-2, which exhibited potent neutralizing activity and fully blocked the receptor-binding domain of S (SRBD) from interacting with human ACE2 [21-26].
Some anti-SARS-CoV-2 MoAbs have been found to be effective in preventing SARS-CoV-2 infection in household contacts of infected patients and during SARS-CoV-2 outbreaks in skilled nursing and assisted living facilities [14-16].

In vivo, the phase 1-2 of a trial on REGN-COV2 cocktail (casirivimab and imdevimab, together at 2 different dosages, 2.4 g and 8 g, developed by Regeneron Pharmaceuticals, Inc, and supported by the National Institute of Allergy and Infectious Disease, NIAID) enrolled 275 non-hospitalized COVID-19 patients with early infection (within 7 days after the onset of symptoms and 72 hours after a positive result on quantitative reverse transcriptase–polymerase-chain-reaction [RT-PCR] testing of nasopharyngeal swab samples) demonstrated that the REGN-COV2 antibody cocktail reduced viral load from day 1 through day 7 by a mean difference (vs placebo group) of −0.41 $\log_{10}$ copies per milliliter (95% CI, −0.71 to −0.10) in the overall trial population, with a greater effect in patients whose immune response had not yet been initiated or who had a high viral load at baseline [−0.56 $\log_{10}$ copies per milliliter (95% CI −1.02 to −0.11)]; a higher median percentage reduction for the dosage of both MoAbs at 2.4 g was observed. Additionally, among patients who were serum antibody-negative at baseline, 15% of the patients in the placebo group and 6% of the patients in the combined REGN-COV2 dose groups reported at least one medically attended visit at day 29 (difference, −9 percentage points; 95% CI, −29 to 11). Safety outcomes were similar in the combined REGN-COV2 dose groups and the placebo group [27]. The phase 3 portion of that adaptive trial including 3088 patients randomized 1:1:1 to receive intravenous REGEN-COV at a dose of 1200 mg (600 mg of each antibody) or 2400 mg (1200 mg of each antibody) or intravenous placebo (doing was estabilshed on the bases of the previous phase 1-2 portion of the trial) Compared to placebo, receipt of REGN-COV2 was associated with 3.3% absolute reduction and 71% relative risk reduction in COVID-19 related hospitalization or all-cause death.

The other randomized, phase 2/3 trial, BLAZE-1 (Blocking Viral Attachment and Cell Entry with SARS-CoV-2 Neutralizing Antibodies, developed by Eli Lilly&co in collaboration with AbCellera and with the NIAID Vaccine Research Center) for the evaluation of anti-spike neutralizing monoclonal antibody treatment on 577 outpatients with mild or moderate COVID19 published the final analysis on phase 2 portion. This trial included 5 cohorts: 3 groups with varying doses of bamlanivimab (LY-CoV555) monotherapy (700 mg, 2800 mg and 7000 mg, whose interim analysis was previously published by Chen et al [28]), 1 group with a combination therapy of bamlanivimab and etesevimab (LY-CoV555and LY-CoV016, both at the dosage of 2800 mg), and a placebo group. Even though, was not found a significant difference in change in viral load with the three different doses of bamlanivimab monotherapy compared with placebo, the treatment with the combination of the two MoAbs significantly decreased SARS-CoV-2 log viral load at day 11 compared with placebo (between-group difference, –0.57 [95%CI, –1.00 to –0.14], p = 0.01). The proportion of hospitalizations or emergency department visits was 5.8% for placebo and 0.9% for combination treatment and particularly, a post hoc analysis revealed that among patients $\geq$65 years or with a BMI $\geq$35, no patients were hospitalized with a difference vs placebo by –13.5% (95%CI, –22.7%to –4.2%); p=0.04. Only 2 immediate hypersensitivity reactions were reported in the combination treatment group and 1 in placebo. The combination group had the largest reductions in viral load, the monotherapy groups all performed comparably with the combination group on several clinical endpoints (mean total symptom score and hospitalization rate) [29]. Interestingly, in the exploratory analysis of ongoing viral sequencing, putative bamlanivimab-resistant variants were observed in all treatment groups and specifically, the bamlanivimab monotherapy groups had a higher frequency

of patients who had a variant detected at more than one time-point during the viral time course (4.1% for the 700 mg group, 5.9% for the 2800 mg group, and 7.2% for the 7000 mg group) than the placebo group or the bamlanivimab and etesevimab combination group (both 0%). Additionally, a recent company release described the phase 3 data that further strengthen the thought that the MoAbs combination of bamlanivimab and etesevimab had the potential to be an important treatment that significantly reduced hospitalizations and death in high risk COVID19 patients by 70%.

The Phase 3 study for the prevention of COVID-19 in residents and staff at long-term care facilities (BLAZE-2, NCT04497987) was recruiting a LY-CoV555 is being tested in the National Institutes of Health-led ACTIV-2 studies of outpatients COVID-19 patients.
No added benefit for these antibodies was shown in trials involving hospitalized patients (NCT04426695 and NCT04342897), maybe because in later stages of the disease, inflammation, coagulopathy and their clinical consequences have been already established.
In addition to Lilly's and Regeneron's MoAbs, other trials are ongoing. Notably, data on the VIR-7831 (or GSK4182136) and VIR-7832 MoAbs, produced by the alliance between US Biotech Vir Biotechnology and the GlaxoSmithKline group, are becoming available [30]; these MoAbs have demonstrated an enhanced ability to neutralize SARS-CoV-2 variants in vitro, due to the fact that they bind to a highly conserved epitope of the SARS-CoV-2 spike protein. For the first of the two, results were announced from the phase 3 COMET-ICE (COVID-19 Monoclonal antibody Efficacy Trial - Intent to Care Early) clinical trial, which evaluated VIR-7831 as monotherapy for the early treatment of COVID-19 in adults at high risk of hospitalization. Results of the interim analysis, based on data from 583 patients enrolled in the trial, demonstrated an 85% (p =.002) reduction in hospitalization or death in those receiving VIR-7831 compared to placebo [31]. Consequently, the Independent Data Monitoring Committee recommended that the study be discontinued due to evidence of profound efficacy. In light of these data, GlaxoSmithKline and Vir Biotechnology announced the submission of an application to the US FDA and EMA to seek emergency use authorisation (EUA) for VIR-7831 (GSK4182136) and recently, these agencies concluded that sotrovimab can be used to treat confirmed COVID-19 in adults and adolescents (aged 12 years and above and weighing at least 40 kg) who do not require supplemental oxygen therapy and who are at risk of progressing to severe COVID-19. Interestingly, the efficacy of the combination of bamlavinimab (LY-CoV555) 700 mg with VIR-7831 (GSK4182136) 500 mg in non-hospitalised patients with mild-to-moderate COVID-19 is currently being evaluated in the BLAZE-4 trial, which is reported to have demonstrated a 70% ($p < .001$) reduction in persistently high viral loads (>5.27) at day 7, compared to placebo, achieving the primary endpoint as defined above [32].
On the basis of the results of the above studies the regulatory authorities (first the FDA, then the European Medicines Agency - EMA - and, finally, AIFA) have come out in favor of the use of caserivimab/imdevimab, bamlanivimab/etesevimab combinations and sotrovimab in non-hospitalised patients who do not require supplementary oxygen therapy and who are at high risk of progressing to severe forms of the disease [33-37].
More recently, a press release coming from the company AstraZeneca revealed first results from Tackle Trial, a Phase III, randomised, double-blind, placebo-controlled, multi-centre trial assessing

the safety and efficacy of a single 600mg IM dose of AZD7442 compared to placebo for the outpatient treatment of COVID-19. These results showed a dose of 600mg of AZD7442 given by intramuscular (IM) injection was able to reduce the risk of developing severe COVID-19 or death (from any cause) by 50% compared to placebo in outpatients who had been symptomatic for seven days or less [38].
Due to the adaptive design of this study, other arms or substitution of arms will be planned. This in case of one of the experimental arms will be stopped for futility rules, as well as for releasing more consistent data from clinical development of new MoAbs (e.g. Phase 3 studies) or issuing of new racommendations from regulatory authorities.

The emergence of SARS-CoV-2 variants are threatening all efforts to contain the COVID-19 pandemic: the prototypic VOC with increased fitness variant B.1.1.7,emerged in the United Kingdom [39-41], the variant B.1.351 dominant in South Africa [42] and variant P.1 emerged in Brazil [43]. These variants of concern harbor mutations in the RBD that reduce neutralization by antibodies, including E484K, present in B.1.351 and P.1 and can evade immune control with a selective advantage [44-46]. More recently, the emergence of B.1.617 lineage, identified in India, is responsible of a steep increase of cases and deaths and of a very rapid spread throughout the world as its S protein-driven entry was partially resistant against neutralization by antibodies elicited upon infection or vaccination with the Comirnaty/BNT162b2 vaccine [47,48].
While some MoAbs, such as the combination of Casirivimab and Imdevimab seem to maintain the efficacy against variant B1.351 and B1.617, even though reduced as compared with the WT or other VOCs, Bamlanivimab failed to inhibit the cell entry by variant B1.351 [49] and is unable to block the entry of variant B1.617. Etesevimab blocked entry driven by the WT and B.1.617 S proteins with comparable efficiency but failed to inhibit B.1.351 S protein-driven cell entry.
Finally, a cocktail of bamlanivimab and etesevimab was less effective in inhibiting B.1.617 S protein-driven cell entry compared with the WT SARS-CoV- 2 S protein and failed to block entry driven by the B.1.351 S protein. These in vitro results suggest that bamlanivimab monotherapy may not be suitable for treatment of patients infected with variant B.1.617[47].
A preprint learning health system adaptive platform trial with the aim to evaluate the comparative effectiveness of the available moAbs (bamlanivimab vs bamlanivimab/etesivamab vs carivimab/imdevimab) found a 91% and 94% probability of inferiority of bamlanivimab alone respectively to bamlanivimab-etesevimab and casirivimab-imdevimab, and an 86% probability of equivalence between bamlanivimab-etesevimab and casirivimab-imdevimab with regard to the odds of improvement in hospital-free days by 28 days. Notably, the VOCs examined in this trial were predominantly alpha variant with delta variant not still widespread [50]. So much so, the US government reinstated the use of bamlanivimab-etesevimab on August 27, 2021 in areas where variant resistance to this mAb is < 5%, based on in vitro data of activity against the Delta variant, and lack of activity against the Beta, Gamma, Delta plus (with the additional mutation K417N), and B.1.621 variants [51,52].

