**PROPOSTA STUDIO EFFICACIA ANTICORPI MONOCLONALI IN COVID-19**

| **SEZIONE AMMINISTRATIVA** |
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| **IDENTIFICAZIONE DELLA SPERIMENTAZIONE CLINICA** |
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| **STUDY TITLE**<br>A phase 3, multicentre, single-blinded, randomized controlled study to compare the efficacy and safety of Casirivimab and Imdevimab or Bamlanivimab and Etesevimab or Sotrovimab in COVID-19 home patients at high risk of hospitalization.<br><br>**SHORT TITLE**<br>Monoclonal Antibodies In COVID-19: MAI COVID-19 |
| **SPONSOR**<br>Azienda Ospedaliero-Universitaria di Modena<br>Via del Pozzo 71, 41124 Modena |
| **COORDINATING CENTRE**<br>Azienda Unità Sanitaria Locale (AUSL) di Modena<br>Via San Giovanni del Cantone 23 – 41121 Modena – Italy |
| **PARTICIPANT CENTRES**<br>▪ AUSL Modena, including 12 *Unità Speciali di Continuità Assistenziale* (USCA)<br>▪ AUSL Reggio Emilia, including 29 USCA<br>▪ AUSL Piacenza, including 6 USCA<br>▪ AUSL Parma, including 7 USCA<br>As the USCA organization spreads over the whole Emilia-Romagna Region, if necessary, this project could involve the other 27 USCA operating on the territory. |

**SYNOPSIS**

**Study design**

This is a phase 3, multicentre, single-blinded, randomized controlled study aimed at comparing the efficacy and safety of Casirivimab and Imdevimab or Bamlanivimab and Etesevimab or Sotrovimab in COVID-19 home patients at high risk of hospitalization.

Patients who meet all inclusion criteria and have no exclusion criteria and have signed written informed consent will be randomly assigned to one of the three arms in a ratio 1:1:1.

**Study population**

This study will enrol mild to moderate COVID-19 adult home patients at high risk for progressing to severe COVID-19 and/or hospitalisation.

**Inclusion Criteria (all required)**

1. Positive SARS-CoV-2 diagnostic (on pharyngeal swab of deep airways material) for all variants, except for beta and gamma. Positive patients will be considered eligible even when the information on variants is not timely available because of technical or organizational issues.
2. Age ≥18 years of age at the time of randomization
3. Are not hospitalized at the time of randomization
4. Have one or more mild or moderate COVID-19 symptoms according to NIH classification, which onset within <10 days:
    - Fever (>37.5 °C)
    - Cough
    - Sore throat
    - Malaise
    - Headache
    - Muscle pain
    - Gastrointestinal symptoms
    - Shortness of breath with exertion
5. Meet at least one of the following criteria, which define patients at high risk for progressing to severe COVID-19 and/or hospitalization:
    - Body Mass Index (BMI) ≥30
    - Chronic kidney disease
    - Diabetes
    - Primary or secondary Immunodeficiency
    - ≥55 years of age and at least of the following criteria:
        - cardiovascular disease, OR
        - hypertension, OR
        - chronic obstructive pulmonary disease/other chronic respiratory disease.
    - ≥65 years of age
6. Signed informed consent

**EXCLUSION CRITERIA**

Participants are excluded from the study if any of the following criteria apply:

**Medical Conditions**

1. Positive SARS-CoV-2 diagnostic (on pharyngeal swab of deep airways material) for variants beta and gamma
2. Have severe COVID-19 requiring hospital admission or access to the emergency room. Severe COVID-19 is defined as one of the following clinical features: SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300, respiratory rate ≥30 per minute, heart rate ≥125 per minute
3. Require oxygen therapy due to COVID-19, or require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.
4. Require mechanical ventilation or anticipated impending need for mechanical ventilation
5. Have received any dose of vaccine antiSARS-CoV-2 within < 15 days
6. Have known allergies to any of the components used in the formulation of the interventions
7. Have hemodynamic instability requiring use of pressors within 24 hours of randomization
8. Have suspected or proven serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking intervention
9. Have any co-morbidity requiring surgery within <7 days, or that is considered life-threatening within 29 days
10. Have any serious concomitant systemic disease, condition or disorder that, in the opinion of the investigator, should preclude participation in this study
11. Are pregnant or breast feeding

**Other Exclusion Criteria**

12. Have received an investigational intervention for SARS-CoV-2 prophylaxis in the last 30 days
13. Have received treatment with a SARS-CoV-2 specific monoclonal antibody in the last 30 days
14. Have a history of convalescent COVID-19 plasma treatment in the last 30 days
15. Have participated, within the last 30 days, in a clinical study involving an investigational intervention. If the previous investigational intervention has a long half-life, 5 half-lives or 30 days, whichever is longer, should have passed.
16. Are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
17. Withdrawn or refusal of the informed consent.
18. Are investigator site personnel, which are directly affiliated with this study.

**INTERVENTIONS**

All patients, in addition to the standard of care, will receive in a single-blind manner one of the following interventions.

**Intervention Group 1 (Casirivimab and Imdevimab)**

Patients in this group will be given Casirivimab and Imdevimab at a dose of 1,200 mg each, administered together as a single intravenous (IV) within 10 days of symptom onset. Casirivimab and Imdevimab will be diluted in a final volume of 250 mL, which will be administered as a single IV infusion bag over 60 minutes.

**Intervention Group 2 (Bamlanivimab and Etesevimab)**

Patients in this group will be given Bamlanivimab at a dose of 700 mg and Etesevimab at a dose of 1.200 mg administered together as a single IV within 10 days of symptom onset. Bamlanivimab and Etesevimab will be diluted in a final volume of 250 mL, which will be administered as a single IV infusion bag over 60 minutes.

**Intervention Group 3 (Sotrovimab)** Patients in this group will be given Sotrovimab at a dose of 500 mg as a single IV within 10 days of symptom onset. Sotrovimab will be diluted in a final volume of 100 mL, which will be administered as a single IV infusion bag over 30 minutes.

**AIMS**

Aim of this study is to compare efficacy and safety of Casirivimab and Imdevimab or Bamlanivimab and Etesevimab or Sotrovimab in mild to moderate COVID-19 home patients.

**END-POINTS**

**Primary Efficacy Endpoint**

Clinical worsening, defined as the progression of the disease to a more severe state, such as hospitalization or death, whichever comes first, through day 29. The follow up will start the day in which the treatment is administered.

**Primary Safety Endpoint**

Early safety, defined as the occurrence of any adverse event within 24 hours from the beginning of treatment administration, such as any symptoms that can be related to drug hypersensitivity, which include: anaphylaxis, fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash (including urticaria), pruritus, myalgia, dizziness or any other symptom, according to the clinical judgment of the attending physician.

**Secondary Efficacy Endpoint**

The occurrence of:

a) death, defined as all-cause mortality;
b) any hospital admission;
c) any access to the emergency department,

up to 6 weeks from the beginning of treatment administration.

**Secondary Safety Endpoint**

Late safety, defined as the occurrence of any adverse event occurring after 24 hours and through day 29 from the beginning of the intervention.

**Ancillary Studies**

Ancillary studies will seek to assess the performance of the main validated scores usually used in clinical practice to evaluate the risk of hospitalization in COVID-19 home patients.

**Planned study duration**

We expect that the study will take approximately 12 months**,** as detailed below

**Enrollment period:** we expect that the enrollment will be completed over a period of approximately 9 months.

**Treatment period:** the treatment period includes about one hour of infusion and one hour of observation.

**Follow-up period:** each patient will be followed up through 6 weeks after the drug infusion.

**Data analysis and Final Study Report:** the data analysis and the quality check will take three weeks, whereas the study report writing will take three more weeks.

**Sample size and statistical analysis**

Considering the number of centers involved in the study and the current COVID-19 region situation, we foresee to enroll about 552 patients over a period of approximately 9 months.

This sample size will allow us to detect a statistically significant relative reduction (alpha=0.025 and beta=0.20) of at least 80% of the proportion of patients who experience clinical worsening across the interventions. Hypothesizing a proportion of clinical worsening of 10% in any arms, such reduction will result in a proportion of clinical worsening of 2% in any other arm, which corresponds to an absolute risk reduction of 8%.

**Ad interim analysis**

Considering the statistical approach, an interim analysis will be conducted after the randomization of 276 patients, which roughly correspond to 50% of the sample size. This analysis is aimed at assessing whether the results show larger than expected benefit and/or harm on any arms.

O'Brien-Fleming method will be used with an alpha set to 0.025. According to this method, the study will be stopped after enrolling 50% of the patients if the z value is beyond the following boundaries: -3.34 and 3.34.

All AEs which occur during the course of the study will be forwarded to the independent Data Safety Monitoring Board (DSMB).

