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ORIGINAL ARTICLE



# Bamlanivimab and Etesevimab administered in an outpatient setting for SARS-CoV-2 infection

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**ABSTRACT**

The early administration of anti-SARS-CoV-2 monoclonal antibodies (mAb) could decrease the risk of severe disease and the need of inpatients care. Herein, our clinical experience with Bamlanivimab/Etesevimab for the treatment of early SARS-CoV-2 infection through an outpatient service was described. Patients with confirmed COVID-19 were selected by General Practitioners (GPs) if eligible to mAb administration, according to manufacturer and AIFA (Agenzia-Italiana-del-Farmaco) criteria. If suitability was confirmed by the Multidisciplinary Team, the patient was evaluated within the next 48–72 hours. Then, all patients underwent a medical evaluation, followed by mAb infusion or hospitalization if the medical condition had worsened. Overall, from March 29th to June 4th, 2021, 106 patients with confirmed COVID-19 were identified by GPs; 26 were considered not eligible and then excluded, while 9 refused treatment. Among the 71 remaining, 6 were not treated because of worsening of symptoms soon after selection. Finally, 65 received mAb therapy. All treated patients survived. However, 2/65 developed adverse events (allergic reaction and atrial fibrillation, respectively) and 6/65 needed hospitalization. By performing univariate logistic regression analysis, diabetes was the only risk factor for hospitalization after mAb administration [aOR = 9.34, 95%CI = 1.31–66.49, $p$= .026]. Importantly, subjects who worsened awaiting mAb were more frequently obese (OR = 16.66, 95% CI = 1.80–153.9, $p$= .013) and received home corticosteroid therapy for COVID-19 (OR = 14.11, 95%CI = 1.53–129.6, $p$= .019). Establishing a network among GPs and COVID units could be an effective strategy to provide mAb treatment to patients with early SARS-CoV-2 infection to reduce hospitalizations and pressure on healthcare systems.

**KEYWORDS**

SARS-CoV-2; COVID-19; Bamlanivimab; Etesevimab; Outpatients; Public Health

## Introduction

The Coronavirus Disease-19 (COVID-19) has significantly challenged healthcare systems worldwide; during the pandemic, rearrangement of healthcare services was necessary to admit and treat a huge number of subjects with severe clinical manifestations of SARS-CoV-2 infection, mainly frailer subjects, as elderly [1] oncologic patients [2] or immunocompromised, who are generally exposed to a more severe form of infection [3]. In up to 20% of cases, Intensive Care Unit (ICU) admission, due to severe lung failure, was needed, and predictors of severity have been intensively investigated [4–8].

Consequently, COVID-19 pandemic had a huge financial and organizational burden on Public Health Systems, also jeopardizing the emergency department and inpatient routine activity [9,10]. In this critical setting, where hospitals are overwhelmed by pandemic waves, introduction of novel pharmacological approaches aimed at preventing progression from early phase of SARS-CoV -2 infection to severe, life-threatening manifestations appeared pivotal. To this issue, early administration of specific monoclonal antibodies (mAb) showed promising results [11–14], limiting the number of subjects requiring hospitalization, and in turn, reducing mortality.

However, the administration of anti-SARS-CoV-2 mAb within a few days from the diagnosis of infection requires the implementation of an accurate linkage between General Practitioners (GPs) and COVID-19 Unit in order to guarantee the appropriate and early

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access to treatment. Accordingly, the institution of an outpatient setting for the administration of mAb may be a useful strategy to reach this goal.

The aim of this study was to describe the model of cooperation established at our Institution between GPs and COVID-19 Units for early administration of Bamlanivimab (LY-CoV555 aka LY3819253) and Etesevimab (LY-CoV016, aka JS016, aka LY3832479) for the treatment of SARS-CoV-2 infection in an outpatient service. Furthermore, we describe clinical characteristics and outcomes of subjects admitted to our COVID-19 outpatient.

## Methods

### *Study design*

In March 2021, Apulian Regional Health Department authorized Monoclonal Antibodies administration. Consequently, an official communication was sent by the State Medical Board of our Region to all (GPs) to inform them of the availability of mAb treatment as outpatient service in 22 Apulian referral Hospitals, including our Center.

The same communication was sent to Special Units for Continuity of Care, a group of physicians who daily assisted COVID-19 patients at home.