Moreover, the presence of the highly prevalent D614G variant, either alone or in combination, did not alter neutralization of sotrovimab. Pseudotyped assessments indicate that sotrovimab retains

activity against the UK (2.3-fold change in EC50 value), South Africa (0.6-fold change in EC50 value), Brazil (0.35- fold change in EC50 value), California (0.7-fold change in EC50 value; CAL.20C: S13I, W152C, L452R, D614G), New York (0.6-fold change in EC50 value), and India (0.7-fold change in EC50 value) variant spike proteins [53].

Following the recommendations from regulatory authorities, since April 2021, we conducted an observational cohort study at our Institute with the aim to assess the impact on hospitalization risk due to COVID-19 of the two different MAbs combinations authorized by AIFA, bamlanivimab+etesevimab (BAM/ETE) and casirivimab+imdevimab (CAS/IMD) [54] (see report enclosed).
A total of 242 patients receiving BAM/ETE infusion (n=76) and CAS/IMD (n=166) were enrolled, with a median age of 65 years (54-74), time from symptoms onset was 4 days (IQR 3-6), 40% of them were vaccinated against SARS-CoV-2. After 30 days of follow-up, 12/76 (15.8%) patients treated by BAM/ETE and 6/166 (3.6%) patients by CAS/IMD experienced clinical failure (OR 5.00;95%CI 1.80-13.89). Two COVID-19 related deaths were observed, both in the BAM/ETE group. After multivariable adjustment, severe obesity (BMI >35), harboring SARS-COV-2 P.1/Gamma variant and exposure to BAM/ETE resulted independently associated to an increased risk of being hospitalized due to severe COVID-19 [54].

1.3 Benefit/Risk assessment

Participants have the guaranteed benefit of receiving MoAbs en effective treatment against COVID-19, offering participants protection from severe COVID-19 and death. Partecipants have also the benefit of a complete clinical and laboratoristic follow-up of the infection managed by specialists in COVID-19 disease.
There are no identified risks associated with the administration of MoAbs. Potential risks are associated with the administration of any immunoglobulin, including polyclonal immunoglobulin preparations and MoAbs. The important potential risks associated with the administration of immunoglobulin, include, but are not limited to, anaphylaxis and other serious hypersensitivity reactions, including immune complex disease. To date, there have been no serious adverse events following the administration of any of the MoAbs mentioned above, similar events of immediate hypersensitivity reactions (anaphylaxis or other allergic reactions) were observed [28-29].
Other potential risks include, but are not limited to, injection site reactions, infusion-related reactions, and ADE disease. Antibody-dependent enhancement of disease is a theoretical risk even though more frequently induced by vaccines, it should not be provoked by MoAbs.
Although benefits for patients with COVID-19 are potential, the scarceness of effective treatments of SARS-CoV-2, make this investigation warranted and establishing the therapeutic or prophylactic efficacy of monoclonal antibodies would be a major advance in the control of the COVID-19 pandemic. Overall, the potential risks identified in association with MoAbs are justified by the anticipated benefits that may be afforded to participants at risk of COVID-19. This strategy may prevent progression of COVID-19 and would greatly reduce the concerns and uncertainty associated with SARS-CoV-2 infection and give physicians a therapeutic tool they must have for their patients.

2. OBJECTIVES AND ENDPOINTS

This is an open-label, randomized study assessing efficacy of two different combined MoAbs compared to SoC in not hospitalized patients with mild symptoms of COVID-19.

2.1 Primary Objective

To estimate the efficacy of any MoAbs in the study protocol in the prevention of the composite endpoint of either severe COVID-19 or hospitalization or access in an emergency department or death from any cause through study Day 29.

2.2 Key Secondary objectives

- To evaluate the effect of any MoAbs in the study protocol in the prevention of hospitalization for COVID-19 complications or sequelae through study 29 and within 90 days;
- To determine if any MoAbs in the study protocol will prevent respiratory failure through study Day 29;
- To determine if any MoAbs in the study protocol reduces SARS-CoV-2 detection or levels of RNA in nasal swabs through Day 29;
- To characterize the effect of any MoAbs in the study protocol compared to SoC on symptom resolution;
- To characterize the effect of any MoAbs in the study protocol compared to SoC on clinical progression;
- To explore baseline and emergent viral resistances (sequence analysis of the SARS-CoV-2 spike gene, with particular focus on D614G, N501Y, N501Y.V2, L452Y, L452R, E484K/Q, Y453F,N439K, P681R, T478K and K417N).

2.3 Other secondary objectives

- To evaluate differences in symptom duration between the MoAbs and SoC through day 29;
- To evaluate differences in long-term symptoms and duration between the MoAbs and SoC after viral clearance;
- To investigate the humoral response to non-Spike SARS-CoV-2 antigens;
- To investigate the cell-mediated immune response to Spike and non-Spike SARS-CoV-2 antigens (in a subgroup of patients)
- To explore if baseline and follow-up hematology, chemistry, coagulation, viral, and inflammatory biomarkers are associated with clinical and virologic outcomes in relation to any MoAbs in the study protocol.
- To set-up an algorithm of drug efficacy prediction

2.4 Primary endpoint

Survival without experiencing clinical failure at day 29 after randomization. Clinical failure is assessed by a composite endpoint including: A) death for any cause; B) progression to severe COVID 19; C) scoring 5 or more in the WHO severity scale. Severe COVID-19 is defined by pneumonia (fever,

cough, tachypnea, or dyspnea) AND lung infiltrates >50% OR hypoxemia (SpO2 < 92% in room air and/or severe respiratory distress).

2.5 Secondary endpoints

- Proportion of participants who experience hospitalization or Emergency Room (ER) visit within day 29 and within 90 days;
- Proportion of participants experiencing severe COVID-19 by day 29 after randomization;
- Variation of SARS-CoV-2 viral load measured by semi-quantitative RT-PCR between day of randomization and day 7 , 14 and 29;
- Proportion of participant with undetectable SARS-CoV-2 RNA at day 7, 14 and 29 after randomization;
- Variation of symptoms score from day of randomization to days 7, 14, and 29 after randomization;
- Proportion of participants demonstrating symptom resolution (i.e. scoring 0 in the WHO scale) at Days 7, 14 and 29 after randomization;
- Proportion of participants with any adverse event (grade ≤ 2 according to CTCAE) at day 7, 29 after randomization;
- Proportion of participants with severe adverse events (grade ≥ 3 according to CTCAE) at day 7, 29 after randomization;
- Variation of Hematology, chemistry, coagulation, and inflammatory markers between the day of randomization and day 7, 29 after randomization;
- Proportion of SARS-CoV-2 spike mutation gene (including D614G, N501Y, N501Y.V2, L452Y, L452R, E484K/Q, Y453F, N439K, P681R, T478K and K417N) among participant experiencing the primary endpoint;
- Proportion of SARS-CoV-2 spike mutation gene (including D614G, N501Y, N501Y.V2, L452Y, L452R, E484K/Q, Y453F, N439K, P681R, T478K and K417N) among participant with a detectable SARS-COV-2 viral load at day 29 after randomization.

2.6 Other endpoints

- Time to return to usual (pre-COVID-19) health through Day 29;
- Duration of fever through Day 29 defined as the last day in the participant-reported symptom diary on which a temperature greater than 37.8°C was recorded or a potentially antipyretic drug, such as acetaminophen or ibuprofen, was taken;
- The proportion of patients who report long-COVID-19 symptoms from day 29 to day 90 according to arm treatment;
- The proportion of participants who have a post-treatment sero-response defined as a rise in IgG titers from day of dosing baseline value to the N antigen of SARS-CoV-2 through Day 29 and 90.
- Combinations of personal, clinical, biological factors associated with efficacy of treatments.

3. STUDY DESIGN AND STATISTICAL PLAN

3.1 Study design overview

This is an adaptive phase 4 (i.e. post approval), multi-arm, multi-stage, open label, multicenter, individually randomized clinical trial for adult subjects (aged ≥18 years) with molecularly confirmed mild to moderate SARS-CoV-2 infection, no need for immediate hospitalization and significant risk factor for severe/critical COVID-19.

This study will compare the efficacy of the three currently approved anti-SARS-CoV-2 MoAbs to provide high quality evidence, which can be directly implemented into new clinical guidance. The study is designed to randomize participants with 1:1:1 ratio to receive either: 1) sotrovimab (Xevudy) or 2) casirivimab/imdevimab (Regeneron) or 3) bamlanivimab/etesevimab (Lylli). The bamlanivimab/etesevimab will serve as the active control arm.

The adaptive design of the study is aimed to meet the most topical needs of translational medical research programs implemented during the global epidemic emergency due to SARS-CoV-2. The adaptive components used in this trial include:

A. 3-stage sequential design
B. Multi-arm design (multiple comparison are adjusted according to Dunnet method)
C. Binding stopping rule for efficacy (alpha spending function according to O'Brien and Flemming)
D. Binding stopping rule for futility (beta spending function according to O'Brien and Flemming)
E. Open sample size recalculation

Adaptation is a carefully considered an investigational procedure for modifying study parameters while the trial is ongoing, based on reviews of the interim data analyses. In this trial we have 2 variable parameters, namely the sample size and the study duration.

The performance of the study according to the adaptive sequential design with binding stopping rules and open sample size recalculation is reported in the simulation section.

3.2 Study hypothesis, alpha error and power

Previous observational data suggested that, in high-risk population for severe COVID-19, the survival rate without hospitalization at day 29 after therapy was 85% in those who received bamlanivimab/etesevimab.

The study is designed on the (superiority) hypothesis that at least one of test arms, either sotrovimab or casirivimab/imdevimab, improves the survival rate, with no failure at day 29 after therapy, from the expected 85% in the control arm to ≥ 92.5% in at least one test arm (i.e. RD ≥ 7.5%). If the experimental hypothesis is true, the study has a one-tailed alpha-error of <0.025 and an overall power >90% and an average sample size of 936 (between 300 and 1239) participants. Potential inflation of statistical error (due to application of stopping rules) is managed by O'Brien and Fleming alpha-spending function and O'Brien and Flemming beta-spending function for type 1 and type 2 statistical error, respectively.

3.3 Sequential design procedures

The sequential procedure of the trial (grey boxes) and the eventual decisions about the implementation of new guidance and/or new studies is reported in annex figure 1.

In brief:

A. If superiority hypothesis is met for neither of the test arms, current guidance will not change (red boxes);
B. If superiority assumption is met for one arm only but second-best arm is expected to be better in term of cost-efficacy, has easier administration route and/or has better logistics profile (i.e. it has a better trade-offs) a new guidance for removing bamlanivimab/etesevimab will be given and a new non-inferiority trial will be proposed (orange boxes);
C. If superiority assumption is met for one arm only and the best arm is also expected to be better in term of cost-efficacy, has easier administration route and/or has better logistics profile (i.e. it has a better trade-offs) a new guidance for using best arm in all setting will be given (blue boxes);
D. If superiority assumption is met for both test arms, a new guidance for removing bamlanivimab/etesevimab will be given and a new superiority trial will be proposed (green boxes).