In case of the occurrence of any SAE, the DSMB will be requested to assess the opportunity to continue/interrupt the study. In the meantime, the enrollment will be suspended until the DSMB decision will be notified to the Steering Committee.

**Statistical Analysis**

All patients enrolled in the study will be entered in the full analysis set independently of their treatment time.

The intention to treat population will be considered for primary analysis.

A descriptive statistical analysis will be carried out to summarize all the relevant variables.

At baseline, categorical data will be summarized by using counts and percentages, whilst continuous variables will be presented using the number of patients, mean, standard deviation, median, minimum, and maximum.

The 3 arms will be compared for the primary outcome in terms of:

- proportion of patients experiencing clinical worsening up to 29 days;
- time to clinical worsening.

The 3 arms will also be compared for the secondary outcomes in terms of proportion of patients experiencing any secondary outcome and time to its occurrence up to 6 weeks.

Clinical worsening, and each single outcome defining it, will be summarized in terms of proportion and compared by using RR as measure of association. Time to the occurrence of these events will also be summarized by using Kaplan-Meier curves and compared between arms by HRs.

All measures of association will be presented with their 95% confidence intervals. A result will be considered as statistically significant if its p-values will be less than 0.05 (5%).

The analyses will be performed by using STATA software.

**Subgroup analysis**

This study is not powered for subgroup analyses; therefore, all subgroup analyses will be treated as exploratory.

Subgroup analyses will be conducted only for the primary endpoint and may include:

- Duration since symptom onset to randomization (< 5 vs ≥ 5 days)
- Vaccination (Yes vs No)
- Baseline BMI (< 30 kg/$m^2$ vs ≥ 30 kg/$m^2$)
- Age (< 65 vs ≥ 65 years old)

**Organizational issues and feasibility**

**Involvement of Primary Care Departments and USCA**

The study will involve, besides the proposing academic Hospital of Modena, the primary care services of the Emilia-Romagna region, in particular Modena, Reggio Emilia, Parma and Piacenza provinces. These neighboring districts are situated in the Northern Italy and have an incident population of about 1.9 million inhabitants.

The primary health care service in this area is provided by the Azienda Unità Sanitaria Locale (AUSL), that through their Primary Care Departments coordinate about 1000 general practitioners (GP), which ensure a widespread network of skilled physicians able to manage COVID-19 patients at home, and to promptly identify those in need of hospital care.

Moreover, in order to better tackle the ongoing pandemic, which seriously impact the healthcare systems, the Emilia-Romagna Region instituted 81 special units of healthcare continuity (Unità Speciali di Continuità Assistenziale, USCA) aimed at supporting GPs in the management of COVID-19 patients at home. Each USCA is an integrated team composed by a physician and a nurse, specially trained in providing care to COVID-19 at home patients and tightly connected with GPs network.

Right now, 54 USCA have been set up in the provinces of Modena, Reggio Emilia, Parma and Piacenza. From the beginning of this service (April 20th) up to their first report published on Region Emilia-Romagna webpage (May, 3rd 2020), these USCA provided more than 1000 patients' phone screening, and home visits, and administered about 1700 home therapies. In addition, the USCA performed more than 100 further procedures, including pharyngeal swab, electrocardiogram and bed-side thoracic echography [13].

**Feasibility**

About 7000 cases of COVID-19 have been reported in Emilia Romagna Region in the last 30 days; among them, one third (about 2310 patients) is considered to have mild to moderate symptoms. Considering the provinces involved in the study, such as Modena, Reggio Emilia, Piacenza and Parma, approximately 1000 patients per month are considered as potentially eligible for the study.

The established network of GPs and USCA represents a suitable setting that can ensure a timely and reliable screening, enrolment and follow-up of at home mild to moderate COVID-19 patients at risk of clinical worsening.

As the USCA organization spreads over the whole Emilia-Romagna Region, if necessary, this project could involve the other USCA operating on the territory.

## STUDY PROTOCOL

### BACKGROUND AND RATIONALE

In December 2019, a cluster of acute respiratory illness caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) occurred in Wuhan, Hubei Province, China. The disease has rapidly spread from Wuhan to many other countries worldwide, rapidly becoming a global health emergency. At the time of January 25, 2021, there have been 97.831.595 confirmed cases of COVID-19, the disease provoked by (SARS-CoV2), including 2.120.877 deaths, as reported by WHO [1].

The spectrum of clinical manifestations of COVID-19 is very wide, ranging from asymptomatic infection to severe pneumonia with acute respiratory distress syndrome (ARDS) and death.

In general, adults with SARS-CoV-2 infection can be grouped into the following severity of illness categories, according to the National Institute for Health's indications:

| Illness severity | Clinical features |
|---|---|
| Asymptomatic or Presymptomatic Infection | Individuals who test positive for SARS-CoV-2 using a virologic test (i.e., a nucleic acid amplification test or an antigen test) but who have no symptoms that are consistent with COVID-19. |
| Mild Illness | Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging. |
| Moderate Illness | Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have saturation of oxygen (SpO2) ≥94% on room air at sea level. |
| Severe Illness | Individuals who have SpO2 <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 mm Hg, respiratory frequency >30 breaths/min, or lung infiltrates >50%. |
| Critical Illness | Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction |

*Modified from:* https://www.covid19treatmentguidelines.nih.gov.

Of note, the same Guidelines report that patients with one or more of the following conditions are at a higher risk of progressing to severe COVID-19:

- being 65 years or older;
- having cardiovascular disease, chronic lung disease, sickle cell disease, diabetes, cancer, obesity, or chronic kidney disease;
- being pregnant;
- being a smoker;
- being a recipient of transplant or immunosuppressive therapy. [2]

Among 72,314 persons with COVID-19 in China, 81% of cases were reported to be mild (defined in this study as no pneumonia or mild pneumonia), 14% were severe (defined as dyspnea, respiratory frequency ≥30 breaths/min, saturation of oxygen [SpO2] ≤93%, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen [PaO2/FiO2] <300 mm Hg, and/or lung infiltrates >50% within 24 to 48 hours), and 5% were critical (defined as respiratory failure, septic shock, and/or multiorgan dysfunction or failure) [3]

Approximately 17% to 35% of hospitalized patients with COVID-19 are treated in ICU, most commonly because of hypoxemic respiratory failure. Among patients in the ICU with COVID-19, 29% to 91% require invasive mechanical ventilation. Overall, in-hospital mortality from COVID-19 is approximately 15% to 20%, but up to 40% among patients requiring ICU admission. Hospital mortality ranges from less than 5% among patients younger than 40 years to 35% for patients aged 70 to 79 years [4].

The high in-hospital mortality, despite the huge commitment of technical and economic resources, prompted the healthcare systems to advance the treatment of COVID-19 patients in the primary care setting, aiming at avoiding, or reducing, the need for hospitalization of these subjects.

Recently, three recombinant human monoclonal antibodies (mAbs) targeting the receptor-binding domain (RBD) of the spike protein of SARS-CoV-2 have been developed: Casirivimab (previously REGN10933), Imdevimab (previously REGN10987) and Bamlanivimab (also known as LY-CoV555 and LY3819253). [5,6]

Either the Casirivimab and Imdevimab combination or Bamlanivimab alone block the binding of the RBD to the host cell and have been evaluated for the treatment of COVID-19 both in hospitalized and home patients [7-9].

While the treatment of hospitalized patients with Bamlanivimab failed to show any benefit [7], the use of Casirivimab and Imdevimab or Bamlanivimab, alone or in combination with Etesevimab showed to be effective in reducing the viral load of COVID-19 outpatients with mild to moderate symptoms [8-9]. Moreover, all the studies reported a very good profile of safety of the investigated mAbs.

Later, Sotrovimab (previously VIR-7831), a further mAb targeting the spike glycoprotein of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has been developed [10]. Of note, the VIR-7831/VIR-7832 epitope does not overlap with mutational sites in the current variants of concern and continues to be highly conserved among circulating sequences consistent with the high barrier to resistance observed in vitro [10]. From a clinical perspective, this means that Sotrovimab retains activity against monoclonal antibody resistance mutations that confer reduced susceptibility to some other currently authorized mAbs [11].

The efficacy and safety of Sotrovimab have been assessed in the COMET-ICE multicenter, double-blind, phase 3 trial. In this study, non-hospitalized patients with symptomatic Covid-19 and at least one risk factor for disease progression were randomized (1:1) to an intravenous infusion of Sotrovimab 500 mg or placebo. The primary endpoint was the proportion of patients with hospitalization for more than 24 hours or death, due to any cause, through day 29. In a recently published interim analysis of the COMET-ICE study,

Sotrovimab significantly reduced by 85% (P = 0.002) the risk of the occurrence of hospitalization or death in high-risk adult symptomatic COVID-19 outpatients. [12]

The Italian Medicines Agency (AIFA) granted the use of Casirivimab and Imdevimab or Bamlanivimab and Etesevimab, and a few months later of Sotrovimab, by an emergency procedure [13,14].