Accordingly, GPs and Special Units for Continuity of Care were instructed to select COVID-19 patients eligible to mAb administration in line with the following manufacturer and AIFA (Agenzia Italiana del Farmaco) criteria:

i) not hospitalized;

ii) COVID-19 confirmed by RT-PCR testing on throat/nasopharyngeal swab;

iii) at least one mild-moderate COVID-19 symptom (including fever, cough, dyspnea, fatigue, hypoxia, ageusia, anosmia, tachypnea, sore throat, nausea, vomiting, diarrhea, myalgia, arthralgia, confusion, headache, conjunctivitis) within the last 10 days;

iv) at least one risk factor including: Body Mass Index (BMI) >35 kg/m2, chronic hemodialysis, decompensated diabetes mellitus, primary or secondary immunosuppression, age ≥ 65 years (with at least one of the previous conditions), age ≥ 55 years (with chronic lung diseases and/or cerebrovascular diseases);

v) not requiring oxygen therapy to achieve a room air saturation (SpO2) ≥ 94%; or (for patients already treated with oxygen due to other medical conditions) not requiring an increased oxygen flow if compared to baseline to achieve a room air saturation (SpO2) ≥ 94%.

Therefore, a detailed description of clinical characteristics of patients and symptoms was submitted by GPs through a dedicated email address to a COVID-19 multidisciplinary team that verified the eligibility. If suitability was confirmed, the patient was admitted to our COVID-19 outpatient service within the next 48–72 hours.

The day of Mab administration, a dedicated ambulance transported the patients to our hospital, observing isolation rules for COVID-19; the same vehicle transported the patients at home after administration. The flowchart of mAb administration network is resumed in Figure 1.

### *Treatment*

On the day of administration, all patients underwent a full medical evaluation to check and confirm eligibility. If confirmed according to the abovementioned inclusion criteria, a single administration of Bamlanivimab 700 mg + Etesevimab 1400 mg was performed. Thereafter, the patient remained one hour under medical monitoring before discharge.

Conversely, patients no more eligible due to clinical worsening were either hospitalized or discharged for home treatment, without mAb administration.

### *Follow up*

Every patient was interviewed after 7, 14, 28 days for clinical follow-up.

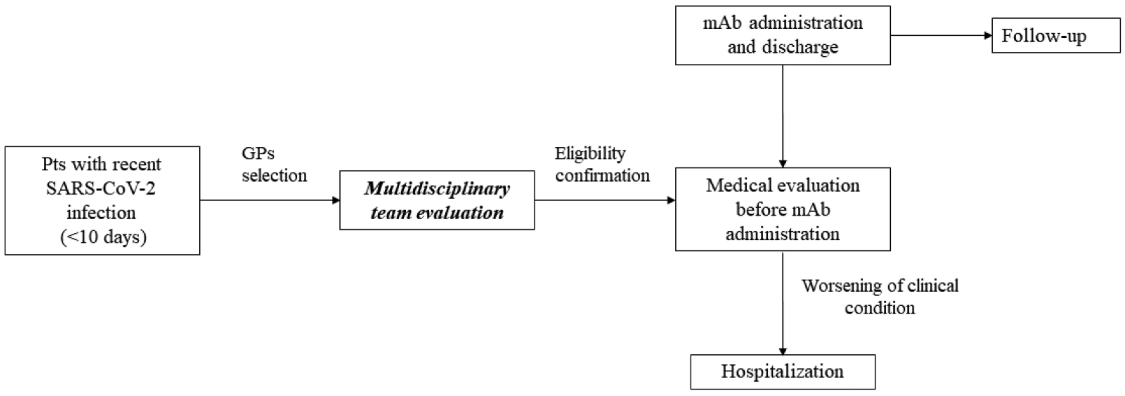


Figure 1. Diagram of mAb administration network.

### Statistical analysis

Study outcomes were recovery, hospitalization, or hospitalization in Intensive Care Unit (ICU) within 28 days after mAb administration.

Descriptive statistics were produced for demographic and clinical features of patients. Mean and standard deviations (SD) were obtained for normally distributed variables, and median and interquartile range (q1-q3) for non-normally distributed variables, numbers, and percentages for categorical variables.

The distribution between hospitalized or not hospitalized patients after mAb administration was analyzed by univariable parametric or nonparametric tests, with Kruskal Wallis or Mann Whitney U Test (where appropriate) for continuous variables, and with Pearson's $\chi^2$ test (Fisher's exact test where appropriate) for categorical variables, according to data distribution.

To assess predictors of hospitalization (or hospitalization without mAb administration) a univariate logistic regression model was performed; odds ratio (OR), adjusted odds ratio (aOR), 95% confidence intervals (CI) and p value (p) were produced accordingly.