3.4 Sample size re-calculation

Sample size is re-calculed at each interim analyses. Sample size at stage 1 includes 300 participants (i.e. 100 per arm). Subsequent enrollments include an average 125 participants per arm according to constant allocation ratio with maximum allowed reduction 0.3 (i.e. 38 per arm) and maximum allowed increase 3 (i.e. 375 per arm). The number of participants is calculated according to 90% conditional power for next stage for observed efficacy (ML estimate).

3.5 Trial simulation

Trial simulation has been used to assess the performance of the trial in real life scenarios where observed data may significantly depart from the *a priori* hypothesis about the efficacy of the three MoAbs. In particular, the simulation assesses how stopping rules and sample size recalculation work according to the variation of observed frequency of primary endpoint in the three different arms. We assumed that the true efficacy of either one of the test arm (i.e.sotrovimab [test-1] or casirivimab/imdevimab [test-2]) may vary form 85% (i.e. equal to those expected for control) to 100% (i.e. all participants meets criteria for primary endpoint). Efficacy in control arm (i.e. bamlanivimab/etesevimab) is fixed at 85%.

3.5 .1 Effect of departure from a priori hypothesis: probability to find a superior arm

The effect of departure form *a priori hypothesis* on trial performance is reported in annex figure 2. The graph shows the variation of the probability to find an effective arm according to true efficacy of either one of test arm (i.e.sotrovimab [test-1] or casirivimab/imdevimab [test-2]).

The green circles show a 91% probability to find a superior arm when only one test arms has a true efficacy equal to 92.5%. In this scenario, the primary hypothesis is true and power is confirmed to be >90%. The red circle represents the probability to find a superior arm when no arm is truly effective and coincide with one tailed alpha-error of 2.5% (i.e. P=0.025). These estimated confirm the good performance of the alpha and beta spending function applied.

3.5.2 Effect of observed efficacy on stopping rules

Probability to apply stopping rule and thus to early termite the trial either by stage 1 or by stage 2 is reported in annex figure 3.

The graph A shows the probability to find a superior arm by trial stages. Black dotted line represents the probability to terminate the trial by stage 3 and to find an effective arm. It resembles the graph reported in annex figure 2 and confirms that trial performance includes a power ≥ 90% (green circle) and one tailed alpha error of 2.5 % (red circle) when primary hypothesis is true.

Graph B represents the probability to terminate the trial for futility either by stage 1 or by stage 2. The graph confirms that the probability to terminate the trial for futility (green circles) is well below 10% when the primary hypothesis is true, confirming the good performance of the beta-spending function that preserve the power above 90% even after application of stopping rules.

Graph C represents the cumulative probability to probability to early terminate either by stage 1 or by stage 2 (futility plus efficacy). The graph emphasizes the parsimony of our approach and demonstrate the high probability of early termination either in case of extraordinary efficacy or in case of negligible efficacy.

3.5.3 Effect of observed efficacy on the sample size (sample size recalculation)

Annex figure 4 shows the performance of the trial in terms of optimization of the sample size provided by the synergy of the three adaptive components; namely: stopping rules for efficacy, stopping rules for futility and recalculation of the sample size. In particular, these three components help in containing the needed patients to enroll while preserving a good trial performance. We estimate an average sample size of 936 participants if primary hypothesis is true. The average sample size may vary from a minimum of 300 to a maximum of 1239 according to the variation of the true efficacy of either one of the test arm

3.6 Definition of End of Trial

The end of study is defined as the date at which the last patient completes the last study assessment, withdraws from the study or is lost to follow-up.

3.7 Duration of study

The total duration of the study will be 90 days from the day of enrolment of the last volunteer.

Duration of Recruitment: 9 months

Anticipated Start Date: 1 DECEMBER 2021

Anticipated End Date: the end of study is defined as the date the last patient completes the last study assessment, withdraws from the study or is lost to follow-up.

Data analysis and Final Study Report: 31 DECEMEBER 2022

3.8 Analysis of efficacy (primary outcome)

Interim analysis and final analysis will be carried out by taking into account the potential effect of each individual component of the adaptive design. The interim analysis will provide:

A. estimate of efficacy as risk difference and relative 95% CI

B. criteria for stopping rule for efficacy
C. criteria for futility
D. if the stopping rule is not met the analysis will provide the number of participants to be randomized for the subsequent stage in each arm.

Final analysis will provide efficacy as difference estimate of efficacy as risk difference and relative 95% C.I

All analysis will be carried out according free combination test for inverse normal methods and O'Brien and Fleming sequential design with formal alpha and beta spending function. Sample size will be re-calculated according to a 100 per arm for stage 1 and eventually a flexible number of enrollment between 38 and 375 per arm with 90% power for next stage calculated on observed efficacy.

3.9 Analysis of secondary outcome and other explorative analysis

Analysis of secondary and explorative endpoints will be carried out by regression models. In particular, outcomes expressed by binary variables will be assessed by logistic regression model, outcome expressed by continuous variables will be assessed by linear regression model and variable expresses by censored measure will be assessed by interval regression model.

All regression models will always include the outcome as the only dependent variable and at least three dependent variables including age and sex (as a *priori confounders*) and the allocation arm as the only explicative independent variable. The inclusion of additional potential confounders will be decided case-by-case if any potential imbalance of randomization occurs in the dataset used for sub-analysis.

Three-level mixed linear regression model with random intercept at laboratory, random intercept at participant level, random slope at the level of the time after randomization will be used to model temporal kinetics of repeated continuous measures of virological and biochemical assays carried out by local laboratory. The best shape of the association between the each virological or hemato-chemical parameter dependent variable) and time after randomization (independent variable) will be produced by a sequential polynomial approach (i.e. variation of each parameters will be expressed as increasing polynomial function of time). The best-fitted function for association will be selected by likelihood ratio test (LRT) for nested model so that the simplest model (i.e. that with the lowest polynomial function) will be selected over the most complex one if LRT p-value >0.100. In addition the best fitted polynomial model will be tested against a saturated model that contain time a categorical variable with a level for each time of sampling. Potential confounders will be included if significant imbalance will be found in these sub-analysis.

4. TREATMENT

4.1 Study intervention

Participants who satisfy the inclusion and exclusion criteria will be randomized (1:1:1:1) to receive:

- **Arm A**: participants will receive one single infusion of Sotrovimab (VIR-7831) 500 mg via a single one-hour intravenous infusion (IV);

- **Arm B**: participants will receive one single infusion of REGN-COV2 casirivimab 1200 mg and imdevimab 1200 mg (REGN10933 and REGN10987), via a single one-hour intravenous infusion (IV);
- **Arm C**: participants will receive one single infusion of the combination of bamlanivimab 700 mg and etesevimab 1400 mg (LY-CoV555 and LY-CoV016) via a single one-hour intravenous infusion (IV);

4.2 Experimental treatment

- Participants in the experimental arm A will receive one single infusion of Sotrovimab (VIR-7831) 500 mg intravenously (IV);
- Participants in the experimental arm B will receive one single infusion of REGN-COV2 casirivimab 1200 mg and imdevimab 1200 mg (REGN10933 and REGN10987), intravenously (IV);
- **Arm C**: participants will receive one single infusion of the combination of bamlanivimab 700 mg and etesevimab 1400 mg (LY-CoV555 and LY-CoV016) via a single one-hour intravenous infusion (IV);

In all the arms are permitted acetaminophen, antibiotics and pre-existent medications. No antivirals for SARS-COV-2 are allowed.

Study intervention must be administered within 3 days of the first positive SARS-CoV-2 test sample collection.
The infusion rate may be reduced as deemed necessary if an infusion reaction is observed. Participants will be monitored for at least 2 hours after completion of the infusion.
Premedication for infusions is not planned. However, if an infusion reaction occurs during administration or if the participant has a medical history suggesting a potential benefit from premedication, the study investigator(s) should determine the appropriate premedication. The investigators may decide to use premedication if the frequency of infusion reactions among participants warrants it.
If minor infusion reactions are observed, administration of acetaminophen, 500 mg to 1000 mg, antihistamines and/or other appropriately indicated medications may be given prior to the start of infusions for subsequent participants. The decision to implement premedication for infusions in subsequent participants will be made by the investigator and sponsor and recorded in the study documentation.

4.3 Investigational medicinal product

Drug characteristics

Mechanism of action of all MoAbs considered: neutralizing immunoglobulin G (IgG)-1 monoclonal antibody (MoAb) binding to the receptor binding domain (RBD) of the spike (S) protein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). This antibody blocks S protein attachment

to human angiotensin-converting enzyme 2 (ACE2) receptors, preventing subsequent viral entry into human cells and viral replication.

4.3.1 Arm A

Justification for dose chosen:
A 500 mg IM dose was selected to ensure that VIR-7831 concentrations in lung are maintained at or above levels anticipated to be neutralizing for the duration of the treatment window. Furthermore, serum levels of VIR-7831 are expected to ≥ 2x lung tissue adjusted EC90 through the Week 26 end of study visit. A mean trough concentration of >2x tissue-adjusted EC90 is expected to ensure that levels of VIR-7831 remain at or above tissue-adjusted EC90 in all patients for the duration of the study.
Prior clinical experience with a 500 mg IV dose of VIR-7831 has been gained in the setting of the early treatment of COVID-19 (COMET-ICE; NCT04545060) and hospitalised treatment in ACTIV-3-TICO. In the COMET-ICE study, there have been no significant safety concerns identified at the IDMC reviews conducted to date. One severe allergic reaction was reported during infusion in ACTIV-3-TICO, an ongoing blinded study.
VIR-7831 is provided in single-use vial (62.5 mg/mL) at the unit dose of 500 mg/vial (500 mg/8 mL) and stored at appropriate temperature (usually at 2°-8°C).

4.3.2 Arm B

Justification for dose chosen: The mean and individual concentration–time profiles for the components of REGN-COV2, casirivimab and imdevimab, increased in a dose-proportional manner and were consistent with linear pharmacokinetics for single intravenous doses. The mean (±SD) day 29 concentrations of casirivimab and imdevimab in serum were 68.0±45.2 mg per liter and 64.9±53.9 mg per liter, respectively, for the low (1.2 g) doses and 219±69.0 and 181±64.9 mg per liter, respectively, for the high (4.0 g) doses.

Casirivimab and Imdevimab are provided in single vial of 11.1 mL or four 2.5mL and must be stored between 2ºC and 8ºC. One 11.1 mL vial of one antibody may be prepared with four 2.5 mL vials of the other antibody to create one treatment course.

Due to the adaptive design of the study, other arms or substitution of arms were planned. This in case of one of the experimental arms will be stopped for futility rules, as well as for releasing more consistent data from clinical development of new MoAbs (e.g. Phase 3 studies) or issuing of new racommendations from regulatory authorities.

