**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.