In all cases, a p value <0.05 was considered statistically significant. Statistical analysis was performed using STATA 'Special Edition' version 16.1 (STATA Corp., Lakeway Drive, Texas 77,845, USA).

## Results

### Patient distribution

Overall, from March 29th to June 4th, 2021, 106 patients with confirmed COVID-19 were identified by GPs as susceptible to treatment with mAb. Of them, 26 were considered not eligible by COVID-19 Multidisciplinary Team and thus excluded; in detail, in five cases the exclusion was due to clinical worsening and hospitalization in another center, while 11 patients were excluded because of lack of risk factors for disease progression and the mAb administration was not possible according to AIFA criteria; finally, 10 subjects were excluded because the symptom onset was beyond 10 days Nine additional patients refused treatment after the eligibility confirmation; these patients were lost to follow up, and no data about their COVID-19 outcome are available. Of the 71 remaining subjects, six were not treated with mAb because of worsening of symptoms soon after selection, while waiting for mAb administration; among the latter, one patient died due to COVID-19. Finally, 65 received mAb therapy (Figure 2).

In Table 1, the general characteristics of patients at time of mAb administration are described.

### Outcomes and predictors of hospitalization after mAb administration

Among the 65 patients who received treatment with mAb, 59 patients (91%) fully recovered, while the remaining six patients (9%) were hospitalized within 7 days from mAb administration, including two patients (3%) who needed ICU admission.

In Table 2 clinical features, need of ICU stay and outcome of subjects hospitalized after mAb administration or without treatment are described.

In a univariate logistic regression analysis (Table 3) of the possible risk factors for hospitalization, only diabetes was significantly associated with the risk of hospitalization after mAb [OR = 11.11, 95%CI = 1.76–69.94, $p$= .010). This association was confirmed after adjusting the analysis for age and sex (aOR = 9.43, 95% CI = 1.31–66.49, $p$= .026).

A stepwise multivariable regression was not performed due to the low sample size.

Notably, all patients who underwent mAb survived to COVID-19, independently from the need of hospitalization. However, one patient was still hospitalized, needing O2 therapy 30 days after mAb therapy (ES13569).

Furthermore, clinical symptoms among those who were discharged after mAb administration were investigated: 29% of subjects were still symptomatic at day 7, 12% at day 14, and only 3% at day 28. Remarkably, median time from symptoms onset to mAb administration was five days in both groups, ranging from three to nine days.

### Adverse events

Adverse events after mAb administration occurred in two patients. In one case, drug infusion was followed by the onset of diffuse erythematous itchy rash; of note, the patient had a medical history of allergy to drugs (rosuvastatin, carvedilol). The adverse event was fully managed with antihistaminic medication and the patient was safely discharged, with no further reactions. Interestingly, in the other case, the adverse event was an episode of atrial fibrillation no previous episodes of cardiac arrhythmia were known in the medical history of this patient. The patient was hospitalized in the Internal Medicine COVID unit, with a confirmed diagnosis of atrial fibrillation. Despite mAb administration, he developed severe respiratory failure, requiring ICU admission and mechanical noninvasive ventilation. The patient recovered and was discharged.

### Characteristics of the patients who did not receive mAb due to clinical worsening after eligibility

Finally, in Table 4 the general characteristics of the six subjects who were hospitalized due to worsening of their clinical condition within 48–72 h after eligibility