4.3.3 Arm C

Justification for dose chosen: the dose is determined based on some key variables and on the results of the BLAZE-1, where the dosage of 700 mg and 1400 mg seemed to perform better. The key variables considered are: projected human PK of the MoAb, including lung tissue distribution, in vitro binding potency to the viral targets, neutralization of virus cell entry and replication, and

antibody-viral dynamic modeling and simulation. The projected human half-life is expected to be in the 2-4 weeks range. The dose levels are fixed, not body weight based. Given the planned dose levels, the predicted impact of body weight on therapeutic response will be minimal.
LY-CoV555 and LY-CoV016 are provided in vials of 20 ml solution containing 700 mg antibody each. LY-CoV555 must be stored between 2ºC and 8ºC.

4.3.4 Management of Infusion Reactions

All participants should be monitored closely, as there is a risk of infusion reaction and hypersensitivity (including anaphylaxis) with any biological agent.

4.3.4 Symptoms and Signs

Symptoms and signs that may occur as part of an infusion reaction include, but are not limited to fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, and dizziness.
Infusion-related reactions severity will be assessed and reported using the Division of Allergy and Infectious Diseases (DAIDS) Table for Grading the Severity of Adult and Pediatric Adverse Events, version 2.1 (July 2017).

4.3.5 Management of Infusion Reactions

Investigators should determine the severity of the infusion reaction and manage infusion reactions based on standard of care and their clinical judgment. If an infusion reaction occurs, then supportive care should be used in accordance with the signs and symptoms.

5. STUDY POPULATION

Participants will be outpatient adults with documented positive SARS-CoV-2 test and mild-to moderate symptoms of COVID-19, who do not require supplemental oxygen therapy for COVID-19 and who are at high risk of progression to severe COVID-19 as defined by Center for Disease Control and prevention (CDC). Underlying Medical Conditions Associated with Higher Risk for Severe COVID-19 are:

- Aged ≥65 years
- Obesity (BMI >30) or weight >95% percentile adjusted for age and sex
- Diabetes mellitus, type 1 and type 2
- Heart conditions (such as
    - heart failure,
    - coronary artery disease
    - cardiomyopathies
    - congenital heart disease
    - hypertension
- Cerebrovascular disease
- Chronic lung diseases
    - COPD chronic obstructive pulmonary disease

  - moderate-to-severe asthma
  - interstitial lung disease
  - cystic fibrosis
  - pulmonary hypertension
  - Pulmonary embolism
  - Bronchopulmonary dysplasia
  - Bronchiectasis
- Chronic liver diseases limited to:
  - Cirrhosis
  - Non-alcoholic fatty liver disease
  - Alcoholic liver disease
  - Autoimmune hepatitis
- Smoking, current and former
- Chronic kidney disease
- Hemoglobinopathies
  - Sickle cell disease
  - Thalassemia
- Immunocompromised state
  - Primary immunodeficiencies
  - secondary immunodeficiencies
  - HIV (human immunodeficiency virus)
  - Use of corticosteroids or other immunosuppressive medications
- Solid organ or blood stem cell transplantation
- Cancer, previous or current;
- Mental health disorders limited to:
  - Mood disorders, including depression
  - Schizophrenia spectrum disorders
- Tuberculosis
- Down syndrome
- Neurodevelopmental disorders
  - cerebral palsy or other conditions that confer medical complexity
  - genetic or metabolic syndromes
  - severe congenital anomalies
- Neurologic conditions, including dementia and Alzheimer disease
- Substance use disorders
- Medical-related technological dependence as
  - tracheostomy
  - gastrostomy, or
  - positive pressure ventilation that is not related to COVID-19)
- Pregnancy and recent pregnancy (lactating).

Patients with the following inclusion criteria and without any of the exclusion criteria will be enrolled in the study.

Patients with the following inclusion criteria and without any of the exclusion criteria will be enrolled in the study.

5.1 Inclusion criteria

- Age ≥ 18 years
- Signed informed consent provided by the patient, or by the patient's legally authorized representative(s), as applicable
- Virological diagnosis of SARS-CoV-2 infection (SARS-CoV-2 infection confirmed by RT-PCR test OR 3rd generation antigenic ; patients must have sample taken for test confirming viral infection no more than 10 days prior to randomization
- Have one or more mild or moderate COVID-19 symptoms: fever, cough, sore throat, malaise, headache, muscle pain, gastrointestinal symptoms, or shortness of breath with exertion for no more than 10 days

5.2 Exclusion criteria

- Pregnancy/lactation
- Have oxygen saturation (SpO2) less than or equal to (≤)93 percent (%) on room air and persisting for more than 10 days
- Virological diagnosis of SARS-CoV-2 infection (SARS-CoV-2 infection confirmed by PCR test) more than 10 days before
- Have any serious concomitant systemic disease, condition or disorder that, in the opinion of the investigator, should preclude participation in this study
- Enrolment in another concurrent clinical interventional study within 30 days
- Existence of any life-threatening co-morbidity or any other medical condition, which, in the opinion of the investigator, makes the patient unsuitable for the study
- Has known allergy or hypersensitivity to components of study drug

6. STUDY ASSESSMENT AND PROCEDURES

Study procedures and their timing are summarized in the **Table 1.**

6.1 Screening (day -1/day 1)

Adherence to the study design requirements, including those specified in the Table 1, is essential and required for study conduct. All screening evaluations must be completed and reviewed to confirm that potential participants meet all eligibility criteria. The investigator will maintain a screening log to record details of all participants screened and to confirm eligibility or record reasons for screening failure, as applicable. Procedures conducted as part of the participant's routine clinical management (eg, blood count) and obtained before signing of the ICF may be utilized for screening or baseline purposes, provided the procedures have met the protocol-specified criteria and were performed within the timeframe defined in the Table1.

At screening the investigators or medically qualified designee have to check the eligibility of patient for the study and obtain informed consent.
The following procedures will be performed:

- Demographic characteristics
- Focused medical history and current medication
- Physical examination and vital signs (blood pressure, heart rate, respiratory rate, temperature)
- Urine pregnancy test at screening (for women of childbearing potential)
- Routine blood tests (blood count, creatinine, BUN, sodium, potassium, ALT, AST, LDH, fibrinogen, D-dimers, ferritin, PCR)
- SARS-CoV2 serology
- SARS-CoV T cells response (in a subgroup of patients)
- PCR SARS-Cov2 on nasopharyngeal swab (if recent SARS-CoV-2 PCR on other respiratory specimen is not available) no more than 3 days prior to randomization
- Nasopharyngeal swab will be stored for genotypic sequencing in failed patient to explore treatment-emergent variants

- Pocket/wallet card with site staff contact information will be delivered

6.2 Baseline (day 1)

Screening, randomization and baseline visit may be performed on the same day and no other procedures need to be repeated.

On baseline visit, eligible participants will be randomized (1:1:1) to receive:

- **Treatment Group A (experimental arm):** participants will receive one single infusion of Sotrovimab (VIR-7831) 500 mg via a single one-hour intravenous infusion (IV);
- **Treatment Group B (experimental arm)**: participants in the experimental arm B will receive one single infusion of REGN-COV2 casirivimab 1200 mg and imdevimab 1200 mg (REGN10933 and REGN10987), via a single one-hour intravenous infusion (IV);
- **Treatment group C (control arm)**: participants in the control arm will receive one single infusion of the combination of bamlanivimab 700 mg and etesevimab 1400 mg (LY-CoV555 and LY-CoV016) via a single one-hour intravenous infusion (IV);

After randomization, the following evaluations will be performed on baseline:

- Physical examination and vital signs (blood pressure, heart rate, respiratory rate, temperature)
- Instructions on what to do if participants have worsening symptoms/become hospitalized
- Study Symptom Diary will be supplied to the patient and participants will be trained by the site staff on how to complete the diary
- Concomitant medications
- Review of adverse events

After infusion participants will be monitored for at least 1 hour after completion of the infusion. At the end of observation time physical examination with vital signs recording (blood pressure, heart rate, respiratory rate, temperature) need to be performed.

6.3 Daily Study Assessment (day 7, 14, 29 and day 90)

During follow-up visits (after Day 1) through Day 29, peripheral oxygenation saturation measures < 96% should be reviewed by an investigator and referral for medical attention made at the discretion of the investigator. The participant should be assessed for severe COVID-19, characterized by a minimum of either pneumonia (fever, cough, tachypnea, or dyspnea, AND lung infiltrates) or hypoxemia (SpO2 < 92% in room air and/or severe respiratory distress) and a score of 5 or higher in the WHO Clinical Progression Scale in Appendix A. If the patient develops severe Covid-19 as defined above, genotypic sequencing of SARS-CoV2 on nasopharyngeal swab will be performed by protocol. When severe COVID-19 is suspected, diagnostic procedure including TC or Thoracic Ultrasound and evaluation of hypoxemia by arterial blood gas analysis will be evaluated by medical investigator according to current guidelines.

The following evaluations are to be completed at days 7,14, 29 and 90:

- Physical examination and vital signs (blood pressure, heart rate, respiratory rate, temperature)
- Routine blood tests (blood count, creatinine, BUN, sodium, potassium, ALT, AST, LDH, fibrinogen, D-dimers, ferritin, PCR) at days 7,14 and 29
- SARS-CoV2 serology (IgA, IgG, IgM and neutralizing antibodies) at days 7, 14, 29 and 90
- T cell response to S and N (in a subgroup of patients) at day 7, 14, 29 and 90.
- PCR SARS-Cov2 on nasopharyngeal swab by quantitative reverse transcriptase–polymerase chain reaction (RT-PCR) at days 7, 14 and 29

Genotypic sequencing will be performed at failure and at day 29 if SARS-Cov2 on nasopharyngeal swab is still detectable;

Concomitant medications

Review of adverse events

If partecipants are unable to attend the examination, visit on Day 29 should be performed by telephone to assess vital state of patients and evaluate the outcome.

6.3.1 Study Intervention Administration

Study intervention is defined as any investigational intervention(s) or procedure intended to be administered to a study participant according to the study protocol.

Study intervention and the participant-reported symptom diary will be dispensed to the participant according to the study protocol, based on AIFA indication and regional organization, as following:

- Hospital-based outpatient clinics in a dedicated area of hospitals for COVID-19 positive patients;
- Territorial outpatient clinics with prepared ambulatory setting by general practitioners (GP)
- At home visit by GP o USCAR, if admitted by AIFA indications and regional organization

All the trial procedures, including drug administration and follow-up management will be performed according with AIFA statements and regulatory dispositions, and by organization at regional level.