However, no head-to head comparative study has been so far performed to directly compare the efficacy of these therapeutic options in Italy, where almost all the new infections are due to the delta (lineage B.1 .617.2) SARS-CoV-2 variant.

Thus, we decided to compare the effect of Casirivimab and Imdevimab or Bamlanivimab and Etesevimab or Sotrovimab in mild to moderate COVID-19 home patients in terms of preventing clinical worsening, defined as the occurrence of hospital admission or death, whichever occurs first.

**STUDY DESIGN**

This is a phase 3, multicentre, single-blinded, randomized controlled study aimed at comparing the efficacy and safety of Casirivimab and Imdevimab or Bamlanivimab and Etesevimab or Sotrovimab in COVID-19 home patients at high risk of hospitalization.

Patients who satisfy all inclusion criteria and no exclusion criteria and have signed written informed consent will be randomly assigned to one of the three arms in a ratio 1:1:1.

**STUDY POPULATION**

This study will enrol mild to moderate COVID-19 adult home patients at high risk for progressing to severe COVID-19 and/or hospitalisation.

**Inclusion Criteria (all required)**

1. Positive SARS-CoV-2 diagnostic (on pharyngeal swab of deep airways material) for all variants, except for beta and gamma. Positive patients will be considered eligible even when the information on variants is not timely available because of technical or organizational issues.
2. Age ≥18 years of age at the time of randomization
3. Are not hospitalized at the time of randomization
4. Have one or more of the following mild or moderate COVID-19 symptoms according to NIH classification, which onset within <10 days:
    - Fever (>37.5 °C)
    - Cough
    - Sore throat
    - Malaise
    - Headache

- Muscle pain
- Gastrointestinal symptoms
- Shortness of breath with exertion

5. Meet at least one of the following criteria, which define patients at high risk for progressing to severe COVID-19 and/or hospitalization:
    - Body Mass Index (BMI) ≥30
    - Chronic kidney disease
    - Diabetes
    - Primary or secondary Immunodeficiency
    - ≥55 years of age and at least of the following criteria:
        - cardiovascular disease, OR
        - hypertension, OR
        - chronic obstructive pulmonary disease/other chronic respiratory disease.
    - ≥65 years of age
6. Signed informed consent

**EXCLUSION CRITERIA**

Participants are excluded from the study if any of the following criteria apply:

**Medical Conditions**

1. Positive SARS-CoV-2 diagnostic (on pharyngeal swab of deep airways material) for variants beta and gamma
2. Have severe COVID-19 requiring hospital admission or access to the emergency room. Severe COVID-19 is defined as one of the following clinical features: SpO2 ≤ 93% on room air at sea level or PaO2/FiO2 < 300, respiratory rate ≥30 per minute, heart rate ≥125 per minute
3. Require oxygen therapy due to COVID-19, or require an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity.
4. Require mechanical ventilation or anticipated impending need for mechanical ventilation
5. Have received any dose of vaccine antiSARS-CoV-2 within < 15 days
6. Have known allergies to any of the components used in the formulation of the interventions
7. Have hemodynamic instability requiring use of pressors within 24 hours of randomization
8. Have suspected or proven serious, active bacterial, fungal, viral, or other infection (besides COVID-19) that in the opinion of the investigator could constitute a risk when taking intervention

9. Have any co-morbidity requiring surgery within <7 days, or that is considered life-threatening within 29 days
10. Have any serious concomitant systemic disease, condition or disorder that, in the opinion of the investigator, should preclude participation in this study
11. Are pregnant or breast feeding

**Other Exclusion Criteria**

12. Have received any investigational intervention for SARS-CoV-2 prophylaxis in the last 30 days
13. Have received treatment with a SARS-CoV-2 specific monoclonal antibody in the last 30 days
14. Have a history of convalescent COVID-19 plasma treatment in the last 30 days
15. Have participated, within the last 30 days, in a clinical study involving an investigational intervention. If the previous investigational intervention has a long half-life, then 5 half-lives or 30 days, whichever is longer, should have passed.
16. Are concurrently enrolled in any other type of medical research judged not to be scientifically or medically compatible with this study
17. Withdrawn or refusal of the informed consent.
18. Are investigator site personnel, which are directly affiliated with this study.

**INTERVENTIONS**

All patients, in addition to the standard of care for COVID-19 home patients, according to the Italian Health Ministry advice [15], will receive in a single-blind manner one of the following interventions.

**Intervention Group 1 (Casirivimab and Imdevimab)**

Patients in this group will be given Casirivimab and Imdevimab at a dose of 1,200 mg each, administered within 10 days of symptom onset.

Casirivimab and Imdevimab will be administered together as a single IV infusion over at least 70 minutes via pump or gravity (see Table 1), in a setting ensuring that health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

Patients will be clinically monitored during infusion and observed for at least 1 hour after infusion is complete.

*Dosage*

The dosage in adults is 1,200 mg of Casirivimab and 1,200 mg of Imdevimab administered together as a single intravenous infusion. Casirivimab and Imdevimab solutions must be diluted prior to administration.

Casirivimab and Imdevimab should be given as soon as possible after a positive viral test for SARS-CoV-2 and within 10 days of symptom onset.

**Table 1:** Recommended Dilution Instructions for Casirivimab and Imdevimab for IV Infusion

| | Antibody Dose | Volume to Withdraw from Vial | Number of Vials Needed (b) | Standard/Maximum Infusion Rate | Minimum Infusion Time |
|---|---|---|---|---|---|
| Casirivimab and Imdevimab 2,400 mg Dose (a) | Casirivimab 1,200 mg | 10 mL | 1 vial of 11.1 mL **OR** 4 vials of 2.5 mL | 214 / 250 mL/hr | 70 minutes |
| | Imdevimab 1,200 mg | 10 mL | 1 vial of 11.1 mL **OR** 4 vials of 2.5 mL | | |

(a) 1,200 mg of Casirivimab and 1,200 mg of Imdevimab are to be administered together as a single intravenous infusion for a combined 2,400 mg dose.

(b) 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.

**Dose Preparation, Administration and Storage**

*Preparation*

Casirivimab and Imdevimab are each supplied in individual single-dose vials. Casirivimab and Imdevimab solutions must be diluted prior to administration. Casirivimab and Imdevimab infusion solution should be prepared by a qualified healthcare professional using aseptic technique:

1. Remove the Casirivimab and Imdevimab vials from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. Do not expose to direct heat. Do not shake the vials.

2. Inspect Casirivimab and Imdevimab vials visually for particulate matter and discoloration prior to administration. Should either be observed, the solution must be discarded, and fresh solution prepared. The solution for each vial should be clear to slightly opalescent, colourless to pale yellow.

3. Obtain an IV infusion bag containing 250 mL of 0.9% Sodium Chloride Injection, and withdraw from it 20 mL (see Table 1)

4. Withdraw 10 mL of Casirivimab and 10 mL of Imdevimab from each respective vial using two separate syringes and dilute together in the infusion bag containing 230 mL of 0.9% Sodium Chloride Injection (see Table 2). Discard any product remaining in the vial.

5. Gently invert infusion bag by hand approximately 10 times. Do not shake. This product is preservative-free and therefore, the diluted infusion solution should be administered immediately. If immediate administration is not possible, store the diluted Casirivimab and Imdevimab infusion solution in the

refrigerator between 2°C to 8°C for no more than 36 hours and at room temperature up to 25°C for no more than 4 hours, including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.

*Administration*

Casirivimab and Imdevimab infusion solution should be administered by a qualified healthcare professional using aseptic technique.

- Gather the recommended materials for infusion:
  - Polyvinyl chloride (PVC), Polyethylene (PE)-lined PVC, or Polyurethane (PU) infusion set
  - In-line or add-on 0.2-micron polyethersulfone (PES) filter
- Attach the infusion set to the IV bag.
- Prime the infusion set.
- Administer as an IV infusion via pump or gravity over at least 70 minutes through an intravenous line containing a sterile, in-line or add-on 0.2-micron polyethersulfone (PES) filter.
- The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of Casirivimab and Imdevimab injection with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.
- After infusion is complete, flush with 0.9% Sodium Chloride Injection.
- Discard unused product.
- Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.

*Storage*

This product is preservative-free and therefore, the diluted infusion solution should be administered immediately. If immediate administration is not possible, store the diluted Casirivimab and Imdevimab infusion solution in the refrigerator between 2°C to 8°C for no more than 36 hours and at room temperature up to 25°C for no more than 4 hours, including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 30 minutes prior to administration.

*Dosage forms*

Casirivimab is a sterile, preservative-free, clear to slightly opalescent, colourless to pale yellow solution available as:

- Injection: 300 mg/2.5 mL (120 mg/mL) or 1,332 mg/11.1 mL (120 mg/mL) in a single-dose vial

Imdevimab is a sterile, preservative-free, clear to slightly opalescent, colourless to pale yellow solution available as:

- Injection: 300 mg/2.5 mL (120 mg/mL) or 1,332 mg/11.1 mL (120 mg/mL) in a single-dose vial

**Intervention Group 2 (Bamlanivimab and Etesevimab)**

Patients in this group will be given Bamlanivimab at a dose of 700 mg and Etesevimab at a dose of 1.400 mg, administered within 10 days of symptom onset.

Bamlanivimab and Etesevimab will be administered as a single IV infusion over at least 70 minutes via pump or gravity (see Table 3), in a setting ensuring that health care providers have immediate access to medications to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary.

Patients will be clinically monitored during infusion and observed for at least 1 hour after infusion is complete.

*Dosage*

The dosage of Bamlanivimab and Etesevimab for the treatment of mild-to-moderate COVID-19 in adults is:

• Bamlanivimab 700 mg

• Etesevimab 1,400 mg.

Administer Bamlanivimab and Etesevimab together as soon as possible after positive viral test for SARS-CoV-2 and within 10 days of symptom onset.

Bamlanivimab and Etesevimab must be diluted and administered as a single IV infusion over at least 70 minutes.

**Table 3**: Recommended Dilution and Administration Instructions for Bamlanivimab and Etesevimab

| Drug | Number of Vials | Volume of Bamlanivimab / Etesevimab | Standard/Maximum Infusion Rate | Minimum Infusion Time |
|---|---|---|---|---|
| Bamlanivimab (700 mg/20 mL) | 1 Vial | 20 mL | 214 / 250 mL/hr | 70 minutes |
| Etesevimab (700 mg/20 mL) | 2 Vial | 40mL | | |

**Dose Preparation, Administration and Storage**

*Preparation*

Bamlanivimab and Etesevimab solution for infusion should be prepared by a qualified healthcare professional using aseptic technique:

• Gather the materials for preparation:

  • Polyvinyl chloride (PVC) or polyethylene (PE)-lined PVC, sterile infusion bag prefilled with 250 mL of 0.9% Sodium Chloride Injection.

  • One vial of Bamlanivimab (700 mg/20 mL) and two vials of Etesevimab (700 mg/20 mL).

• Bamlanivimab and Etesevimab are supplied in individual single-dose vials but are administered together using a single infusion bag.

• Remove 1 Bamlanivimab vial and 2 Etesevimab vials from refrigerated storage and allow to equilibrate to room temperature for approximately 20 minutes before preparation. Do not expose to direct heat. Do not shake the vials.

• Inspect both Bamlanivimab and Etesevimab vials visually for particulate matter and discoloration.

  • Bamlanivimab and Etesevimab are clear to opalescent and colourless to slightly yellow to slightly brown solutions.

• Obtain an IV infusion bag containing 250 mL of 0.9% Sodium Chloride Injection and withdraw from it 60 mL of Sodium Chloride solution.

• Withdraw 20 mL from one Bamlanivimab vial and 40 mL from two Etesevimab vials and inject all 60 mL into the prefilled infusion bag containing 190 mL of 0.9% Sodium Chloride.

• Discard any product remaining in the vials.

• Gently invert the bag by hand approximately 10 times to mix. Do not shake.

• These products are preservative-free and therefore, the diluted infusion solution should be administered immediately.

• If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C) and up to 7 hours at room temperature (20°C to 25°C) including infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 20 minutes prior to administration.

*Administration*

Bamlanivimab and Etesevimab infusion solution should be administered by a qualified healthcare professional.

• Gather the materials for infusion:

  o Polyvinyl chloride (PVC) or polyethylene (PE)-lined PVC infusion set.

  o Use of an in-line or add-on 0.2/0.22 micron polyethersulfone (PES) filter is strongly recommended.

• Attach the infusion set to the IV bag.

• Prime the infusion set.

• Administer the entire infusion solution in the bag via pump or gravity according to the size of infusion bag used. Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.

• The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of Bamlanivimab and Etesevimab injection with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.

• Once infusion is complete, flush the tubing with 0.9% Sodium Chloride to ensure delivery of the required dose.

• Clinically monitor patients during administration and observe patients for at least 1 hour after infusion is complete.

• If the infusion must be discontinued due to an infusion reaction, discard any unused product.

• The use of closed system transfer devices (CSTDs), elastomeric pumps, and pneumatic transport with Bamlanivimab has not been studied.

*Storage*

This product is preservative-free and therefore, the diluted infusion solution should be administered immediately. If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C) and up to 7 hours at room temperature (20°C to 25°C) including transportation and infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 20 minutes prior to administration.

*Dosage forms*

Bamlanivimab is a sterile, preservative-free, clear to opalescent and colourless to slightly yellow to slightly brown solution available as:

- Injection: 700 mg/20 mL (35 mg/mL) as in a single-dose vial.

Etesevimab is a sterile, preservative-free, clear to opalescent and colourless to slightly yellow to slightly brown solution available as:

- Injection: 700 mg/20 mL (35 mg/mL) in a single-dose vial.

**Intervention Group 3 (Sotrovimab)**

Patients in this group will be given Sotrovimab at a dose of 500 mg as a single IV within 10 days of symptom onset. Sotrovimab will be diluted in a final volume of 100 mL, which will be administered as a single IV infusion bag over 30 minutes.

**Dose Preparation, Administration and Storage**

*Preparation*

Sotrovimab is supplied in a single-dose vial and must be diluted prior to administration.

Sotrovimab injection should be prepared by a qualified healthcare professional using aseptic technique.

• Gather the materials for preparation:

  o Polyvinyl chloride (PVC) or polyolefin (PO), sterile, prefilled infusion bag. Choose one of the following sizes: prefilled 50-mL or 100-mL infusion bag containing 0.9% Sodium Chloride Injection, and

  o One vial of Sotrovimab (500 mg/8 mL).

• Remove one vial of Sotrovimab from refrigerated storage and allow to equilibrate to room temperature, protected from light, for approximately 15 minutes.

• Inspect the vial of Sotrovimab visually for particulate matter and discoloration prior to administration. Should either be observed, the solution must be discarded and a fresh solution prepared. Sotrovimab is a clear, colorless or yellow to brown solution.

• Gently swirl the vial several times before use without creating air bubbles. Do not shake the vial.

• Withdraw 8 mL of Sotrovimab from one vial and inject into the prefilled infusion bag containing 0.9% Sodium Chloride Injection.

• Discard any product remaining in the vial.

• Prior to the infusion, gently rock the infusion bag back and forth by hand 3 to 5 times. Do not invert the infusion bag. Avoid forming air bubbles.

• This product is preservative-free; therefore, the diluted infusion solution should be administered immediately. If immediate administration is not possible, store the diluted solution of sotrovimab up to 4 hours at room temperature (20°C to 25°C [68°F to 77°F]) or refrigerated up to 24 hours (2°C to 8°C [36°F to 46°F]).

*Administration*

Sotrovimab infusion solution should be administered by a qualified healthcare professional.

• Gather the materials for infusion:

  o Polyvinyl chloride (PVC) or polyolefin (PO) infusion set, and

  o Use of a 0.2 micron polyethersulfone (PES) filter is strongly recommended.

• Attach the infusion set to the IV bag using standard bore tubing.

• Prime the infusion set.

• Administer the entire infusion solution in the bag over 30 minutes. Due to potential overfill of prefilled saline bags, the entire infusion solution in the bag should be administered to avoid underdosage.

• Do not administer as an IV push or bolus.

• The prepared infusion solution should not be administered simultaneously with any other medication. The compatibility of sotrovimab with IV solutions and medications other than 0.9% Sodium Chloride Injection is not known.

• Once infusion is complete, flush the tubing with 0.9% Sodium Chloride to ensure delivery of the required dose.

• If the infusion must be discontinued due to an infusion reaction, discard unused product.

• Clinically monitor patients during infusion and observe patients for at least 1 hour after infusion is complete.

*Storage*

This product is preservative-free; therefore, the diluted infusion solution should be administered immediately. If immediate administration is not possible, store the diluted infusion solution for up to 24 hours at refrigerated temperature (2°C to 8°C [36°F to 46°F]) or up to 4 hours at room temperature (20°C

to 25°C [68°F to 77°F]) including transportation and infusion time. If refrigerated, allow the infusion solution to equilibrate to room temperature for approximately 15 minutes prior to administration.

*Dosage forms.*

Sotrovimab is a sterile, preservative-free, clear, colorless or yellow to brown solution available as:

- Injection: 500-mg/8-mL (62.5-mg/mL) solution in a single-dose vial for intravenous infusion after dilution.

*Warnings*

There are limited clinical data available for Sotrovimab. Serious and unexpected adverse events may occur that have not been previously reported with use of Sotrovimab.

**CONTRAINDICATIONS**

**Casirivimab and Imdevimab**

No contraindications have been reported

**Bamlanivimab and etesevimab**

No contraindications have been reported

**Sotrovimab**

No contraindications have been reported.

**WARNINGS AND PRECAUTIONS**

**Casirivimab and Imdevimab**

There are limited clinical data available for Casirivimab and Imdevimab. Serious and unexpected adverse events, which have not been previously reported with Casirivimab and Imdevimab use, may occur.

**Hypersensitivity including Anaphylaxis and Infusion-Related Reactions**

There is a potential for serious hypersensitivity reactions, including anaphylaxis, with administration of Casirivimab and Imdevimab. If signs or symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care. Infusion-related reactions have been observed with administration of Casirivimab and Imdevimab.

Signs and symptoms of infusion related reactions may include:

- fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, dizziness.

If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.

**Bamlanivimab and Etesevimab**

There are limited clinical data available for Bamlanivimab and Etesevimab. Serious and unexpected adverse events, which have not been previously reported with use of Bamlanivimab and Etesevimab together, may occur.

**Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions**

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of Bamlanivimab with and without Etesevimab. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive therapy.

Infusion-related reactions have been observed with administration of Bamlanivimab and Etesevimab together. These reactions may be severe or life threatening.

Signs and symptoms of infusion related reactions may include:

- fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, dizziness and diaphoresis.

If an infusion-related reaction occurs, consider slowing or stopping the infusion and administer appropriate medications and/or supportive care.

**Sotrovimab**

There are limited clinical data available for sotrovimab. Serious and unexpected adverse events may occur that have not been previously reported with use of Sotrovimab.

Hypersensitivity Including Anaphylaxis and Infusion-Related Reactions

Serious hypersensitivity reactions, including anaphylaxis, have been observed with administration of sotrovimab [see Full EUA Prescribing Information, Overall Safety Summary (6.1)]. If signs and symptoms of a clinically significant hypersensitivity reaction or anaphylaxis occur, immediately discontinue administration and initiate appropriate medications and/or supportive care.

Infusion-related reactions, occurring during the infusion and up to 24 hours after the infusion, have been observed with administration of Sotrovimab. These reactions may be severe or life threatening.

Signs and symptoms of infusion-related reactions may include: fever, difficulty breathing, reduced oxygen saturation, chills, fatigue, arrhythmia (e.g., atrial fibrillation, sinus tachycardia, bradycardia), chest pain or discomfort, weakness, altered mental status, nausea, headache, bronchospasm, hypotension, hypertension, angioedema, throat irritation, rash including urticaria, pruritus, myalgia, vaso-vagal reactions (e.g., pre-syncope, syncope), dizziness, and diaphoresis.

Consider slowing or stopping the infusion and administer appropriate medications and/or supportive care if an infusion-related reaction occurs.
Hypersensitivity reactions occurring more than 24 hours after the infusion have also been reported.

**ALLOWED CONCOMITANT THERAPIES**

All patients will receive the standard of care for COVID-19 home patients, according to the Italian Health Ministry advice [15].
In details, the recommended treatment for mild to moderate at-home COVID-19 patients includes:

- Careful monitoring of oxygen saturation by portable devices
- Administration of paracetamol or NSAID (Non-Steroidal Anti-inflammatory Drug) for symptomatic relief of fever, headache or myalgia.
- Continuing the administration of ongoing treatments for previous chronic diseases
- Avoiding the administration of corticosteroids, except for those patients who do not experience a clinical improvement after 72 hours from the diagnosis and requiring oxygen supplementation because of worsening of oxygen saturation.
- Avoiding the administration of heparin or low-molecular weight heparin, except for those patients who have severe restriction of mobility
- Avoiding the administration of antibiotics, except for those patients who experience fever for more than 72 hours and/or with suspected or proven concomitant bacterial infection
- Avoiding the administration of hydroxychloroquine.

Casirivimab and Imdevimab, Bamlanivimab and Etesevimab, Sotrovimab are monoclonal antibodies (mAbs), which are not renally excreted or metabolized by cytochrome P450 enzymes. Therefore, interactions with concomitant medications - which are renally excreted or that are substrates, inducers, or inhibitors of cytochrome P450 enzymes - are unlikely. Therefore, any concomitant treatment either for COVID 19 or for previous diseases will be allowed.
Any other concomitant therapies, such as: antiviral-agents, Hydroxychloroquine, Chloroquine, Baricitinib, Heparin, Enoxaparin, Fondaparinux, Warfarin, Apixaban, Dabigatran, Edoxaban, Rivaroxaban, Antiplatelet agents, Anti-hypertensive drugs, oral Antidiabetic agents, insulin, immunosuppressive drugs, will be collected. These pieces of information could be useful to assess the possible association between the clinical worsening and the treatments in particular subgroups of patients stratified by concomitant therapies.

**NOT ALLOWED CONCOMITANT THERAPIES**

Oxygen therapy due to COVID-19, or an increase in baseline oxygen flow rate due to COVID-19 in those on chronic oxygen therapy due to underlying non-COVID-19 related comorbidity, is not allowed because this is an exclusion criterion.

**AIMS**

Aim of this study is to compare efficacy and safety of Casirivimab and Imdevimab or Bamlanivimab and Etesevimab or Sotrovimab in mild to moderate COVID-19 home patients

**END-POINTS**

**Primary Efficacy Endpoint**

Clinical worsening, defined as the progression of the disease to a more severe state, such as hospitalization or death, whichever comes first, through day 29.

The follow up will start the day in which the treatment is administered.

**Primary Safety Endpoint**

Early safety, defined as the occurrence of any adverse event within 24 hours from the beginning of treatment administration, such as any symptoms that can be related to drug hypersensitivity, which include: anaphylaxis, fever, chills, nausea, headache, bronchospasm, hypotension, angioedema, throat irritation, rash (including urticaria), pruritus, myalgia, dizziness or any other symptom, according to the clinical judgment of the attending physician.

**Secondary Efficacy Endpoint**

The occurrence of:

a) death, defined as all-cause mortality;
b) any hospital admission;
c) any access to the emergency department,

up to 6 weeks from the beginning of treatment administration.

**Secondary Safety Endpoint**

Late safety, defined as the occurrence of any adverse event occurring after 24 hours and through day 29 from the beginning of the intervention.

**Definition of an AE**

Any untoward medical occurrence in a patient or clinical investigation subject, temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease (new or exacerbated) temporally associated with the use of a medicinal product. For marketed medicinal products, this also includes failure to produce expected benefits (i.e. lack of efficacy), abuse or misuse.

**Definition of a SAE**

A serious adverse event is any untoward medical occurrence that, at any dose of medicinal product:

- results in death
- is life-threatening
- requires hospitalization
- results in disability/incapacity
- is a congenital anomaly/birth defect.

*Notes:*

The term 'life-threatening' in the definition of 'serious' 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.

The term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance such as uncomplicated headache, nausea, vomiting, diarrhoea, influenza, and accidental trauma (e.g. sprained ankle) which may interfere or prevent everyday life functions but do not constitute a substantial disruption. Medical or scientific judgement should be exercised in deciding whether reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization but may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed in the above definition. These should also be considered serious.

**Disease-related events or outcomes not qualifying as SAEs**

An event which is part of the natural course of the disease under study (e.g., disease progression) does not need to be reported as SAE. Death due to progressive disease is to be recorded on the 'Record of Death' CRF page and not as SAE. However, if the progression of the underlying disease is greater than that which would normally be expected for the subject, or if the investigator considers that there was a causal relationship between treatment with randomized therapy or protocol design/procedures and the disease progression, then this must be reported as SAE.

**Lack of efficacy**

"Lack of efficacy" per se will not be reported as an AE. The signs and symptoms or clinical sequelae resulting from lack of efficacy will be reported if they fulfil the AE or SAE definition (including clarifications).

**Time period, frequency, and method for collecting AEs and SAEs information**

All AEs and SAEs will be collected from the time the informed consent form (ICF) is signed up to the end of the study.

Adverse events that begin before the start of study intervention but after signing of the ICF will be recorded on the Adverse Event CRF.

Although all AEs after signing the ICF are recorded by the site in the CRF/electronic data entry, SAE reporting to sponsor begins after the participant has signed the ICF and has received study intervention. However, if an SAE occurs after signing the ICF, but prior to receiving study intervention, it needs to be reported within the SAE reporting timeframe if it is considered reasonably possibly related to study procedures.

All SAEs will be recorded and reported to the sponsor or designee immediately and under no circumstance should this exceed 24 hours. The investigator will submit any updated SAE data to the sponsor within 24 hours of it being available.

Investigators are not obligated to actively seek AEs or SAEs after conclusion of the study participation. However, if the investigator learns of any SAE, including a death, at any time after a participant has been discharged from the study, and he/she considers the event to be reasonably related to the study intervention or study participation, the investigator must promptly notify the sponsor.

From the time a patient consents to participate in the study until he/she has completed the study (including any follow-up period), all SAEs assessed as related to study participation (e.g., protocol- mandated procedures, invasive tests, or change in existing therapy), will be reported promptly to the Coordinating Centre. All AEs and SAEs will be collected from the study treatment infusion to the end of follow-up, that is 28 days, and recorded on the CRF. SAEs brought to the attention of the investigator at any time after cessation of study treatment and considered by the investigator to be related or possibly related to study treatment must be reported if and when they occur. Additionally, in order to fulfil international reporting obligations, SAEs that are related to study participation (e.g., procedures, invasive tests, change from existing therapy) or are related to a concurrent medication will be collected and recorded from the time the subject consents to participate in the study until he/she is discharged. The investigator or designee will inquire about the occurrence of AEs/SAEs at every visit/contact during the study and throughout the 6 weeks' follow-up period by asking the following standard questions:

1. How are you feeling?
2. Have you had any (other) medical problems since your last visit?
3. Have you taken any new medications since your last visit/assessment?

**Recording of AEs and SAEs**

When an AE/SAE occurs, it is the responsibility of the investigator to review all documentation (e.g., hospital progress notes, laboratory, and diagnostics reports) relative to the event. The investigator will then record all relevant information regarding an AE or SAE on the CRF. It is not acceptable for the investigator to send photocopies of the subject's medical records in lieu of completion of the appropriate AE or SAE CRF pages. The investigator will attempt to establish a diagnosis of the event based on signs, symptoms, and/or other clinical information. In such cases, the diagnosis should be documented as the AE/SAE and not the individual signs/symptoms. Any AEs or SAEs occurring during the study must be documented in the subject's medical records and on the appropriate page of the CRF. Each AE or SAE is to be recorded individually. Deaths due to progressive disease are to be recorded on the 'Record of Death' CRF page and not as an SAE.

**Evaluating AEs and SAEs**

**Assessment of intensity**

The investigator will make an assessment of intensity of each AE and SAE reported. In this protocol, the intensity of AEs and SAEs will be graded on a scale of 1 to 5 according the National Cancer Institute (NCI) Common Toxicity Criteria for Adverse Events (CTCAE) Version 5.0 and are available at https://ctep.cancer.gov/protocoldevelopment/electronic_applications/docs/CTCAE_v5_Quick_Reference_5x7.pdf. For SAEs, the maximum intensity (or grade) will be reported in the CRFs. For non-serious AEs, each change in intensity (or grade) will be reported in the CRFs.

**Assessment of causality**

The investigator is obligated to assess the relationship between the study medical product and the occurrence of each AE/SAE. The investigator will use clinical judgement to determine the relationship. Alternative causes, such as natural history of the underlying diseases, concomitant therapy, other risk factors, and the temporal relationship of the event to the study drugs will be considered and investigated. There may be situations when an SAE has occurred and the investigator has minimal information to include in the initial report. However, it is very important that the investigator always make an assessment of causality for every event prior to transmission of the SAE form to the Coordinating Centre. The investigator may change his/her opinion of causality in light of follow-up information, amending the SAE CRF accordingly. The causality assessment is one of the criteria used when determining regulatory reporting requirements. The investigator will provide the assessment of causality as per instructions on the SAE form in the Investigators File.

**Follow-Up of AEs and SAEs**

After the initial AE/SAE report, the investigator is required to proactively follow each subject at subsequent visits/contacts and provide further information on the subject's condition. All AEs and SAEs documented at a previous visit/contact and designated as ongoing, will be reviewed at subsequent visits/contacts. All SAEs will be followed until resolution, stabilization, the event is otherwise explained, or the participant is lost to follow-up. AEs that are ongoing with a toxicity of Grade 3 or 4, or have a relationship to study drug that is suspected (Reasonable Possibility) will be queried for resolution at study conclusion. Once resolved, the appropriate AE/SAECRF page(s) will be updated. The investigator will ensure that follow-up includes any supplemental investigations as may be indicated to elucidate the nature and/or causality of the AE or SAE. This may include additional laboratory tests or investigations, histopathological examinations, or consultation with other health care professionals. If a subject die during participation in the study or during a recognized follow-up period, national coordinating centre will be provided with a copy of any post-mortem findings, including histopathology. New or updated information will be recorded on the originally completed SAE form in the Investigator's File, with all changes signed and dated by the investigator.

**Regulatory reporting requirements for adverse events**

The Principal Investigator at CC has a legal responsibility to notify, as appropriate, both the local regulatory authority and other regulatory agencies about the safety of a product under clinical investigation. Prompt notification of SAEs by the investigator to the appropriate project contact for SAE receipt is essential so that legal obligations and ethical responsibilities towards the safety of other subjects are met. The Principal Investigator at CC, or responsible person according to local requirements, will comply with the applicable local regulatory requirements related to the reporting of SAEs to regulatory authorities and the Independent Ethics Committee (IEC). In particular, all the Suspected Unexpected Serious Adverse Reactions (SUSARs) that occur while on treatment and within 30 days since the investigational drug administration, and that have a suspected relationship to study drug (Reasonable Possibility) will be notified with urgency procedure to the local regulatory Agency (AIFA) and IEC with the following timelines:

-SUSARs that are considered life-threatening: notification within 7 days.

-SUSARs that are not considered life-threatening: notification within 15 days.

The notification with urgency procedure is not required for SAEs that are expected with the drugs used in the protocol, and for non-serious AEs, both expected or unexpected. For these events (expected SAEs and AEs), the CC will notify local regulatory agency and IECs by annual safety report. The CC is responsible for provide to all the investigators involved in the trial, with appropriate timelines, all the safety information relevant for patient safety.

**ANCILLARY STUDY**

Ancillary studies will seek to assess the performance of the main validated scores usually used in clinical practice to evaluate the risk of hospitalization in COVID-19 home patients.

**PLANNED STUDY DURATION**

We expect that the study will take approximately 12 months. The details of such an estimation are reported below.

*Enrollment period*

Under the hypothesis that:

a. at least 20 USCA will be involved in the study;
b. each USCA will be able to enroll on average 3 patients per month;

we expect that the enrollment will be completed over a period of approximately 9 months.

*Treatment period*

the treatment period includes about one hour of infusion and one hour of observation.

*Follow-up period*

Each patient will be followed up for 6 weeks' days after the drug infusion.

*Data analysis and Final Study Report*

The data analysis and the quality check will take three weeks, whereas the study report writing will take three more weeks.

**Sample size and statistical analysis**

Considering the number of centers involved in the study and the current COVID-19 region situation, we foresee to enroll about 552 patients over a period of approximately 9 months.

This sample size will allow us to detect a statistically significant relative reduction (alpha=0.025 and beta=0.20) of at least 80% of the proportion of patients who experience clinical worsening across the interventions. Hypothesizing a proportion of clinical worsening of 10% in any arms, such reduction will result in a proportion of clinical worsening of 2% in any other arm, which corresponds to an absolute risk reduction of 8%.

**Ad interim analysis**

Considering the statistical approach, an interim analysis will be conducted after the randomization of 276 patients, which roughly correspond to 50% of the sample size. This analysis is aimed at assessing whether the results show larger than expected benefit and/or harm on any arms.

O'Brien-Fleming method will be used with an alpha set to 0.025 [18]. According to this method, the study will be stopped after enrolling 50% of the patients if the z value is beyond the following boundaries: -3.34 and 3.34.

All AEs which occur during the course of the study will be forwarded to the independent Data Safety Monitoring Board (DSMB).

In case of the occurrence of any SAE, the DSMB will be requested to assess the opportunity to continue/interrupt the study. In the meantime, the enrollment will be suspended until the DSMB decision will be notified to the Steering Committee.

**Statistical Analysis**

The Methodologic and Statistical Support Unit, which is part of Servizio Formazione, Ricerca e Innovazione at the Azienda Ospedaliero-Universitaria of Modena, will be in charge of the management of data and data analysis.

All patients enrolled in the study will be entered in the full analysis set independently of their treatment time.

The intention to treat population will be considered for primary analysis.

A descriptive statistical analysis will be carried out to summarize all the relevant variables.

At baseline, categorical data will be summarized by using counts and percentages, whilst continuous variables will be presented using the number of patients, mean, standard deviation, median, minimum, and maximum.

The 3 arms will be compared for the primary outcome in terms of:

- proportion of patients experiencing clinical worsening up to 29 days;
- time to clinical worsening.

The 3 arms will also be compared for the secondary outcomes in terms of proportion of patients experiencing any secondary outcome and time to its occurrence up to 6 weeks.

Clinical worsening, and each single outcome defining it, will be summarized in terms of proportion and compared by using RR as measure of association. Time to the occurrence of these events will also be summarized by using Kaplan-Meier curves and compared between arms by HRs.

All measures of association will be presented with their 95% confidence intervals. A result will be considered as statistically significant if its p-values will be less than 0.05 (5%).

The analyses will be performed by using STATA software.

**Subgroup analysis**

This study is not powered for subgroup analyses; therefore, all subgroup analyses will be treated as exploratory.

Subgroup analyses will be conducted only for the primary endpoint and may include:

- Duration since symptom onset to randomization (<5 vs ≥5 days)
- Vaccination (Yes vs No)
- Baseline BMI (<30 kg/$m^2$ vs ≥30 kg/$m^2$)
- Age (<65 vs ≥65 years old)

**Organizational issues and feasibility**

**Involvement of Primary Care Departments and USCA**

The study will involve, besides the proposing academic Hospital of Modena, the primary care services of the Emilia-Romagna region, in particular Modena, Reggio Emilia, Parma and Piacenza provinces. These neighboring districts are situated in the Northern Italy and have an incident population of about 1.9 million inhabitants.

The primary health care service in this area is provided by the Azienda Unità Sanitaria Locale (AUSL), that through their Primary Care Departments coordinate about 1000 general practitioners (GP), which ensure a widespread network of skilled physicians able to manage COVID-19 patients at home, and to promptly identify those in need of hospital care.

Moreover, in order to better tackle the ongoing pandemic, which seriously impact the healthcare systems, the Emilia-Romagna Region instituted 81 special units of healthcare continuity (Unità Speciali di Continuità Assistenziale, USCA) aimed at supporting GPs in the management of COVID-19 patients at home. Each USCA is an integrated team composed by a physician and a nurse, specially trained in providing care to COVID-19 at home patients and tightly connected with GPs network.

Right now, 54 USCA have been set up in the provinces of Modena, Reggio Emilia, Parma and Piacenza. From the beginning of this service (April 20$^{th}$) up to their first report published on Region Emilia-Romagna webpage (May, 3$^{rd}$ 2020), these USCA provided more than 1000 patients' phone screening, and home visits, and administered about 1700 home therapies. In addition, the USCA performed more than 100 further procedures, including pharyngeal swab, electrocardiogram and bed-side thoracic echography [13].

**Feasibility**

About 7000 cases of COVID-19 have been reported in Emilia Romagna Region in the last 30 days; among them, one third (about 2310 patients) is considered to have mild to moderate symptoms. Considering the provinces involved in the study, such as Modena, Reggio Emilia, Piacenza and Parma, approximately 1000 patients per month are considered as potentially eligible for the study.

The established network of GPs and USCA represents a suitable setting that can ensure a timely and reliable screening, enrolment and follow-up of at home mild to moderate COVID-19 patients at risk of clinical worsening.

As the USCA organization spreads over the whole Emilia-Romagna Region, if necessary, this project could involve the other USCA operating on the territory.

**STUDY PROCEDURES**

**Training of involved USCA, Pharmacies and Public Health Service personnel**

Personnel of:

a) Pharmacies involved in the preparation of Monoclonal Antibodies;
b) USCA involved in their administration
c) Public Health Service in charge of contacting people who resulted positive to the SARS-CoV-2 test

will be properly trained before the start of the study.

Regarding Pharmacies, the personnel working there will be trained to properly manage the treatment to be administered to each randomised patient. The pharmacy will ensure that the infusion solution is prepared using aseptic techniques.

Regarding the USCA, the personnel working there will be trained to:

a) manage the infusion bag transfer, storage and delivery;
b) have immediate access to medications (including steroids and epinephrine) and devices to treat a severe infusion reaction, such as anaphylaxis, and the ability to activate the emergency medical system (EMS), as necessary;
c) Basic Life Support (BLS), including Cardio Pulmonary Resuscitation, basic airways management, defibrillation by Automated External Defibrillator, etc.

Regarding the Public Health Service, the personnel in charge of contacting people who resulted positive to the SARS-CoV-2 test will be trained to collect the information useful for identifying patients eligible for the study.

Both USCA and pharmacies personnel will be trained to promptly manage the information coming from the Web platform notifying that a patient has been randomised.

**Step-by-step study procedures**

The process will start with an early identification of patients with mild to moderate COVID-19 cared for at home. An important role in the identification of COVID-19 patient at high risk of hospitalization will be played by the Public Health Service operating in the territory involved in this study. The Public Health Service is in charge of communicating the results to people, who underwent the SARS-COV2 swab tests.

**Step 1** The Public Health Service will contact by telephone the people who resulted positive to the test, except for those who are positive to beta and gamma variants, if this information is available. During the

telephone call, the staff, by using an ad hoc developed short questionnaire, will ask the patient a few questions that will help to early identify if she/he is potentially eligible to be enrolled in the study. In case the person is considered to be at high risk of hospitalization, the public health office staff will refer this information to USCA.

**Step 2**. Once USCA has been informed, it will contact the patient or his/her carer by telephone. During the telephone call, USCA will start collecting information about the patient's health conditions and clinical history. If the high risk of hospitalization is confirmed, the USCA will inform the patient about the possibility to participate to the study. In case the patient is willing to participate, USCA will schedule an appointment for a home visit.

**Step 3.** During the home visit, USCA will thoroughly verify whether she/he can be considered at high risk of hospitalisation. The following information will be collected: physical parameters, medical history, ECOG performance status; baseline signs and symptoms, medication(s) received in the previous 2 weeks, blood pressure, pulse rate, body temperature, height, body weight, pregnancy test for women of childbearing potential, SpO2 evaluation.

**Step 4.** In case the patient is actually eligible to be involved in the study, USCA staff will provide him/her further information, answer patient's questions and give informative material inherent the study. If the patient does agree to participate to the study, she/he will be asked to sign the informed consent.

**Step 5.** Once the patient has accepted to participate, USCA will register her/him on the platform specifically developed for this study. The platform will allow the randomisation of patients to one of the three arms. The information about the allocated arm will be sent to the coordinating hospital pharmacy, which is in charge of preparing the drugs to be infused. At the same time, the USCA coordinating centre, which is in charge of administering the treatment to patients, will receive the notification about the occurred randomization. USCA will end the visit by scheduling the next appointment for the infusion.

**Step 6.** The coordinating hospital pharmacy will prepare the infusion bag containing the drugs, properly diluted, which will be collected by USCA staff within 24 hours from its preparation and will be taken to the patient's home to be infused.

**Step 7.** The USCA staff arrives at home with the infusion bag, which has been properly stored. Before the infusion USCA will collect information on patient's health conditions. Then USCA staff will proceed with the drug infusion.

**Step 8.** The duration of the drug infusion will last 30 or 60 minutes, according to the schedule of administration of each monoclonal intervention. An extra hour will be spent by USCA staff to monitor any

possible occurrence of adverse events. A patient's card will be provided to the her/him to inform any health professionals, who are not involved in the trial, about his/her participation to the study.

**Step 9.** Each patient will be followed up to 6 weeks after the day of the treatment. Each patient will be contacted by phone 8 times during this time frame:

1. within 24 hours;
2. + 2 days;
3. + 4 days;
4. + 6 days;
5. + 8 days;
6. + 14 days;
7. + 29 days;
8. + 6 weeks.

A brief standardised questionnaire aimed at assessing the patient's health status will be developed and administered to patient during each phone meeting.

**Web-based platform for managing patient enrolment, randomisation and analysis**

The Methodologic and Statistical Support Unit, which is part of Servizio Formazione, Ricerca e Innovazione at the Azienda Ospedaliero-Universitaria of Modena, will be in charge of the management the Web-based platform. It has a long experience in managing multicentre randomised studies (ref. COVID-19 HD, STAUNCH study, SHORT-HER, etc).

The web-based platform will allow the assessment of patient's inclusion/exclusion criteria, as well as the randomisation and the management of follow-up visits. The platform will include the eCRF and an area in which documents, such as the study protocol, amendments, authorizations, and newsletters, will be stored.

The web-based platform is planned to manage adaptive studies, which means that it will allow this RCT to include and assess the efficacy and safety of new anti SARS-CoV2 monoclonal antibodies, which may be available during the course of the study.

The data collected for each patient will be imputed in the eCRF and will be centrally stored in a server belonging to the Azienda Ospedaliero-Universitaria of Modena. The access to the platform regarding patient's data and randomisation will be allowed only to the investigators formally involved in the study through the use of personal credentials given by the coordinating centre.

**Randomization**

All patients will be centrally randomized to study intervention using an eCRF. Before the study is initiated, the log in information and directions for the eCRF will be provided to each site.

Patients will be stratified by vaccination (Yes vs No), age (<65 vs ≥65) and BMI (<30 vs ≥30). All eligible participants will be randomized, initially following an equal allocation to treatment arms.