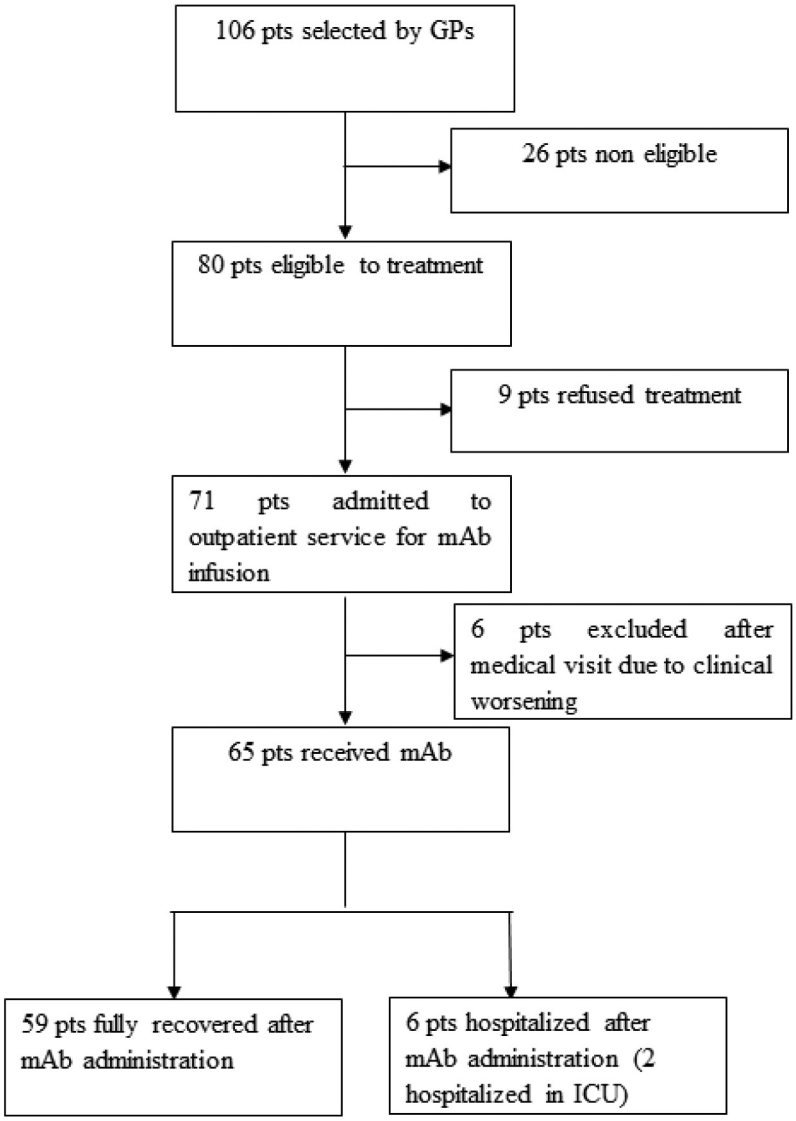


Figure 2. Diagram of the study enrollment.

confirmation are reported. In a univariate logistic regression analysis, obesity (OR = 16.66, 95%CI = 1.80–153.9, $p$= .013) and home corticosteroid therapy prescribed for COVID-19 (OR = 14.11, 95%CI = 1.53–129.6, $p$= .019) were significantly associated with hospitalization. However, a stepwise multivariate logistic regression to identify possible independent associations was not performed due to the low sample size.

## Discussion

The development of strategies for reducing COVID-19 associated hospitalization and mortality is imperative to abate pressure on healthcare systems. Accordingly, an interesting approach could be represented by the administration of mAb to patients affected by early COVID-19, to decrease the risk of disease progression and, consequently, to reduce hospitalization. To date, in our Country, the overall hospital admission rate for COVID-19 was 9%, including symptomatic and asymptomatic subjects [15].

In this setting, the establishment of a network between GPs and COVID-19 units is crucial for the identification of patients suffering from mild-moderate disease, who could take advantage of early administration of mAb. Hence, the creation of a Multidisciplinary team and the institution of dedicated outpatients nearby COVID-19 hospitals could be an effective strategy. Notwithstanding, with our model at least 24–48 hours from diagnosis of SARS-CoV-2 infection were needed to implement this process. Since early administration of these antibodies, possibly within the first three days from symptoms onset, is a major issue for efficacy of therapy, the creation of automatized systems of alert could be considered a possible solution to improve our model

**Table 1.** Main features of 65 COVID-19 patients treated with mAb.

| | Overall (n = 65) | Recovered (n = 59) | Hospitalized (n = 6) | p value |
|---|---|---|---|---|
| Gender (male), n (%) | 40 (62) | 35 (59) | 5 (83) | .249 |
| Age, median (q1-q3) | 67 (54–73) | 64 (53–73) | 73 (69–85) | .069 |
| Obesity (BMI > 35), n (%) | 15 [23] | 14 [24] | 1 [17] | .696 |
| Diabetes, n (%) | 13 [20] | 9 [15] | 4 (67) | .003 |
| Chronic Kidney Diseases, n (%) | 5 [8] | 4 [7] | 1 [17] | .387 |
| Hypertension, n (%) | 38 (58) | 33 (56) | 5 (83) | .194 |
| COPD, n (%) | 15 [23] | 14 [24] | 1 [17] | .696 |
| Any Cancer, n (%) | 13 [20] | 11 [19] | 2 (33) | .391 |
| Any Immunosuppression, n (%) | 5 [8] | 5 [8] | 0 | .458 |
| Home Heparin Therapy, n (%) | 13 [20] | 11 [19] | 2 (33) | .391 |
| Home Corticosteroid Therapy, n (%) | 17 [26] | 15 [25] | 2 (33) | .674 |
| Home Oxygen Therapy, n (%) | 2 [3] | 2 [3] | 0 | .647 |
| Days from symptoms onset to mAb administration, median (q1-q3) | 5 [4–8] | 5 [4–8] | 5 [4–9] | .918 |

**Legend**: mAb = monoclonal antibody; q1-q3 = interquartile range; BMI = body mass index; COPD = chronic obstructive pulmonary disease.