The investigator or designee, is responsible for record maintenance of the study intervention (ie, administration IMP form and vital signs form) that will be considered source documents and will be

archived with the patient's documentation.
Refer to the pharmacy manual for details regarding administration of the study intervention.

6.3.2 Handling/Storage/Accountability

The investigator or designee must confirm appropriate temperature conditions havebeen maintained during transit for all study intervention received, and any discrepancies are reported and resolved before use of the study intervention.
Only participants enrolled in the study may receive study intervention, and only authorized site staff may supply or administer study intervention (Clinic staff involved in the study).
All study interventions must be stored in a secure, environmentally controlled, and monitored (manual or automated) area in accordance with the labeled storage conditions with access limited to the investigator and authorized site staff.
The investigator or designee, is responsible for study intervention accountability, reconciliation, and record maintenance (ie, receipt, reconciliation, and final disposition records).
For all study sites, the investigator or designee will provide appropriate documentation that must be completed for drug accountability and return, or local discard and destruction if appropriate. Where local discard and destruction is appropriate, the investigator is responsible for ensuring that a local discard/destruction procedure is documented.
The study site is responsible for recording the lot number, manufacturer, and expiry date for any locally purchased product (if applicable) as per local guidelines unless otherwise instructed.
The investigator or designee shall take responsibility for and shall take all steps to maintain appropriate records and ensure appropriate supply, storage, handling, distribution, and usage of study interventions in accordance with the protocol and any applicable laws and regulations.

6.4 Discontinuation And Withdrawn Visit

Participants who discontinue study intervention prior to completion of the treatment period should be encouraged to continue to be followed for all remaining study visits.
Participants who withdraw from the study should be encouraged to complete all applicable activities scheduled for the Day 29 visit at the time of withdrawal. Any AEs that are present at the time of withdrawal should be followed in accordance with the safety requirements
Survival status at Day 29 is required for all randomized participants and should still be reported for participants who withdraw from the study where permitted by local guidelines.
A participant who considers withdrawing from the study must be informed by the investigator about modified follow-up options (eg, telephone contact, a contact with a relative or treating physician, or Information from medical records).
At the time of withdrawal from the study, if possible, an Early Discontinuation visit should be conducted, as shown in the Table 1. See the Table 1 for data to be collected at the time of study withdrawal and follow-up and for any further evaluations that need to be completed.

6.5 Lost To Follow Up

A participant will be considered lost to follow-up if he or she repeatedly fails to return for scheduled visits and is unable to be contacted by the study site.

The following actions must be taken if a participant fail to return to the clinic for a required study visit:

- The site must attempt to contact the participant and reschedule the missed visit as soon as possible and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain whether or not the participant wishes to and/or should continue in the study.
- Before a participant is deemed lost to follow up, the investigator or designee must make every effort to regain contact with the participant (where possible, 3 telephone calls and, if necessary, a certified letter to the participant's last known mailing address or local equivalent methods). These contact attempts should be documented in the participant's medical record.
- Should the participant continue to be unreachable, he/she will be considered to have withdrawn from the study.
- Site personnel, or an independent third party, will attempt to collect the survival status of the participant within legal and ethical boundaries for all participants randomized, including those who did not get the IMP. Public sources may be searched for survival status information. If survival status is determined as deceased, this will be documented and the participant will not be considered lost to follow-up.

6.6 Participant-Reported Symptom Diary

During the first 29 days, participants will be asked to report their COVID-19 symptoms and temperature in diary (Appendix B). On Day 1, participants will be trained by the site staff on how to complete the diary. It is important that the participant responds to questions without being influenced by anyone else. Day 1 assessments must be completed before administering IMP. Participants will be asked to complete subsequent entries in the diary each evening on Day 1 through 29 (the entry on Day 29 may be completed with the site staff during the Day 29 visit, if the visit occurs on Day 29 versus another day in the Day 29 visit window). From day 29 to day 90 the diary must be filled in once a week.

COVID-19 signs/symptoms will be reported daily using a paper Symptom Diary on Days 1 to 29. Targeted symptoms assessed in the diary include shortness of breath or difficulty breathing, muscle or body aches, fatigue, feeling hot or feverish, chills, headache, nausea, vomiting and diarrhea. On Day 1, participants will complete the Symptom Diary prior to the dose of study treatment. Completion of the Symptom Diary will be observed at the site or in-home visit and documented, including time of participant completion, by study staff/home healthcare professional. Following Day 1, participants should complete the diary daily at approximately the same time every day through Day 29, recording and rating each symptom at its worst (reported as none, mild, moderate or severe) during the prior 24 hours.

In the event of hospitalization, the Symptom Diary should be completed during hospitalization if possible. If not completed during hospitalization, completion of the diary should be restarted by the participant after discharge.

6.7 Diary Reminder And Staff Review Of Diary

Participant will be reminded every day through the end of the study to complete their diary. This reminder will be received through the electronic device. In the event an electronic device is not available when the participant is randomized, there will be a paper diary alternative with detailed instructions for participants and site staff. The diary will be reviewed by study staff in person with each participant according to the study procedures.

The participant's answers on the diary will be transcribed into the eCRF.

Participants who report worsening symptoms from any cause during the study may be referred to their healthcare provider or closest emergency room. Such instances will be recorded at the time of the notification, and during follow-up to assess study endpoints, ie, hospitalization or death.

6.8 App-Enabled Symptoms Collection And Analysis

The Healthentia App will be used to monitor symptoms and other clinical data on daily basis, creating the Symptom Diary and information to create the eCRF. Healthentia is a customizable eClinical environment, managed by Policlinico Gemelli Real World Data department, which facilitates clinical trial processes. Healthentia is a Class I Medical Device with CE mark; it is intended for monitoring of non-vital parameters to support decision making during clinical trials, based on Real World Data gathered from patient taking part of clinical investigation. Healthentia will monitor and collect all participant-reported symptoms as described in Appendix B. There is the option to add standard questionnaire regarding quality of life which are already available, and will be activated during the trial if appropriate. The App can also generate actionable alerts to the investigator / research staff (e.g. in case of adverse events/serious adverse events); likewise, being easily reconfigurable, through the software the investigators can define threshold values for symptoms or groups of symptoms, which can be useful to detect trends in the participant's response even in the presence of minor changes. Beside monitoring and data analysis, through Healthentia the research staff will be able to manage planning instructions, notifications and reminders, practical guidelines to the participants – this include as well instructions and coordination with research staff and care givers who participate to the research in the different centers / geographic areas.

TABLE 1 – Study procedures flow chart

	Screening (day -1/day 1)	Baseline (day 1)	Daily visits (day 7-14-29)	Day 90	Withdrawn
Type of visit: C= Clinic H= Home	C/H*	C/H*	C/H*	C	
Informed Consent	x				
Randomization		x			
Demographic Characteristics	x				
Medical History	x				
Physical Examination	x	x	x	x	x
Vital Signs[a]	x	x	x	x	x
Study Laboratory Testing[b]	x		x (day 7-29)		x
SARS-CoV2 serology[c]	x		x	x	x
T-cell specific response to SARS-CoV-2 S and N[h]			x	x	
PK of COVID-19 Mab[i]			x		
PCR SARS-Cov2 Swab[d]	x		x		x
IMP administration		x			
Adverse Events[e]	x	x	x	x	x
Concomitant Medications[g]	x	x	x	x	x
Participant-reported symptom diary[f]		x		x	
Participant-reported symptom diary review[g]			x		
Pocket wallet card	x				

* Study intervention and procedures will be dispensed to the participant according to the study protocol either by a GP or by USCAR during the home visit or at the clinic in a dedicated area for COVID-19 positive patients, based on AIFA indications, regional organization and also on site's preferences and/or resources availability.

a) blood pressure, heart rate, respiratory rate, temperature;
b) blood count, creatinine, BUN, sodium, potassium, ALT, AST, LDH, fibrinogen, D-dimers, ferritin, PCR will be collected at screening, day 7 and day 29;
c) IgA, IgG, IgM and neutralizing antibodies;
d) Genotypic sequencing will be performed at failure and at day 29 if SARS-Cov2 on nasopharyngeal swab is still detectable. Nasopharyngeal swab will be stored for genotypic sequencing in failed patient to explore treatment-emergent variant
e) Any AE/SAE that occurs between the times a study participant signs the informed consent form and the time s/he departs the study at the end of the final follow-up visit (or at the time of early discontinuation of the subject from the study for any reason) will be captured and recorded;
f) Concomitant medications will be captured and recorded from screening to the final visit (or at the time of early discontinuation of the subject from the study for any reason)
g) Completed daily from Day1 trough Day 29. The first day of diary completion should occur prior to the dose of study intervention. From day 29 to day 90 the diary must be filled in once a week
h) In a subgroup of (20) patients (Immunologic Substudy)
i) In a subgroup of patient (pharmacologic sub-study)

7 IMMUNOLOGIC SUBSTUDY IMMUNE-MONET

7.1 .Background and hypothesis

In the context of SARS-CoV-2 infection, the crucial role played by the immune response, both innate and adaptive, in the etiopathogenesis of the disease is well established. Multiple anomalies have been identified, especially in the initial stages of COVID-19, and among these are recognized an important decrease in circulating lymphocytes, the appearance in the peripheral blood of monocytes with morphological and phenotypic irregularities and the prevalence in the peripheral circulation of plasmablasts directed against SARS-CoV-2. The extent of the induced immunological alterations is so significant that group of characteristics (immunotypes) have been described, capable of predicting the outcome of COVID-19 patients.

The hypothesis of our study is that the early administration of monoclonal antibodies directed against SARS-CoV-2 does not exert its action only by binding to the virus and supporting its elimination from the body, but also by preventing the establishment of the immunological alterations described, preventing the ominous evolution of COVID-19. Furthermore, we expect a peculiar orientation of T cell receptors (TCR) and B cell receptors (BCR) directed against specific SARS-CoV-2 epitopes.

7.2 Setting

For each arm of the study (Sotrovimab 500 mg [Arm A] vs casirivimab 1200 mg and imdevimab 1200 mg [Arm B] vs SOC [Arm C]), **20 patients** will be enrolled for the immunological sub-study called **Immune-Monet**. Each enrolled subject will provide blood samples for the study of serum and peripheral blood mononuclear cells (PBMCs) at enrollment and at days 7, 14 and 28, quantifiable in 1 serum tube and 6 EDTA tubes.

7.3 Primary endpoint

- Quantification of lymphocytes (total and subpopulations) circulating in peripheral blood at the various study timepoints.