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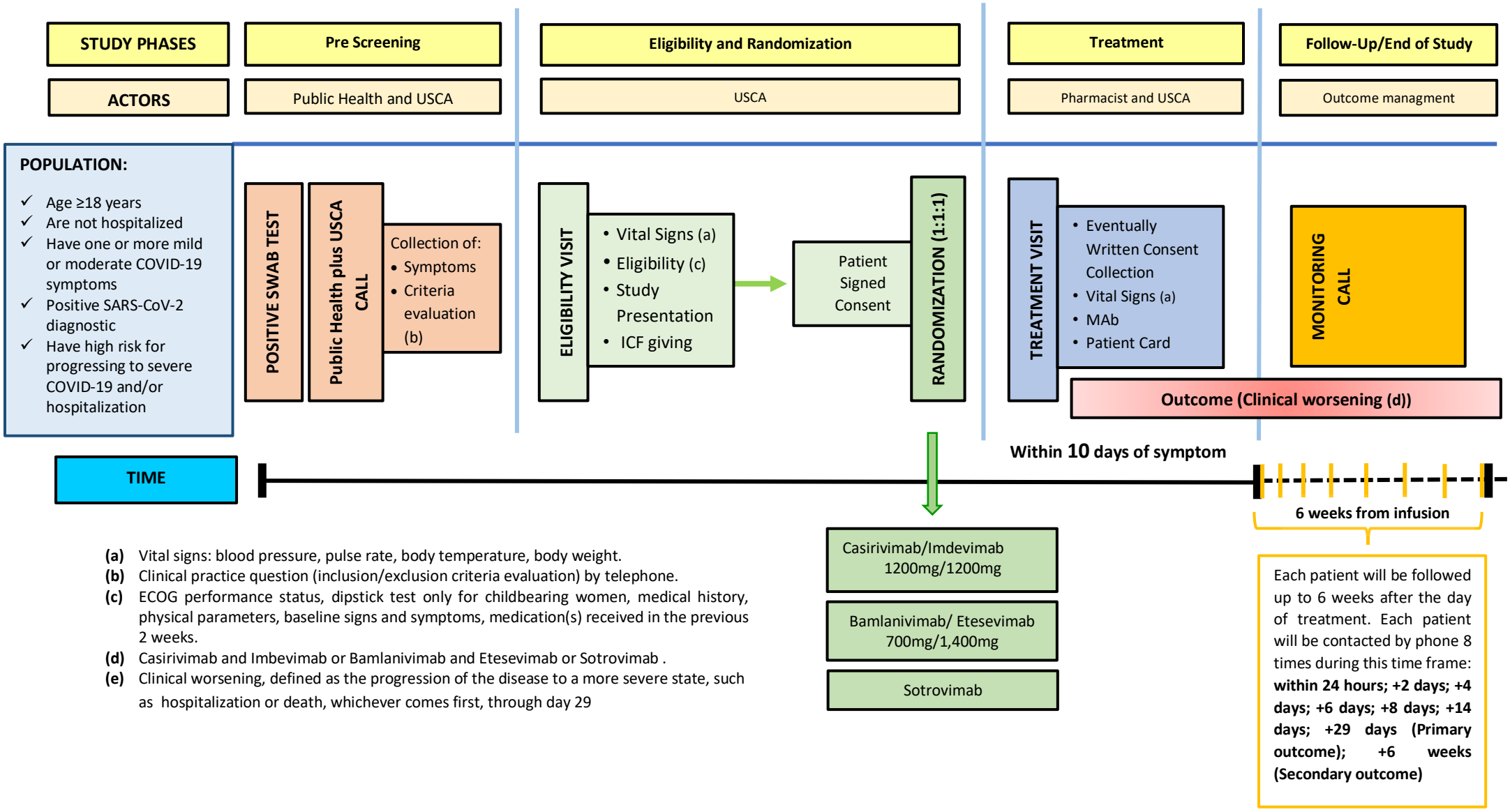
**Economic Plan**

| Costs | TOTAL BUDGET |
|---|---|
| Researchers' Contracts and Salary of Staff | 333500 |
| Equipment | 110000 |
| Supplies | 30000 |
| Subcontracts | 140000 |
| Patient Costs | 35000 |
| Services and Data Bases | 100000 |
| Publication Costs | 12000 |
| E-meeting | 3000 |
| Travels | 5000 |
| Overheads | 38425 |
| Coordination Costs | 35000 |
| **Total** | **841925** |

| Budget Justification | |
|---|---|
| Researchers' Contracts and Salary of Staff | 3 Researchers' Contract, reimbursement to the participating center of the hourly-working cost of USCA operators through a time sheet (hours for drug administration) |
| Equipment | thermometer, oximeter, tablet, portable defibrillator, emergency kit, thermal bags for drug transport and drug refrigerator |
| Supplies | pregnancy test, infusion kit, photoprotective bags, temptale |
| Subcontracts | CRO, courier for transporting clinical study documents and materials/equipment |
| Patient Costs | assurance |
| Services and Data Bases | training BLS-D, e-CRF, data analysis, final report processing and internet lines for tablets |
| Publication | Expenses for publication of research results in international peer-reviewed journals |
| E-meeting | Presentation of results at research e-Meetings. Registration expenses and platforms |
| Travels | In order to present research results at National and International research Meetings |
| Overheads | Administrative and managerial costs, exclusively related to the management of the project. Stationery |
| Coordination Costs | Costs to coordinate the study process and organize seminaries and meetings to present results |

## Appendix 1. STUDY PLAN




**(a)** Vital signs: blood pressure, pulse rate, body temperature, body weight.
**(b)** Clinical practice question (inclusion/exclusion criteria evaluation) by telephone.
**(c)** ECOG performance status, dipstick test only for childbearing women, medical history, physical parameters, baseline signs and symptoms, medication(s) received in the previous 2 weeks.
**(d)** Casirivimab and Imbevimab or Bamlanivimab and Etesevimab or Sotrovimab .
**(e)** Clinical worsening, defined as the progression of the disease to a more severe state, such as hospitalization or death, whichever comes first, through day 29

**Appendix 2. STUDY FLOW CHART**

| | **Pre-Screening Visit * (Step 1-2)** | | **Eligibility Visit (Step 3-6)** | **Treatment Visit ° (Step 7-8)** | **Follow Up/End of Study[§] (Step 9)** |
|---|---|---|---|---|---|
| | Public Health Staff | USCA | USCA | USCA | Study Staff |
| Positive Swab Test | x | | | | |
| Short Questionnaire | x | | | | |
| USCA Questionnaire | | x | | | |
| Symptoms Collection | | x | | | |
| Inclusion/Exclusion Criteria | | x | x | | |
| ICF sign | | | x | | |
| Baseline signs and symptoms | | | x | | |
| Vital Signs Collection** | | | x | x | |
| ECOG performance status | | | x | x | |
| Pregnancy Test*** | | | x | | |
| Medical History | | | x | | |
| Concomitant Medication[#] | | | x | x | x |
| Adverse Event Collection | | | x | x | x |
| Randomization | | | x | | |
| Treatment Mab^ | | | | x | |
| Patient Card Giving | | | | x | |
| Telephone Contact | | | | | x |
| Follow-up Questionnaire * | | | | | x |

* By telephone
** Vital signs: blood pressure, pulse rate, body temperature, body weight, height, SpO2.
*** Only for childbearing women
[#] Medication received in the previous two weeks
° The Treatment Visit must be performed within 10 days of symptoms
^ Casirivimab and Imbevimab or Bamlanivimab and Etesevimab or Sotrovimab
[§] Each patient will be followed up to 6 weeks after the day of treatment. Each patient will be contacted by phone 8 times during this time frame: within 24 hours; +2 days; +4 days; +6 days; +8 days; +14 days; +29 days; +6 weeks

**Appendix 3. GANTT CHART**

| GANTT CHART - MAI COVID-19 Study | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Months | | | | | | | | | | | | | |
| | pre-authorization CE | | post-authorization CE | | | | | | | | | | | |
| **Activities** | 1 | 2 | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| **Project management and coordination** | | | | | | | | | | | | | | |
| **Protocol, Ethics Committee submission, administrative activity for the definition of sub-contracts** | | | | | | | | | | | | | | |
| **Training USCA and pharmacies** | | | | | | | | | | | | | | |
| **Start-up of project in all MAI COVID 19 centres** | | | | | | | | | | | | | | |
| **Patients enrolment** | | | | | | | | | | | | | | |
| **Patients follow-up** | | | | | | | | | | | | | | |
| **Clinical data collection** | | | | | | | | | | | | | | |
| **Data analysis and the quality check** | | | | | | | | | | | | | | |
| **Statistical analysis of results** | | | | | | | | | | | | | | |
| **Report of results, dissemination at meetings/publications** | | | | | | | | | | | | | | |