**Table 2.** Clinical characteristics of patients hospitalized after mAb administration.

| Patient ID | Gender / Age (years) | Comorbidities | Days from symptoms onset to mAb administration | Symptoms | ICU admission | Death |
|---|---|---|---|---|---|---|
| AV16252 | Male/69 | DTII – Hypertension – COPD | 5 | Fever (< 38°C), Cough, Dyspnea | Yes | No |
| CO30948 | Male/72 | DTII – ex smoker | 5 | Fever (<38°C), Cough | No | No |
| DM25835 | Male/85 | Hypertension – Chronic Heart Failure | 9 | Fever (>38°C), Fatigue, Anosmia, Dysgeusia, Myalgia | No | No |
| ES13569 | Male/51 | Hypertension – Chronic Lymphocytic Leukemia | 9 | Cough, Fatigue, Anosmia, Dysgeusia, Myalgia | Yes | No |
| RM27428 | Female/ 94 | DTII-Chronic Renal Failure-Hypertension | 3 | Fever | No | No |
| FM8846 | Male/74 | Obesity – DTII – Hypertension – Prostatic Cancer | 4 | Fever (<38°C), Cough | No | No |

**Legend**: mAb = monoclonal antibody; ICU = intensive care unit; DTII = diabetes type II; BMI = body mass index; COPD = chronic obstructive pulmonary disease

**Table 3.** Predictors of hospitalization after mAb administration.

| | OR | 95%CI | p value | aOR | 95%CI | p value |
|---|---|---|---|---|---|---|
| Gender (male) | 3.42 | 0.37–31.22 | .274 | 3.10 | 0.20–47.75 | .417 |
| Age per 1 year increase | 1.08 | 0.99–1.18 | .051 | 1.08 | 0.99–1.18 | .075 |
| Obesity (BMI > 35) | 0.64 | 0.06–5.97 | .698 | \ | | |
| Diabetes | 11.11 | 1.76–69.94 | .010 | 9.34 | 1.31–66.49 | .026 |
| Chronic Kidney Diseases | 2.75 | 0.25–29.56 | .404 | \ | | |
| Hypertension | 3.93 | 0.43–35.82 | .224 | \ | | |
| COPD | 0.64 | 0.06–5.97 | .698 | \ | | |
| Any Cancer | 2.18 | 0.35–13.45 | .401 | \ | | |
| Any Immunosuppression | \ | | | \ | | |
| Home Heparin Therapy | 2.18 | 0.35–13.45 | .401 | \ | | |
| Home Corticosteroid Therapy | 1.46 | 0.24–8.83 | .676 | \ | | |
| Home Oxygen Therapy | \ | | | \ | | |
| Median (q1-q3) days from symptoms onset to mAb administration | 1.02 | 0.73–1.42 | .898 | \ | | |

**Legend**: mAb = monoclonal antibody; BMI = body mass index; COPD = chronic obstructive pulmonary disease.
* = no cases among patients who met the outcome of interest.
** = all males.

reducing time from diagnosis to treatment. This window of time could be further shortened at first by anticipating Multidisciplinary team evaluation at time of molecular test execution, to confirm eligibility when positive results are obtained. Second, given the feasibility of mAb, a domiciliary administration under supervision of qualified medical team could be considered a possible strategy to promote early administration of therapy. Future studies exploring this topic are warranted. Although the sample size and the study design of this work are not appropriate to draw conclusions regarding clinical factors associated with negative outcomes of mAb administration, in this series, more than 90% of patients did not require inpatient care after mAb therapy (including only symptomatic patients, according to inclusion criteria). This is

Table 4. Patients admitted to hospital without mAb administration.

| General characteristics of the patients who not received mAb due to worsening of clinical picture (n. 6) | |
|---|---|
| Gender (male), n (%) | 4 (67) |
| Median (q1-q3) Age, years | 71 (67–77) |
| Obesity (BMI > 35), n (%) | 5 (83) |
| Diabetes, n (%) | 1 [17] |
| Chronic Kidney Diseases, n (%) | 0 |
| Hypertension, n (%) | 2 (33) |
| COPD, n (%) | 1 [17] |
| Any Cancer, n (%) | 1 [17] |
| Any Immunosuppression, n (%) | 1 [17] |
| Home Heparin Therapy, n (%) | 2 (33) |
| Home Corticosteroid Therapy, n (%) | 5 (83) |
| Home Oxygen Therapy, n (%) | 0 |
| Median (q1-q3) days from symptoms onset to mAb administration | 6 [5–10] |

**Legend**: mAb = monoclonal antibody; BMI = body mass index; COPD = chronic obstructive pulmonary disease.

in line with clinical trials, and several 'real life' experiences now available in literature [12–14]; 16–19] showing the efficacy of mAb in reducing risk of hospitalization; however, possible risk factors for mAb treatment failure need to be investigated.

In our series, patients hospitalized despite mAb administration were more frequently affected by diabetes, if compared to recovered subjects. In fact, diabetes is a predictor of severe COVID-19, since hyperglycemia and SARS-CoV-2 both cause multiple dysfunctions of endothelium [20–25].

We documented a few cases of subjects who rapidly progressed to lung failure while waiting for mAb administration. Among patients included in this group, the majority (83%) received home corticosteroid therapy; although the sample size of our work is too limited to indicate an association, these data are in line with the evidence of a harmful effect of early corticosteroids administration in hospitalized non-hypoxemic COVID-19 patients [26].

Whether shorter time interval from clinical onset to mAb infusion may be more effective in patients with these risk factors remains to be assessed. In our experience, no differences in median time from symptoms onset to mAb administration were observed between hospitalized and recovered patients. Of note, in no case it was possible to provide the infusion during the first three days from symptoms onset due to time needed from COVID-19 confirmation on nasopharyngeal swab to outpatient evaluation and mAb administration.

Adverse events were also recorded in this series: allergic reaction in a subject with a positive clinical history for allergy, and one case of unexpected atrial fibrillation, occurring soon after mAb infusion.

Despite the subsequent hospitalization, the atrial fibrillation persisted, and the patient was discharged with oral anticoagulants.

This study has limitations: first, the sample size hampered multivariate regression analysis to explore the strength of associations. Moreover, the lack of information on the biochemical and immunological status of patients (including serology for SARS-CoV-2, total lymphocyte count, cytokines levels, etc.) might provide additional information on specific risk factors for COVID-19 progression, thus leading clinicians in selecting patients for mAb therapy. Finally, recently emerging variants of SARS-CoV-2 were not analyzed in this study. Collectively, wondering what else we do know about who might benefit from monoclonal antibody therapies and maybe how early can treatment start, the BLAZE-2 study, a phase 3 randomized, double-blind, placebo-controlled trial tested Bamlanivimab in people who were at high risk of exposure. The mAb over placebo in contacts with people who had COVID-19, gained an 80% reduction in risk of COVID-19 if they give it to people who were at risk for exposure [27].

Of note, our real-life experience corroborates these findings; based on our results and the available evidence, it is therefore tempting to speculate that in the outpatient setting, treatment based on mAb could further decrease pressure on health care, reducing hospitalization and mortality of elderly and frail subject.

## Conclusions

According to our experience, the institution of an outpatient service for admission of patients with mild-moderate COVID-19 who could benefit from early mAb administration is a feasible and safe strategy to prevent disease progression and consequently decrease pressure on healthcare system. This model could be improved reducing time from diagnosis to treatment, in order to take best benefit from this treatment.

## Declarations

## Disclosure statement

No author has any conflict of interest to declare.

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## Availability of Data and Material

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

## Author contribution

**BDF, DL, AS**: conception and design of the work, data interpretation, initial draft of the work; **BDF**: formal analysis; **SAG, CS, BE, SC, CM, MM**: data collection, interpretation of the data for the work, revision of the manuscript; **RO, CGE, PVO, VA, DAM, DEA, MG, AM**: critical revision of the manuscript, data interpretation; **All Authors**: final approval of the manuscript.

## Ethics

The research did not require a formal approval from the ethics committee according to the Italian law since it was performed as an observational retrospective study in the context of normal clinical routines (art.1, leg. decree 211/2003). However, the study was conducted in accordance with the Declaration of Helsinki and national and institutional standards. In any case, data were previously anonymized, according to the requirements set by Italian Data protection Code (leg. Decree 196/2003).

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