7.4 Secondary endpoints

- Quantification (total and subpopulations), morphological and phenotypic description of the monocytes circulating in the peripheral blood at the various study timepoints;
- Quantification of the following cytokines: CCL3 / MIP-1α, CXCL10 / IP-10, IL-1α, IL-1β, IL-2, IL-6, IL-7, IL-10, IL-12 p70 and TGF-β , in serum samples at the various study timepoints;
- Transcriptomic analysis of T cell receptors at the various study timepoints;
- Transcriptomic analysis of B cell receptors at the various study timepoints;
- Measurement of the expression of NLRP3 inflammasome, caspase 1,3,4,5 and intracellular pro-inflammatory cytokines (PBMCs).

7.5 Materials

Multiparametric FACS analysis

The analysis involves an extensive immunophenotypic characterization of B and T subpopulations (CD4 + and CD8 +), NK and monocyte/macrophages isolated from the blood of patients with different marker panels capable of identifying specific subpopulations of naïve, memory, with functional effector or regulatory, analysing where possible the specificity for the spike protein and related domains/peptides. For example, the immunophenotypic characterization of B lymphocytes is reported, for which we will analyse: i) the various subclasses intended as transitional (CD20 + CD27- CD38hi IgM + CD24hi) naïve (CD27-IgD +), memory switched (CD27 + IgD-) and not -switched (CD27 + IgD +), plasma cells (CD27 + CD38 + CD138-) and plasma cells (CD20- CD27 + CD38 + CD138 +) with the addition of surface immunoglobulin analysis (IgG, IgA, IgE, IgD, IgM) ; ii) specific subset of B cells defined as regulatory (Breg) identified during viral infections, such as CD19 + CD24 + CD38hi, CD19 + CD24 + CD27 +, CD1d + CD5 + CD21lowCD23low, CD1dhiCD5 +, CD5 + CD43 + CD86 + CD147 +); iii) B cells acting as antigen presenting cells, intended as CD21 − CD86 + CD19 + CD20 +; iv). Definition of the functional states of the different populations of B cells through the expression of molecules involved in signalling, immune-stimulatory or immunosuppressive cytokines, such as those involved in activation (CD69, CD72, FGFR1, SELPLG, CD86), co-stimulation (ICAM3 , TNFRSF13C, CD40, CD72, C3, CD80, CD86, CD27, CD28, ICOS, TNFRSF9, CD40LG), pro-inflammation (TNF, IL12B, IL18, LTA, TNFAIP2, C3, HCK), immunosuppression (IL10, TGFB1), as well as genes associated with the loss of functionality (exhaustion) of B cells (PDCD1, FCRL4, SIGLEC6, CD22).

7.6 Transcriptomic of T and B lymphocytes

The analysis involves the use of bulk transcriptomics (RNAseq, with Illumina NovaSeq platform) and single cell sequencing (scRNASeq) techniques with the Chromium Next GEMSingle Cell V (D) J platform of 10X Genomics) on T lymphocyte populations (CD8 +, CD4 +) and B lymphocyte populations isolated from the blood of enrolled individuals. From the "in bulk" RNAseq it will be possible to define the transcriptional program among the three types of subjects, while transcriptomics at the single cell level will allow the exploration of subpopulations of T and B lymphocytes and the identification of key genes related to the effector function.

These will be accompanied by single cell TCR and BCR analyses to identify clonal lymphocyte subpopulations undergoing expansion specifically induced or expanded following monoclonal antibody therapy. Obtaining the BCR sequences can allow the generation of recombinant monoclonal antibodies specific for protein S, which can be analysed in neutralization assays as indicated above.

7.7 Identification of SARS-CoV-2-specific B and T cells and phenotypic/functional study

The analysis involves the isolation of memory T and B lymphocytes with flow cytometric sorting and their use in functional in vitro assays. In the case of T lymphocytes, in vitro stimulation assays will be performed on CD4 + and CD8 + T lymphocytes using peptide libraries consisting of peptides of 8-9 amino acids partially overlapping and covering the entire sequence of the spike protein, to generate polyclonal lines. or clonal specific antigens. This allows us to analyse the relative frequency of specific T lymphocytes for different epitopes of the spike protein. In addition, the lines obtained are used in functional in vitro assays to characterize the effector activity (production of IFN-g, TNF-

a, granulolysin, granzyme, etc.). In the case of B lymphocytes, they are analysed for their ability to produce specific IgG and IgM for the spike protein or its specific domains.

7.8 HLA assessment

Molecular-level typing will be performed for class I HLA-A, B, C loci and high-resolution class II HLA-DR locus by Reverse SSO with commercial kits (LabType SSO XI reverse SSO) after extraction of Genomic DNA from peripheral blood sample.

7.9 Cytokines quantification

Quantitation of the following cytokines will be performed on serum samples: Chemokine (CC motif) ligand 3 / macrophage inflammatory protein 1-α (CCL3 / MIP-1α), CXC motif chemokine ligand 10 / Interferon gamma-induced protein 10 (CXCL10 / IP -10), IL-1α, IL-1β, IL-2, IL-6, interleukin 7 (IL-7), IL-10, IL-12 p70 and transforming growth factor β (TGF-β). The Luminex platform with custom plate will be used.

7.10 Inflammasome assessment

The analyses will be performed both in basal and stimulated conditions. The mRNA will be extracted from 1 × 106 PBMCs using the guanidinium thiocyanate-phenol-chloroform acid method, dissolved in RNase-free water and purified from genomic DNA with RNase-free DNAse (New England BioLabs, Ipswich, MA, USA). One microgram of RNA will be reverse transcribed in a first strand of cDNA in a final volume of 20 µl containing 1 µM of random hexanucleotide primers, 1 µM of oligo (dT) and 200 U of Moloney murine leukaemia virus reverse transcriptase (Promega , Madison, WI, USA). Inflammasome signalling pathways will be analysed by a PCR array comprising a set of 84 optimized real-time PCR primer assays on 96-well plates (SABiosciences Corporation, Frederick, MD, USA) according to manufacturer's instructions.
For Real-Time PCR experiments (96 CFX Connect Bio-Rad), reactions will be performed using a SYBR Green PCR mix (iTaq ™ Universal SYBR Green Supermix, Bio-Rad). GAPDH and β-Actin will be used as housekeeping genes and the average Ct of these two genes will be used as housekeeping gene. For the detection of NLRP3, Caspase-1, Caspase-3, Caspase-4, Caspase-5 and γ-interferon-inducible protein 16 (IFI16) already optimized primers will be used (PrimePCR, Bio-Rad, Segrate, Italy). Caspase-1 will be measured with the Quantikine ELISA Kit (R&D Systems; Minneapolis, MN, USA) according to the manufacturer.

8 PHARMACOLOGIC SUB-STUDY (PK of COVID-19 Mab,N=150 participants)

MAb in serum or plasma will be measured using a validated, fit for purpose Liquid Chromatography-Mass/ Mass Spectrophotometry (LC-MS/MS) method with a lower limit of quantification of 10 to 25 mg/L. The LC-MS/MS method will be based on the analysis of a unique peptide generated by enzymatic digestion of each monoclonal antibody, so as to allow for each monoclonal antibody to be individually quantitated from the human or plasma serum samples collected during the study.

The same serum or plasma samples will be eventually verified and quantified with immune-enzymatic commercial assays available for detection of mAb (as example with EILSA or SIMOA instruments).
The sampling for pharmacokinetics will take place at each useful timing (es. at each visit) to better define the pharmacokinetic profile of each monoclonal drug.
Blood collection must be carried out with one 7 mL tube (purple cap; EDTA) and one 7 mL tube (red cap for serum). From each tube it will be necessary to collect at least 4 aliquots of 500 microliters of plasma or serum, avoiding working on frozen/thawed sample, to be stored at -80°C until use.

9 ETHICS/PROTECTION OF HUMAN SUBJECTS, QUALITY ASSURANCE AND MONITORING

9.1 ICH guidance E6: Good Clinical Practice: consolidated guideline/Declaration of Helsinki

The study will be conducted with the approval of the Ethics Committee, after verification of compliance with the European Union Clinical Practice Standards and in accordance with ICH Good Clinical Practice (GCP) and the ethical principles expressed in Declaration of Helsinki. The clinical study will be performed under the regulations of the National Agency for Drug Development (AIFA) and of the Italian Ministry of Health.

The study will be carried out adhering to local legal requirements and the applicable national law, whichever represents the greater protection for the individual. Study protocol, patient information and informed consent will be submitted to the appropriate Ethical Committee (IRB/IEC) for approval. Will inform the IRB/IEC about any changes in the study protocol which could interfere with the patient's safety.
In order to minimize the risk of adverse events the following strategies will be used:

- **Patient information**. All patients will be provided with oral and written information on the possible adverse events associated with the use of study drugs.
- **Review of eligibility**. Prior to randomization participating unit will fill a checklist in order to allow verification of eligibility criteria.
- **Monitoring**. Laboratory data and clinical symptoms will be checked during treatment. A total of four lab monitoring visits and daily teleconsultation will be performed for each participant.

The protocol, protocol amendments, ICF, IB, and other relevant documents (eg, advertisements) must be submitted to an IRB/IEC by the investigator and reviewed and approved by the IRB/IEC before the study is initiated.
Any amendments to the protocol will require IRB/IEC and applicable Regulatory Authority approval before implementation of changes made to the study design, except for changes necessary to eliminate an immediate hazard to study participants.

9.2 Study conduct and monitoring

The management of the study was committed to CRO.
CRO reviews clinical data for accuracy, completeness, and consistency. Data are verified versus source documentation according to standard operating procedures. If potential fraud, scientific/research misconduct, privacy incidents/breaches or Clinical Trial-related Significant

Quality Issues are reported, such matters are investigated. When necessary, appropriate corrective and/or preventative actions are defined and regulatory authorities and/or ethics review committees are notified.

9.3 Data Protection

The study will conduct in compliance with all applicable data protection regulations.
Participants will be assigned a unique identifier. Any participant records or datasets that are transferred to the Investigators will contain the identifier only; participant names or any information that would make the participant identifiable will not be transferred.
The participant must be informed that his/her personal study-related data will be used by the Investigators in accordance with local data protection law. The level of disclosure must also be explained to the participant. The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorized personnel appointed by the Promoter, by appropriate IRB/IEC members, and by inspectors from regulatory authorities.
This study will use an Electronic Data Capture (EDC) system. The designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms (eCRF). Investigator site staff will not be given access to the EDC system until they have been trained. Automatic validation programs check for data discrepancies in the eCRFs allow modification or verification of the entered data by the investigator staff. The Principal Investigator is responsible for assuring that the data entered into eCRF is complete, accurate, and that entry and updates are performed in a timely manner.

9.4 Participant confidentiality

All subject related information including Case Report Forms, laboratory specimens, evaluation forms, reports, etc. will be kept strictly confidential. Subjects will be identified only by means of a coded number specific to each subject. All computerized databases will identify subjects by numeric codes only, and will be password protected.
Upon request, subject records will be made available to the study audit, monitoring groups representative of the study promoter, representatives of regulatory agencies (AIFA).

9.5 Data monitoring committee (IDMC)

An external Data Monitoring Committee (IDMC) includes independent experts that do not have direct involvement in the conduct of the study. The IDMC will review the progress of the study and perform interim reviews of efficacy and safety data and protect ethical interests and to ensure the safety of participants and the validity and integrity of study data.
The IDMC will be made of 2 to 4 members, selected among trialists experts in Infectious disease, statisticians, hospital pharmacist and expert in Resuscitation. No member of the IDMC have direct involvement in the design or conducting of the study.
The IDMC should conclude each review with their recommendations as to whether the study should continue without change, be modified, or be terminated.

10 ASSESSMENT OF SAFETY AND PHARMACOVIGILANCE

10.1 Safety monitoring

Article 16 of Directive 2001/20/EC reads as follows: The investigator shall report all serious adverse events immediately to the promoter except for those that the protocol or investigator's brochure identifies as not requiring immediate reporting. The immediate report shall be followed by detailed, written reports. The immediate and follow-up reports shall identify subjects by unique code numbers assigned to the latter. The purpose of this obligation is to ensure that the sponsor has the necessary information to continuously assess the benefit-risk balance of the clinical trial, in accordance with Article 3(a) of Directive 2001/20/EC.

The investigator is responsible for reporting and documenting events falling within the protocol definitions of AEs or SAEs. During the treatment period (when safety must be evaluated), the investigator or designated sub-investigator shall be responsible for reporting AEs and SAEs as described in this section of the protocol. In order to satisfy international safety requirements, the investigator must include in his/her evaluation every SAE caused by participation in the study (e.g. any complications arising from blood sampling).

10.2 Definition of adverse events (AE's) and serious adverse events (SAE's)

10.2.1 Adverse Events

An 'adverse event' is defined in Article 2 (m) of Directive 2001/20/EC as follows: 'Any untoward medical occurrence in a patient or clinical trial subject administered a medicinal product and which does not necessarily have a causal relationship with this treatment'. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product

An "adverse event" is any worsening in the general condition of a subject, or a subject participating in a clinical experiment to whom a pharmaceutical product is administered, regardless of its relationship with the given treatment. An AE may also be any unexpected adverse sign (which can include an abnormal laboratory result of clinical significance), and each symptom or pathology temporarily associated with the use of a pharmaceutical product, regardless of its relationship with the same product. AEs may be **expected** (consistent with the information leaflet provided with the product) or **unexpected** (inconsistent with the information available).

<u>Adverse events include:</u>

- The exacerbation of a pre-existing pathology;
- An increase in the frequency or intensity of an episodic event or pre-existing condition;
- A condition occurring or diagnosed after the administration of the study drug, even if current before the start of the study;
- Persistent diseases/symptoms at the baseline visit that worsen after the start of the study.

Adverse events do NOT include:

- Medical or surgical procedures (e.g. surgery, endoscopy, tooth extraction, transfusions), but the condition requiring the procedure is an adverse event
- Diseases or conditions present at the beginning of the study that have not worsened but remained stable during the course of the study.
- Situations in which no unexpected adverse event has occurred (e.g. hospital admission for elective cosmetic surgery/social problems).
- An overdose of antiviral agents or concomitant drugs without onset of symptoms or associated signs.
- Laboratory abnormalities deemed by the investigator to be of no clinical significance.

Grade 1 and Grade 2 events are not considered adverse events, but details of these events must be documented in detail in the subject's study files.

Stable chronic conditions which are present prior to clinical trial entry and do not worsen are not considered adverse events and will be accounted for in the subject's medical history.

10.2.2 Serious Adverse Events (SAE's)

A 'serious adverse event' is defined in Article 2(o) of Directive 2001/20/EC as follows: 'Any untoward medical occurrence or effect that at any dose results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalizations, results in persistent or significant disability or incapacity, or is a congenital anomaly or birth defect'. These characteristics/consequences have to be considered at the time of the event. For example, regarding a life- threatening event, this refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe. Some medical events may jeopardize the subject or may require an intervention to prevent one of the above characteristics/consequences. Such events (hereinafter referred to as 'important medical events') should also be considered as 'serious' in accordance with the definition. Medical and scientific judgement should be exercised in deciding whether an event is 'serious' in accordance with these criteria

A Serious Adverse Event is defined as an SAE meeting one of the following:

- Death during the period of protocol-defined surveillance
- Life Threatening Event (defined as a participant at immediate risk of death at the time of the event)
- In-patient hospitalization or prolongation of existing hospitalization during the period of protocol-defined surveillance
- Results in congenital anomaly or birth defect
- Results in a persistent or significant disability/incapacity

Any other important medical event that may not result in one of the above outcomes, may be considered a serious adverse experience when, based upon appropriate medical judgment, the event may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed above.

10.2.3 AE/SAE relationship assignment

For all collected AE's/SAE's, the clinician who examines and evaluates the subject will determine the adverse event's causality based on temporal relationship and his/her clinical judgment. The degree of certainty about causality will be graded using the categories below:

- Definitely Related: There is clear evidence to suggest a causal relationship, and other possible contributing factors can be ruled out. The clinical event, including an abnormal laboratory test result, occurs in a plausible time relationship to drug administration and cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (de-challenge) should be clinically plausible. The event must be pharmacologically or phenomenologically definitive, with use of a satisfactory rechallenge procedure if necessary.
- Probably Related: There is evidence to suggest a causal relationship, and the influence of other factors is unlikely. The clinical event, including an abnormal laboratory test result, occurs within a reasonable time sequence to administration of the drug, is unlikely to be attributed to concurrent disease or other drugs or chemicals, and follows a clinically reasonable response on withdrawal (de-challenge). Re-challenge information is not required to fulfill this definition.
- Possibly Related: There is some evidence to suggest a causal relationship (e.g., the event occurred within a reasonable time after administration of the trial medication). However, the influence of other factors may have contributed to the event (e.g., the subject's clinical condition, other concomitant events). Although an adverse drug event may rate only as "possibly related" soon after discovery, it can be flagged as requiring more information and later be upgraded to "probably related" or "definitely related", as appropriate.
- Unlikely: A clinical event, including an abnormal laboratory test result, whose temporal relationship to drug administration makes a causal relationship improbable (e.g., the event did not occur within a reasonable time after administration of the trial medication) and in which other drugs or chemicals or underlying disease provides plausible explanations (e.g., the subject's clinical condition, other concomitant treatments).
- Not related: The AE is completely independent of study drug administration, and/or evidence exists that the event is definitely related to another etiology. There must be an alternative, definitive etiology documented by the clinician.

10.2.4 SAE reporting procedures

Following the subject's written consent to participate in the study, all SAEs will be collected, including those thought to be associated with protocol-specified procedures. The information to be reported for each SAE is: the date of event occurrence, the date of event resolution, a brief description of the event, concomitant therapy, lab test reports, maximum intensity of the event or correlation with the agent. If there is any change in the information over time, an updated SAE report must be sent. All adverse reactions simultaneously defined as serious and unexpected must be reported by the investigator to the study sponsor as soon as possible.

The investigator will report all SAE to Eudravigilance through the specific form, to Ethical Committees, and to the manufacturer, within the timelines of the article 17 of the European Directive 2001/20/EC. All SAEs must be reported within 24 hours by confirmed facsimile

transmission and mailing of the completed SAE page (top, white, original) to the attention of Prof Annalisa Capuano (QPPV at the AOU Università degli studi della Campania "Luigi Vanvitelli" and owned by the patent for the use of the European Electronic Database Eudravigilance" for the electronic upload of Individual Case Safety Reports (ICSRs). All SAEs must be reported within 24 hours by confirmed facsimile transmission and mailing of the completed SAE page (top, white, original) and owned by the patent for the use of the European Electronic Database Eudravigilance" for the electronic upload of Individual Case Safety Reports (ICSRs)

The investigator will provide an annual Development Safety Update Report, including all Serious Adverse Events occurring in the Study, to the Regulatory Agency, and to the Ethical Committee as per local requirements.
Notification deadlines:

- if, in addition to being serious and unexpected, a SAE is also fatal or life-threatening, a preliminary SAE report must be completed as soon as possible and, in any case, within 24 hours after being informed about the event. If only limited information is initially available, follow-up reports are required. In selected circumstances, the protocol may specify conditions that require additional reporting. All SAEs should be followed to resolution or stabilization.
- For all other serious and unexpected adverse events, the investigator must complete a SAE report as soon as possible after the manifestation of the event and, in any case, no later than 15 days after becoming aware of the event.

10.2.5 Monitoring of AE'S/SAE'S

Any AE/SAE that occurs between the times a study participant signs the informed consent form and the time s/he departs the study at the end of the final follow-up visit (or at the time of early discontinuation of the subject from the study for any reason) will be captured and recorded. At each contact with the subject, the investigator (or designate) must seek information on adverse events by specific questioning and, as appropriate, by examination.
All AEs and SAEs must be followed up:

- until their complete resolution
- until their stabilization
- until the event can be attributed a new etiology
- until the patient ceases to be in the care of the Centre

The investigator must ensure that the follow-up reports include all supplementary information allowing a complete evaluation of the nature and/or the cause-effect relationship of the AE or SAE, including further laboratory and other tests, pathology reports, and any specialist examinations.

10.2.6 Suspected unexpected serious adverse reactions (SUSARs)

The investigator shall ensure that all relevant information about suspected serious unexpected adverse reactions that are fatal or life-threatening is recorded and reported as soon as possible to the Database Eudravigilance, and to the Ethics Committee, and in any case no later than seven days

after knowledge by the sponsor of such a case, and that relevant follow-up information is subsequently communicated within an additional eight days.

All other suspected serious unexpected adverse reactions shall be reported to the database Eudravigilance concerned and to the Ethics Committee concerned as soon as possible but within a maximum of 15 days of first knowledge by the coordinator center. The coordinator center should also inform all investigators.

Adverse reaction — causality An adverse reaction' is defined in Article 2(n) of Directive 2001/20/EC as follows: 'all untoward and unintended responses to an investigational medicinal product related to any dose administered'. The definition covers also medication errors and uses outside what is foreseen in the protocol, including misuse and abuse of the product. The definition implies a reasonable possibility of a causal relationship between the event and the IMP. This means that there are facts (evidence) or arguments to suggest a causal relationship.

Unexpected' adverse reaction - Definition: Article 2(p) of Directive 2001/20/EC defines 'unexpected adverse reaction' as follows: 'an adverse reaction, the nature or severity of which is not consistent with the applicable product information (e.g. investigator's brochure for an unauthorised investigational product or summary of product characteristics for an authorised product)'.

The term 'severity' is used here to describe the intensity of a specific event. This has to be distinguished from the term 'serious'. Reports which add significant information on the specificity, increase of occurrence, or severity of a known, already documented serious adverse reaction constitute unexpected events.

10.2.7 Events that Require Expedited Reporting to Sponsor

The following events require reporting to the Sponsor (or designee) within 24 hours of learning of the event:

- Treatment-emergent SAEs.
- AESI (serious and nonserious): AESI for this study are:
  - Grade ≥2 infusion-related reactions
  - Grade ≥2 hypersensitivity reactions
- Pregnancy: Although pregnancy is not considered an adverse event, it is the responsibility of the investigator to report to the Sponsor (or designee), within 24 hours of identification, any pregnancy occurring in a female study patient or female partner of a male study patient for up to 6 months after the last dose of study drug. Any complication of pregnancy affecting a female study patient or female partner of a male study patient, and/or fetus and/or newborn that meets the SAE criteria must be reportedas an SAE. Outcome for all pregnancies should be reported to the Sponsor.

10.2.8 Adverse Events of Special Interest (AESIs)

An AESI (serious or non-serious) is one of scientific and medical interest specific to the Sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the Sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it.

Definitions

- Infusion-related reactions are defined as any relevant adverse events that occurs during the infusion or **up to day 4**.
- Hypersensitivity reactions are defined as any relevant adverse event that occurs during the infusion or **up to study day 29**.

11 FEASIBILITY AND TECHNICAL ASPECTS

Study intervention and the participant-reported symptom diary will be dispensed to the participants, according to the study protocol, either by:

- Hospital-based outpatient clinics in a dedicated area of hospitals for COVID-19 positive patients;
- Territorial outpatient clinics with prepared ambulatory setting by general practitioners (GP) or territorial health agencies (ASL)
- At home visit by GP o USCAR, if admitted by AIFA indications and regional organization

Currently AIFA approved only MoAbs administration in an intra-hospital setting, so all the trial procedures, including drug administration and follow-up management will be performed according with AIFA statements and regulatory dispositions, and by organization at regional level.

In order to expanding administration setting and to create an unprecedented network between healthcare professionals intra- and extra-hospital, the study provides for the possibility of organizing MoAbs infusion in territorial clinics or at patient's home, proceeding to the modulation of the components available at various levels (intra- and extra-hospital), which may vary from center to center but should not affect the participation of the individual center in the study (possibly affecting only the volume of patients enrolled).

To this end SIMIT and other scientific societies could be involved in the study. In particular, the Italian Society of General Medicine and Primary Care (SIMG), which coordinates a network of general practitioners (GPs) who would enroll the patient by telephone, verifying eligibility, and would refer him/her to the relevant infectious disease center and follow up.

The advantage of such collaboration is the capillary diffusion of this network in the territory of different region and the consequent increase of potential caseload.
In addition, territorial health agencies have proven importance for the early treatment of the disease itself and for the prevention of complications, as well as for the reduction of the burden of care on acute hospital facilities. The possibility of early administration of a specific therapy represents an opportunity of fundamental importance in the management of non-hospitalized patients and implies the use of a territorial network that can identify COVID patients at the onset of the first symptoms of disease or in any case in the first hours of laboratory diagnosis.

The logic behind the study, also from the methodological point of view, is of the type "test and

treat", in order to ensure the treatment of all potentially eligible patients directly at the point of care (POC) and with immediate effect, keeping the possibility of collection of the biological samples necessary for subsequent analysis and stratification of the case.

11.1 Screening and deferred enrollment

To meet the criterion of testing and treating simultaneously in all cases where it is technically feasible, screening, enrollment, randomization, administration of therapy, and observation of immediate side effects must occur on the same day, in the care setting in which the patient is first observed. The only exception to this scheme, is given by the possibility to screen the patient by telephone by the GP afferent to the SIMG research network, on the occasion of the telephone intake, usually when the patient is still at home; in this case it is allowed the immediate enrollment and sending, in safe conditions, to the first administration center usable in that context, for the follow-up of competence. Enrolled patients will be sent to the reference center closest to the patient's home.

11.2 Screening, enrollment, randomization, administration and contextual observation

The administration of the drug in territorial POCs (post-acute COVID facilities and territorial residential facilities) can be managed by a specific team (territorial team), which will be responsible for the safe administration of the drug and carry out the observation period.
In the case of administration at a territorial residential facility, the team responsible for the infusion will alert the 118 Operations Center in charge of the territory of the start of administration and will communicate the end of the infusion and the end of the observation period.
In the context of territorial care, the establishment of specific teams for the administration of therapy at a territorial residential facility can be provided, especially in cases where there is an active outbreak of infection by SarsCoV2; alternatively, a similar functional unit of infectious disease can be contacted, if available within a reasonable radius of action.
The following procedures should be performed at the referral center for administration:

- collection of demographic characteristics;
- collection of remote, proximate and pharmacological pathological history;
- execution of the objective examination and verification of vital parameters (blood pressure, heart rate, respiratory rate, temperature);
- performance of laboratory tests (as required by the study protocol, including pregnancy test for women of childbearing age);
- performance of serological test for SarsCoV2;
- performance of nasopharyngeal molecular swab for PCR and genotypic sequencing.

11.3 Follow up

The follow up activities will be carried out at the center of administration of therapy in collaboration with the General Practitioner of the patient and the GP belonging to the research network SIMG who made the enrollment. In case of administration at a residential facility, the follow up will be

carried out by the team that provided the administration in collaboration with the patient's General Practitioner and the GP belonging to the research network SIMG who carried out the enrollment.

The following table summarizes the professional figures involved for each phase and for each POC:

CARE SETTING IN WHICH THE PATIENT IS FIRSTLY EVALUATED	**PROFESSIONALS / OPERATIONAL STRUCTURES INVOLVED BASED ON POINT OF CARE (POC) AND STUDY ASSESMENT**		
	SCREENING, ENROLLMENT	**RANDOMIZATION, ADMINISTRATION AND OBSERVATION**	**FOLLOW-UP**
hospital POC with Infectious Diseases Department	Infectious disease specialist, ER doctor	Infectious Diseases Department, Emergency room	Infectious Diseases Department or GP of the patient and/or GP from the SIMG network who enrolled the patient
hospital POC in a territorial network without Infectious Diseases Department	SIMG Network GP, ER doctor	Personal of COVID-19 Department or equivalent, reference to Infectious Diseases Department	Personal of COVID-19 Department or equivalent or Infectious Diseases Department (after contact) / GP of the patient and/or GP from the SIMG network who enrolled the patient
Territorial POC at dedicated post-acute COVID-19 department	SIMG network GP, USCA doctors	Staff of the post-acute COVID-19 Department, reference to Infectious Diseases Department	Staff of the post-acute COVID-19 department / GP of the patient and/or GP from the SIMG network who enrolled the patient
Residential territorial POC	SIMG network GP, USCA doctors	Territorial team or dedicated infectious disease team	Territorial team / GP of the patient and/or GP from the SIMG network who enrolled the patient

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Appendix A: WHO Clinical Progression Scale for COVID-19

Patient State	Descriptor	Score
Uninfected	Uninfected; no viral RNA detected	0
Ambulatory mild disease	Asymptomatic; viral RNA detected	1
	Symptomatic; independent	2
	Symptomatic; assistance needed	3
Hospitalised: moderate disease	Hospitalised; no oxygen therapy*	4
	Hospitalised; oxygen by mask or nasal prongs	5
Hospitalised: severe diseases	Hospitalised; oxygen by NIV or high flow	6
	Intubation and mechanical ventilation, pO_2/FiO_2 ≥150 or SpO_2/FiO_2 ≥200	7
	Mechanical ventilation pO_2/FIO_2 <150 (SpO_2/FiO_2 <200) or vasopressors	8
	Mechanical ventilation pO_2/FiO_2 <150 and vasopressors, dialysis, or ECMO	9
Dead	Dead	10

*If hospitalized for isolation only, record status as for ambulatory patient.

ECMO Extracorporeal membrane oxygenation; FiO2 Fraction of inspired oxygen; NIV Non-invasive ventilation;

pO2 Partial pressure of oxygen; SpO2 Oxygen saturation.

Source: WHO Working Group 2020

Appendix B: participant-reported symptom diary

Braccio	Protocollo	Giorno	Screening N. (*Centro – Sequenza N.*)	Randomizzazione N.

DIARIO DEI SINTOMI

QUESTA SEZIONE È SOLO PER USO DA PARTE DEL PERSONALE DELLO STUDIO.

Specificare la data di compilazione: _____

GG-mmm-AAAA

Solo i/le partecipanti devono inserire informazioni in questo diario.

La preghiamo di compilare il diario all'incirca alla stessa ora **ogni giorno**. Per ciascun sintomo, considerare **solo** le ultime **24 ore**.

1. La preghiamo di classificare ciascun sintomo tenendo conto del grado peggiore manifestato nelle ultime 24 ore:

a. Tosse	☐ Nessun sintomo	☐ Lieve	☐ Moderata	☐ Grave
b. Mal di gola	☐ Nessun sintomo	☐ Lieve	☐ Moderato	☐ Grave
c. Congestione nasale (naso chiuso)	☐ Nessun sintomo	☐ Lieve	☐ Moderata	☐ Grave
d. Rinorrea (naso che cola)	☐ Nessun sintomo	☐ Lieve	☐ Moderata	☐ Grave
e. Respiro affannoso o difficoltà a respirare	☐ Nessun sintomo	☐ Lieve	☐ Moderato	☐ Grave
f. Dolori muscolari o al resto del corpo	☐ Nessun sintomo	☐ Lieve	☐ Moderati	☐ Gravi
g. Affaticamento (stanchezza)	☐ Nessun sintomo	☐ Lieve	☐ Moderato	☐ Grave
h. Sensazione di calore o febbre	☐ Nessun sintomo	☐ Lieve	☐ Moderata	☐ Grave
i. Brividi	☐ Nessun sintomo	☐ Lieve	☐ Moderati	☐ Gravi
j. Mal di testa	☐ Nessun sintomo	☐ Lieve	☐ Moderato	☐ Grave
k. Nausea	☐ Nessun sintomo	☐ Lieve	☐ Moderata	☐ Grave
l. Vomito	☐ Nessun sintomo	☐ Lieve	☐ Moderato	☐ Grave
m. Diarrea	☐ Nessun sintomo	☐ Lieve	☐ Moderata	☐ Grave

2. Nel corso delle ultime 24 ore, Le è capitato di:

a) Perdere il senso dell'olfatto? ☐ No ☐ Si

b) Perdere il senso del gusto? ☐ No ☐ Si

Dichiaro che le presenti informazioni sono accurate.	Iniziali del/la partecipante	Data:
Ho esaminato le presenti informazioni	Iniziali del personale	Data: