

# Exploratory data on the clinical efficacy of monoclonal antibodies against SARS-CoV-2 Omicron variant of concern

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## Abstract

**Background:** Recent in-vitro data have shown that the activity of monoclonal antibodies (mAbs) targeting severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) varies according to the variant of concern (VOC). No studies have compared the clinical efficacy of different mAbs against Omicron VOC.

**Methods:** The MANTICO trial is a non-inferiority randomised controlled trial comparing the clinical efficacy of early treatments with bamlanivimab/etesevimab, casirivimab/imdevimab, and sotrovimab in outpatients aged 50 or older with mild-to-moderate SARS-CoV-2 infection. As the patient enrolment was interrupted for possible futility after the onset of the Omicron wave, the analysis was performed according to the SARS-CoV-2 VOC. The primary outcome was coronavirus disease 2019 (COVID-19) progression (hospitalisation, need of supplemental oxygen therapy, or death through day 14). Secondary outcomes included the time to symptom resolution, assessed using the product-limit method. Kaplan-Meier estimator and Cox proportional hazard model were used to assess the association with predictors. Log rank test was used to compare survival functions.

**Results:** Overall, 319 patients were included. Among 141 patients infected with Delta, no COVID-19 progression was recorded, and the time to symptom resolution did not differ significantly between treatment groups (Log-rank Chi-square 0.22,  $p$  0.90). Among 170 patients infected with Omicron (80.6% BA.1 and 19.4% BA.1.1), two COVID-19 progressions were recorded, both in the bamlanivimab/etesevimab group, and the median time to symptom resolution was 5 days shorter in the sotrovimab group compared with the bamlanivimab/etesevimab and casirivimab/imdevimab groups (HR 0.53 and HR 0.45, 95% CI 0.36–0.77 and 95% CI 0.30–0.67,  $p$ <0.01).

**Conclusions:** Our data suggest that, among adult outpatients with mild-to-moderate SARS-CoV-2 infection due to Omicron BA.1 and BA.1.1, early treatment with sotrovimab reduces the time to

recovery compared with casirivimab/imdevimab and bamlanivimab/etesevimab. In the same population, early treatment with casirivimab/imdevimab may maintain a role in preventing COVID-19 progression. The generalisability of trial results is substantially limited by the early discontinuation of the trial and firm conclusions cannot be drawn.

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### Editor's evaluation

This paper will be of broad interest to clinicians and scientists in the area, providing clinical trial data on how the efficacy of monoclonal antibodies targeting SARS-CoV-2 varies according to the variant of concern. The clinical outcome data were consistent with previously reported in vitro data, which are being used to inform the clinical use of monoclonal antibodies.

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## Introduction

Coronavirus disease 2019 (COVID-19), which is caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread globally and poses a major challenge to healthcare systems worldwide. A high incidence of hospitalisation and death due to COVID-19 has been reported among older patients and those with certain coexisting conditions, such as obesity, diabetes mellitus, cardiovascular disease, chronic obstructive pulmonary disease, and chronic kidney disease (*Petrilli et al., 2020; Huang et al., 2020*). The implementation of mass vaccination campaigns has markedly reduced the healthcare burden related to COVID-19. Nevertheless, SARS-CoV-2 vaccination rates differ considerably across countries, and growing evidence suggests a reduced efficacy of vaccines against new viral variants of concern (VOC) (*Cao et al., 2022; Planas et al., 2022; Dejnirattisai et al., 2022; Andrews et al., 2022*).

Therapeutic agents directed against SARS-CoV-2 have been developed to prevent the COVID-19 progression, especially addressing high-risk groups of patients. Neutralising monoclonal antibodies (mAbs) target the spike protein of SARS-CoV-2 that mediates viral entry into host cells (*Benton et al., 2020*). Based on the results of randomised placebo-controlled trials showing the efficacy in preventing COVID-19 progression, drug regulatory authorities, such as the US Food and Drug Administration (FDA), the European Medicines Agency, and the Italian Medicines Agency (AIFA), had granted the emergency use authorisation status for bamlanivimab 700 mg combined with etesevimab 1400 mg, casirivimab 600 mg combined with imdevimab 600 mg, and sotrovimab 500 mg to treat early COVID-19 in patients at high risk of progression (*Dougan et al., 2021; Weinreich et al., 2021; Gupta et al., 2021*).

To date, two randomised trials have compared the clinical outcomes of these mAbs in preventing severe COVID-19, showing similar effectiveness of bamlanivimab/etesevimab vs casirivimab/imdevimab in patients infected with the alpha VOC (*McCreary et al., 2022*) and casirivimab/imdevimab vs sotrovimab in patients infected with the Delta VOC, respectively (*Huang et al., 2022*).

This paper reports the results of the MANTICO trial, a non-inferiority randomised controlled trial comparing the clinical efficacy of routinely-used mAbs in a real-life setting of outpatients aged 50 or older with early mild-to-moderate COVID-19. The patient enrolment started in December 2021 and was interrupted after the publication of in-vitro evidence that two treatments under investigation (bamlanivimab/etesevimab and casirivimab/imdevimab) were not effective against the new emerging viral Omicron VOC (*Cao et al., 2022; Planas et al., 2022; Dejnirattisai et al., 2022*). The analysis is therefore restricted to 319 randomised patients, who were enrolled up to the interruption for possible futility, and was performed according to the SARS-CoV-2 VOC (Delta and Omicron).

## Methods

### Trial design

The trial was designed as a pragmatic, randomised, single-blind, non-inferiority, parallel group, multi-centre, and controlled trial. Eligible subjects were outpatients aged 50 years or older, presenting at three trial sites in Italy (Verona, Padua, and Udine) with a positive test (either direct antigen or nucleic acid SARS-CoV-2) and mild-to-moderate COVID-19 symptoms within 4 days of the onset (**COVID-19 Treatment Guidelines Panel, 2019**). COVID-19 symptoms included cough, nasal congestion, sore throat, feeling hot or feverish, myalgia, fatigue, headache, anosmia/ageusia, nausea, vomiting, and/or diarrhoea (**U.S. Department of Health and Human Services Food and Drug Administration, 2022a**). Predefined exclusion criteria included a peripheral oxygen saturation level of 93% or less on room air, a respiratory rate of 30 or more breaths per minute, a heart rate of 125 or more beats per minute, and previous COVID-19 treatments with mAbs.

Sample-size estimation was based on the only available double-blind, randomised, placebo-controlled trial assessing the clinical efficacy of casirivimab/imdevimab (reference standard) in preventing COVID-19 progression in adult outpatients with early mild-to-moderate SARS-CoV-2 (**Weinreich et al., 2021**). This study showed that the hospitalisation related to COVID-19 or all-cause mortality occurred in 7 of 736 patients in the casirivimab/imdevimab 1200 mg group (1.0%) and in 24 of 748 patients in the placebo group (3.2%) (relative risk reduction, 70.4%; **Weinreich et al., 2021**). Therefore, 5% COVID-19 progression was assumed in the casirivimab/imdevimab group. 5% non-inferiority margin was considered clinically relevant by the expert opinion of infectious disease and clinical trial specialists involved in the protocol development, taking into account both the estimates of COVID-19 progression in the study population in the absence of early treatment with mAbs (20%; **Istituto Superiore di Sanità, 2021**) and the efficacy of the reference standard (**Weinreich et al., 2021**). Using these parameters, 420 patients per group were needed to achieve 90% power with a one-sided  $\alpha$  level of 0.025, allowing for 5% dropout.

Participants were randomly assigned in a 1:1:1 ratio to receive a single intravenous infusion over a period of 1 hr, consisting of a combination of 700 mg of bamlanivimab and 1400 mg of etesevimab or 500 mg of sotrovimab or a combination of 600 mg of casirivimab and 600 mg of imdevimab. The study drugs were diluted to 250 mL with normal saline. Patients were masked to treatment group assignment. Randomisation was computer generated in permuted blocks with a stratification based on site. The allocated drug was revealed to the investigator using an online randomisation module within the REDCap data management system (**Harris et al., 2009**).

The trial was conducted in accordance with the principles of the Declaration of Helsinki, the international ethical guidelines of the Council for International Organisations of Medical Sciences, the International Council for Harmonisation Good Clinical Practice guidelines, and applicable laws and regulations. All patients or their legally authorised representatives provided written informed consent. This study is registered with ClinicalTrials.gov, NCT05205759.

### Outcomes

The composite primary outcome was the COVID-19 progression, defined as hospitalisation, need of supplemental oxygen therapy, or death from any cause through day 14. The presence of any of the three variables qualified the presence of the COVID-19 progression. Prespecified secondary outcomes were emergency department visits through day 28, all-cause mortality through day 28, duration of supplemental oxygen therapy, rate and duration of non-invasive ventilation and mechanical ventilation, and time to sustained patient-reported symptom resolution, which was defined as the absence of any symptom related to COVID-19 for at least 24 hr (**U.S. Department of Health and Human Services Food and Drug Administration, 2022b**).

### Predictors

The main predictor was the treatment regimen randomised at enrolment (bamlanivimab/etesevimab, casirivimab/imdevimab, and sotrovimab). All patients were assessed at baseline for the following predictors to be tested for association with the time to symptom resolution: age, sex, BMI, relevant comorbidities (diabetes for which medication was warranted, cardiovascular disease [hypertension, coronary artery disease, and congestive heart failure], chronic kidney disease, chronic liver disease, chronic pulmonary disease, active cancer, transplant, and other immunocompromising conditions),

SARS-CoV-2 serological status (anti-spike IgG), and SARS-CoV-2 vaccination status. The SARS-CoV-2 serological status was categorised as serum antibody-negative (if test results were negative), serum antibody-positive (if test results were positive), or other (inconclusive or unknown results). The SARS-CoV-2 vaccination status was categorised as not vaccinated, partial or complete primary COVID-19 vaccination series administered more than 120 days before the enrolment, complete primary COVID-19 vaccination series administered 120 days or less before the enrolment, and booster vaccination (Andrews *et al.*, 2022). These categories were further collapsed as not vaccinated and partial or complete primary COVID-19 vaccination series administered more than 120 days before the enrolment vs complete primary COVID-19 vaccination series administered 120 days or less before the enrolment and booster vaccination.

## Procedures and tools

Outpatient visits were scheduled at baseline, 14±3 days and 30±3 days after the randomisation. Patients were considered lost to follow-up if they repeatedly did not participate in scheduled visits and could not be contacted by the investigators. Medical evaluation, vital signs recording, and laboratory tests were performed at each visit. If patients missed the visits, they were called by telephone to assess clinical conditions.

The SARS-CoV-2 serological status was assessed using LIAISON SARS-CoV-2 TrimericS IgG assay (DiaSorin), an indirect chemiluminescence immunoassay detecting IgG against the spike viral protein in its native trimeric conformation, which includes receptor-binding domain and N-terminal domain sites from the three subunit S1. According to the manufacturer's instructions, binding antibody units (BAU)/mL ≥33.8 were considered positive for anti-trimeric spike protein specific IgG antibodies.

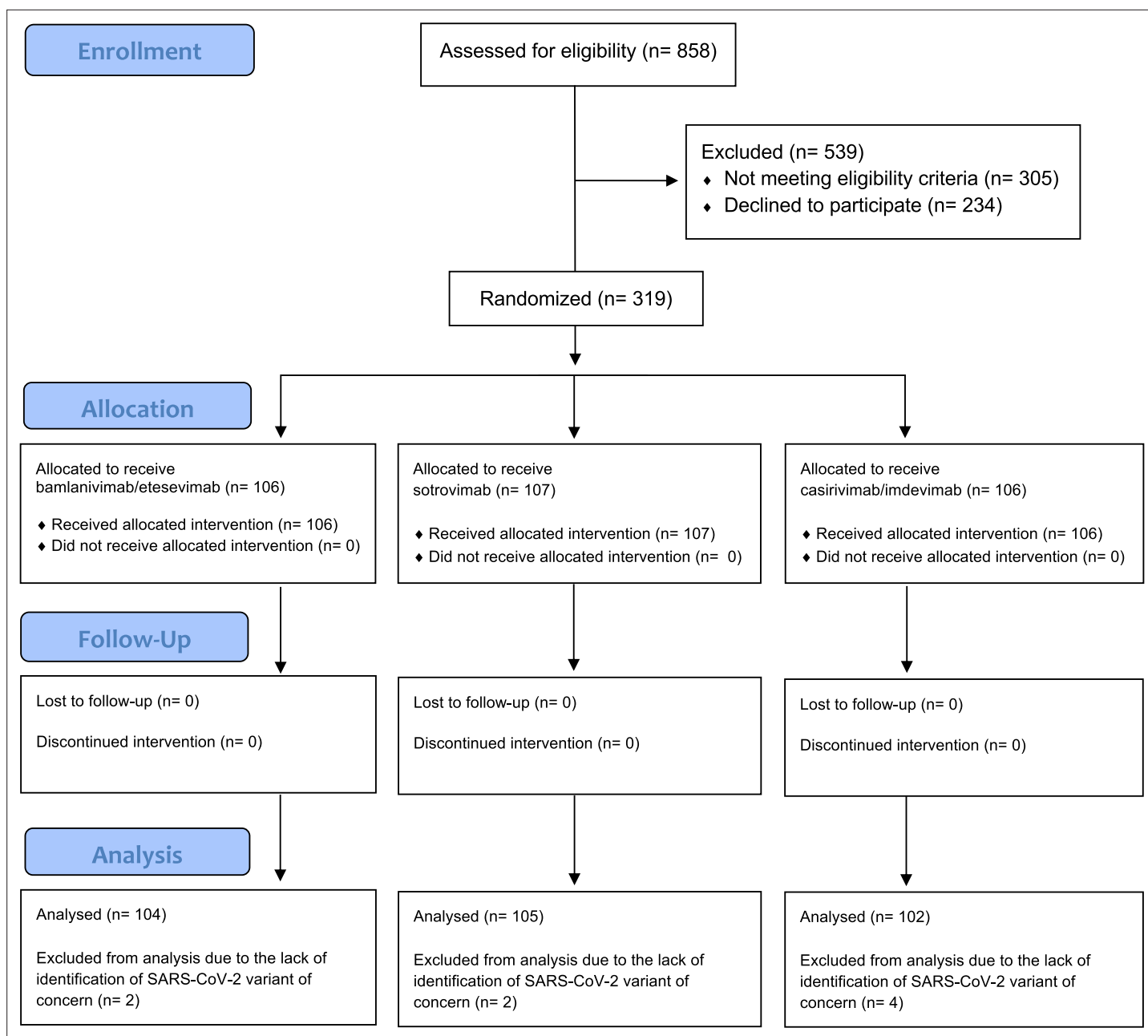
Nasopharyngeal swabs were processed using MagMAX Viral/Pathogen Nucleic Acid Isolation Kit and KingFisher automated extraction system (ThermoFisher Scientific). Viral RNA was detected using COVIDSeq amplicon-based Next Generation Sequencing Test combined with COVIDSeq V4 Primer Pool (Illumina, Inc). Sequencing libraries were synthesised using automated MicroLab STAR liquid handler (Hamilton Company). Pooled samples were quantified using Qubit 2.0 fluorometer (Invitrogen Inc). Next generation sequencing was performed in 150 PE mode on NextSeq 550 Sequencing System (Illumina, Inc) or MiSeq System (Illumina, Inc) using the NextSeq 500/550 Mid Output Kit v2.5 or the MiSeq Reagent Kit v3, respectively.

## Statistical analysis

For continuous variables, mean and SD or median and IQR were calculated. For categorical variables, count and percentages were used. All outcome variables estimates were reported with 95% CI (95% CI). Wilcoxon–Mann–Whitney test was used to compare independent groups. The association between categorical variables was assessed using the Fisher's test. The product-limit method (Kaplan and Meier) was used to describe the time to symptom resolution. Kaplan-Meier estimator and Cox proportional hazard model were used to assess the bivariate association of independent variables with the time-dependent outcome. Kaplan-Meier curves were plotted to depict the association between each predictor and symptom persistence, and the Log-rank test was used to compare survival functions. Predictors associated with the time to symptom resolution with a probability <0.05 were considered significant. A two-sided test of less than 0.05 was considered statistically significant in all analyses. All statistical analyses were performed with the use of Stata Version 17.0 (College Station, TX: StataCorp LP).

## Results

The first patient was enrolled on 9 December 2021. Overall, 319 patients underwent randomisation by 20 January 2022 and were assigned to receive bamlanivimab/etesevimab (106 patients), sotrovimab (107 patients), or casirivimab/imdevimab (106 patients). No patients reported previous SARS-CoV-2 infections. No patients were lost to follow-up. VOC data were available for 311 patients: 170 (53.3%) were infected with Omicron and 141 (44.2%) with Delta. Eight (2.5%) patients were excluded from this analysis due to the lack of SARS-CoV-2 VOC identification. **Figure 1** shows the flow diagram of the progress through the trial phases. Baseline characteristics of the population by type of SARS-CoV-2 VOC are reported in **Table 1**.



**Figure 1.** Flow diagram of the progress through the phases of the MANTICO trial according to the CONSORT statement.

Comparing symptoms at enrolment by VOC, anosmia/ageusia ( $p < 0.001$ ), nausea/vomiting ( $p < 0.001$ ), and feeling feverish or hot ( $p < 0.01$ ) were significantly more frequent among patients infected with Delta, while sore throat ( $p < 0.001$ ) was significantly more frequent among patients infected with Omicron. Serological positivity to anti-SARS-CoV-2 antibodies ( $p < 0.001$ ) and complete primary COVID-19 vaccination series within 120 days of the enrolment or booster vaccination ( $p < 0.001$ ) were significantly more frequent among patients infected with Omicron. **Table 2** shows the bivariate Cox regression of symptom resolution predictors by type of SARS-CoV-2 VOC. No predictors were associated with the time to symptom resolution in both SARS-CoV-2 VOC.

### Delta VOC

Baseline characteristics of 141 patients infected with Delta VOC by type of treatment are reported in **Table 3**. The main detected lineages were 34 AY.4 (24.1%), 33 AY.43 (23.4%), and 26 AY.122 (18.4%).

**Table 1.** Baseline characteristics of the overall study population by type of variant of concern.

Characteristic	Delta N=141	Omicron N=170	p value
Sex (male) – n (%)	69 (48.94)	101 (59.41)	0.068
Age – median (IQR) (range)	65.7 (15.4) (50–92)	64.5 (14.8) (50–90)	0.585
<b>Smoking status – n (%)</b>			
Smoker	8 (5.67)	24 (14.12)	<b>0.015</b>
Former smoker	32 (22.70)	28 (16.47)	0.194
Non-smoker	101 (71.63)	118 (69.41)	0.709
<b>BMI – n (%)</b>			
≤29	101 (71.63)	132 (77.65)	0.239
≥30	40 (28.37)	38 (22.35)	0.239
<b>SARS-CoV-2 serological status – n (%)</b>			
Antibody-positive	70 (49.65)	134 (78.82)	<b>&lt;0.001</b>
Antibody-negative	68 (48.23)	35 (20.59)	<b>&lt;0.001</b>
Other	3 (2.13)	1 (0.59)	
<b>Anti-SARS-CoV-2 vaccination status – n (%)</b>			
3 doses or 2 doses ≤120 days	23 (16.31)	66 (38.82)	<b>&lt;0.001</b>
1 or 2 doses ≥120 days or not vaccinated	113 (80.14)	99 (58.24)	<b>&lt;0.001</b>
Other	5 (3.55)	5 (2.94)	
<b>Comorbidities – n (%)</b>			
Diabetes	3 (2.13)	6 (3.53)	0.519
Cardiovascular disease	56 (39.72)	61 (35.88)	0.557
Chronic kidney disease	7 (4.96)	9 (5.29)	1.000
Chronic liver disease	3 (2.13)	12 (7.06)	0.061
Chronic pulmonary disease	16 (11.35)	33 (19.41)	0.061
Immunocompromising conditions	17 (12.06)	35 (20.59)	<b>0.048</b>
<b>Symptoms at enrolment – n (%)</b>			
Cough	96 (68.09)	118 (69.41)	0.807
Nasal congestion	69 (48.94)	69 (40.59)	0.169
Sore throat	32 (22.70)	69 (40.59)	<b>0.001</b>
Feeling hot or feverish	103 (73.05)	99 (58.24)	<b>0.008</b>
Myalgia	46 (32.62)	54 (31.76)	0.903
Fatigue	47 (33.33)	75 (44.12)	0.062
Headache	59 (41.84)	60 (35.29)	0.244
Anosmia/ageusia	39 (27.66)	4 (2.35)	<b>&lt;0.001</b>
Nausea/vomiting	28 (19.86)	11 (6.47)	<b>&lt;0.001</b>
Diarrhoea	15 (10.64)	12 (7.06)	0.314
<b>Serum C-reactive protein level – n</b>			
Mean (SD), mg/L	136 20.58 (29.00)	161 14.29 (21.72)	<b>0.022</b>

**Table 2.** Bivariate Cox regression of symptom resolution predictors by type of variant of concern.

Predictor	Delta		Omicron	
	HR (95% CI)	p value	HR (95% CI)	p value
Gender	0.80 (0.57–1.11)	0.182	0.84 (0.61–1.14)	0.257
Age	1.00 (0.98–1.02)	0.952	1.00 (0.98–1.01)	0.626
BMI	1.03 (0.72–1.50)	0.855	1.17 (0.82–1.68)	0.393
SARS-CoV-2 serological status	0.93 (0.67–1.31)	0.690	0.82 (0.57–1.20)	0.307
Anti-SARS-CoV-2 vaccination status	1.30 (0.83–2.04)	0.257	0.91 (0.66–1.24)	0.539
Diabetes	0.63 (0.34–1.18)	0.150	1.19 (0.76–1.88)	0.444
Cardiovascular disease	0.96 (0.69–1.35)	0.831	0.85 (0.62–1.17)	0.319
Chronic kidney disease	1.24 (0.58–2.66)	0.581	1.12 (0.57–2.21)	0.733
Chronic liver disease	2.42 (0.76–7.68)	0.135	1.33 (0.74–2.40)	0.341
Chronic pulmonary disease	0.78 (0.46–1.31)	0.346	0.98 (0.67–1.43)	0.902
Immunocompromising conditions	1.00 (0.60–1.66)	0.989	0.80 (0.55–1.17)	0.252

69 (48.9%) were male, median age was 65.7 years (IQR  $\pm$ 15.4), 115 (78.8%) had at least one comorbidity, 70 (49.6%) were serum antibody-positive at the enrolment, and 23 (16.3%) received complete primary COVID-19 vaccination series within 120 days of the enrolment or booster vaccination.

Primary and secondary outcomes of the study population infected with Delta VOC by type of treatment are reported in **Table 4** with the exclusion of time to sustained patient-reported symptom resolution. No COVID-19 progression was recorded in Delta infections. All-cause mortality through day 28 was the same as that through day 14. An emergency department visit without hospitalisation was observed once in one patient in the casirivimab/imdevimab group. This visit was deemed to be unrelated to COVID-19.

The median time to symptom resolution was 7 days (95% CI 6–13) in the bamlanivimab/etesevimab group, 10 days (95% CI 7–14) in the sotrovimab group, and 10 days (95% CI 7–15) in the casirivimab/imdevimab group, not differing significantly across the overall groups of treatment (Log-rank Chi-square 0.22,  $p$  0.895) and for each comparison between treatment groups, namely bamlanivimab/etesevimab with casirivimab/imdevimab (Log-rank Chi-square 0.08,  $p$  0.776), sotrovimab with casirivimab/imdevimab (Log-rank Chi-square 0.40,  $p$  0.527), and bamlanivimab/etesevimab with sotrovimab (Log-rank Chi-square 0.01,  $p$  0.92). **Figure 2A** shows the time to symptom resolution by type of treatment in the Delta study population. The Cox regression analysis confirmed the non-significantly different effects upon the time to symptom resolution between casirivimab/imdevimab (reference standard according to the original trial protocol) and both bamlanivimab/etesevimab and sotrovimab (HR 1.052 and HR 1.097, 95% CI 0.70–1.57 and 0.73–1.65,  $p$  0.805 and 0.657, respectively).

## Omicron VOC

Baseline characteristics of 170 patients infected with Omicron VOC by type of treatment are reported in **Table 5**. The detected lineages were 137 (80.6%) BA.1 and 33 (19.4%) BA.1.1. 101 (59.4%) were male, median age was 64.5 years (IQR  $\pm$ 14.8), 135 (79.4%) had at least one comorbidity, 134 (78.8%)

**Table 3.** Baseline characteristics of the study population infected with Delta by type of treatment.

Characteristic	Total N=141	Sotrovimab N=43	Bamlanivimab/ etesevimab N=48	Casirivimab/ imdevimab N=50
Sex (male) – n (%)	69 (48.94)	22 (51.16)	21 (43.75)	26 (52.00)
Age – median (IQR) (range)	65.7 (15.4) (50–92)	65.8 (16.4) (50–90)	68.6 (11.8) (50–92)	63.2 (12) (50–89)
<b>Smoking status – n (%)</b>				
Smoker	8 (5.67)	2 (4.65)	4 (8.33)	2 (4.00)
Former smoker	32 (22.70)	8 (18.60)	11 (22.92)	13 (26.00)
Non-smoker	101 (71.63)	33 (76.74)	33 (68.75)	35 (70.00)
<b>BMI – n (%)</b>				
≤29	101 (71.63)	29 (67.44)	36 (75.00)	36 (72.00)
≥30	40 (28.37)	14 (32.56)	12 (25.00)	14 (28.00)
<b>SARS-CoV-2 serological status – n (%)</b>				
Antibody-positive	70 (49.65)	20 (46.51)	29 (61.70)	21 (43.75)
Antibody-negative	68 (48.23)	23 (53.49)	18 (38.30)	27 (56.25)
Other	3 (2.13)	0	1 (2.08)	2 (4.00)
<b>Anti-SARS-CoV-2 vaccination status – n (%)</b>				
3 doses	16 (11.35)	6 (13.95)	3 (6.25)	7 (14.00)
2 doses ≤120 days	7 (4.96)	2 (4.65)	2 (4.17)	3 (6.00)
1 or 2 doses ≥120 days	54 (38.30)	14 (32.56)	26 (54.17)	14 (28.00)
Not vaccinated	59 (41.84)	19 (44.19)	15 (31.25)	25 (50.00)
Other	5 (3.55)	2 (4.65)	2 (4.17)	1 (2.00)
<b>Comorbidities – n (%)</b>				
Diabetes	3 (2.13)	0	2 (4.17)	1 (2.00)
Cardiovascular disease	56 (39.72)	18 (41.86)	20 (41.67)	18 (36.00)
Chronic kidney disease	7 (4.96)	1 (2.33)	2 (4.17)	4 (8.00)
Chronic liver disease	3 (2.13)	0	1 (2.08)	2 (4.00)
Chronic pulmonary disease	16 (11.35)	6 (13.95)	4 (8.33)	6 (12.00)
Immunocompromising conditions	17 (12.06)	6 (13.95)	6 (12.50)	5 (10.00)
<b>Symptoms at enrolment – n (%)</b>				
Cough	96 (68.09)	28 (65.12)	36 (75.00)	32 (64.00)
Nasal congestion	69 (48.94)	20 (46.51)	22 (45.83)	27 (54.00)
Sore throat	32 (22.70)	10 (23.26)	8 (16.67)	14 (28.00)
Feeling hot or feverish	103 (73.05)	31 (72.09)	36 (75.00)	36 (72.00)
Myalgia	46 (32.62)	11 (25.58)	16 (33.33)	19 (38.00)
Fatigue	47 (33.33)	13 (30.23)	15 (31.25)	19 (38.00)
Headache	59 (41.84)	15 (34.88)	15 (31.25)	29 (58.00)
Anosmia/ageusia	39 (27.66)	12 (27.91)	15 (31.25)	12 (24.00)
Nausea/vomiting	28 (19.86)	6 (13.95)	9 (18.75)	13 (26.00)
Diarrhoea	15 (10.64)	1 (2.33)	5 (10.42)	9 (18.00)

Table 3 continued on next page



Table 3 continued

Characteristic	Total N=141	Sotrovimab N=43	Bamlanivimab/ etesevimab N=48	Casirivimab/ imdevimab N=50
Serum C-reactive protein level – n	136	41	46	49
Mean (SD), mg/L	20.58 (29.00)	22.84 (33.70)	25.27 (34.20)	14.29 (15.99)

were serum antibody-positive at the enrolment, and 66 (38.8%) received complete primary COVID-19 vaccination series within 120 days of the enrolment or booster vaccination.

Primary and secondary outcomes of the study population infected with Omicron VOC by type of treatment are reported in **Table 6** with the exclusion of time to sustained patient-reported symptom resolution. Two of 57 in the bamlanivimab/etesevimab group (3.5%) had COVID-19 progression leading to hospitalisation, and no COVID-19 progression was recorded in the casirivimab/imdevimab and sotrovimab groups. The primary reasons for the two hospitalisations were deemed to be related to COVID-19. Both patients admitted to hospital were serum antibody-negative at enrolment and underwent non-invasive mechanical ventilation at hospital admission. One of these patients, a man aged 71–75 who received three doses of SARS-CoV-2 vaccine and was affected by non-Hodgkin lymphoma under active chemotherapy and chronic heart failure, died 12 days after the symptom onset, 10 days after the administration of bamlanivimab/etesevimab, and 4 days after the hospitalisation. The other patient, a man aged 66–70 who was not vaccinated against SARS-CoV-2 and was affected by obesity (BMI, 31) and type 2 diabetes, was admitted 7 days after the symptom onset and 4 days after the administration of bamlanivimab/etesevimab; the length of his hospital stay was 22 days, including non-invasive mechanical ventilation for 13 days and low-flow oxygen therapy for 8 days. All-cause mortality through day 28 was the same as that through day 14.

An emergency department visit without hospitalisation was observed once in one patient in the bamlanivimab/etesevimab group. This visit was deemed to be unrelated to COVID-19.

The median time to symptom resolution was 12 days (95% CI 8–14) in the bamlanivimab/etesevimab group, 12 days in the casirivimab/imdevimab group (95% CI 9–16), and 7 days in the sotrovimab group (95% CI 6–9), differing significantly across the overall groups of treatment (Log-rank Chi-square 20.29,  $p$  0.0001) and between sotrovimab and both bamlanivimab/etesevimab (Log-rank Chi-square 11.09,  $p$  0.009) and casirivimab/imdevimab (Log-rank Chi-square 19.51,  $p$  0.0001), whereas the comparison between bamlanivimab/etesevimab and casirivimab/imdevimab was not significant (Log-rank

**Table 4.** Efficacy outcomes of the study population infected with Delta by type of treatment with the exclusion of time to sustained patient-reported symptom resolution.

Outcome	Total N=141	Sotrovimab N=44	Bamlanivimab/ etesevimab N=47	Casirivimab/ imdevimab N=50
<b>Composite primary outcome – n (%)</b>	0	0	0	0
Hospitalisation	0	0	0	0
Need of supplemental oxygen therapy	0	0	0	0
Death from any cause through day 14	0	0	0	0
<b>Secondary outcomes</b>				
Emergency department visits through day 28 – n (%)	1 (0.71)	0	0	1 (2)
All-cause mortality through day 28 – n (%)	0	0	0	0
Duration of supplemental oxygen therapy – days	0	0	0	0
Rate of non-invasive ventilation – n (%)	0	0	0	0
Duration of non-invasive ventilation – days	0	0	0	0
Rate of mechanical ventilation – n (%)	0	0	0	0
Duration of mechanical ventilation – days	0	0	0	0



**Table 5.** Baseline characteristics of the study population infected with Omicron by type of treatment.

Characteristic	Total N=170	Sotrovimab N=61	Bamlanivimab/ etesevimab N=57	Casirivimab/ imdevimab N=52
Sex (male) – n (%)	101 (59.41)	36 (59.02)	30 (52.63)	35 (67.31)
Age – median (IQR) (range)	64.5 (14.8) (50–90)	64.2 (15) (50–90)	64.8 (14.6) (50–86)	65.3 (14.8) (50–86)
<b>Smoking status – n (%)</b>				
Smoker	24 (14.12)	6 (9.84)	11 (19.30)	7 (13.46)
Former smoker	28 (16.47)	9 (14.75)	11 (19.30)	8 (15.38)
Non-smoker	118 (69.41)	46 (75.41)	35 (61.40)	37 (71.15)
<b>BMI – n (%)</b>				
≤29	132 (77.65)	53 (86.89)	42 (73.68)	37 (71.15)
≥30	38 (22.35)	8 (13.11)	15 (26.32)	15 (28.85)
<b>SARS-CoV-2 serological status – n (%)</b>				
Antibody-positive	134 (78.82)	45 (73.77)	45 (78.95)	44 (84.62)
Antibody-negative	35 (20.59)	16 (26.23)	11 (19.30)	8 (15.38)
Other	1 (0.59)	0	1 (1.75)	0
<b>Anti-SARS-CoV-2 vaccination status – n (%)</b>				
3 doses	62 (36.47)	24 (39.34)	19 (33.33)	19 (36.54)
2 doses ≤120 days	4 (2.35)	2 (3.28)	1 (1.75)	1 (1.92)
1 or 2 doses ≥120 days	57 (33.53)	16 (26.23)	22 (38.60)	19 (36.54)
Not vaccinated	42 (24.71)	18 (29.51)	13 (22.81)	11 (21.15)
Other	5 (2.94)	1 (1.64)	2 (3.51)	2 (3.85)
<b>Comorbidities – n (%)</b>				
Diabetes	6 (3.53)	2 (3.28)	2 (3.51)	2 (3.85)
Cardiovascular disease	61 (35.88)	18 (29.51)	17 (29.82)	26 (50.00)
Chronic kidney disease	9 (5.29)	4 (6.56)	2 (3.51)	3 (5.77)
Chronic liver disease	12 (7.06)	4 (6.56)	5 (8.77)	3 (5.77)
Chronic pulmonary disease	33 (19.41)	11 (18.03)	15 (26.32)	7 (13.46)
Immunocompromising conditions	35 (20.59)	15 (24.59)	11 (19.30)	9 (17.31)
<b>Symptoms at enrolment – n (%)</b>				
Cough	118 (69.41)	42 (68.85)	37 (64.91)	39 (75.00)
Nasal congestion	69 (40.59)	28 (45.90)	25 (43.86)	16 (30.77)
Sore throat	69 (40.59)	22 (36.07)	27 (47.37)	20 (38.46)
Feeling hot or feverish	99 (58.28)	37 (60.66)	32 (56.14)	30 (57.69)
Myalgia	54 (31.76)	20 (32.79)	18 (31.58)	16 (30.77)
Fatigue	75 (44.12)	31 (50.82)	20 (35.09)	24 (46.15)
Headache	60 (35.29)	23 (37.70)	20 (35.09)	17 (32.69)
Anosmia/ageusia	4 (2.35)	1 (1.64)	2 (3.51)	1 (1.92)
Nausea/vomiting	11 (6.47)	4 (6.56)	5 (8.77)	2 (3.85)
Diarrhoea	12 (7.06)	5 (8.20)	4 (7.02)	3 (5.77)

Table 5 continued on next page

Table 5 continued

Characteristic	Total N=170	Sotrovimab N=61	Bamlanivimab/ etesevimab N=57	Casirivimab/ imdevimab N=52
Serum C-reactive protein level – n	161	57	56	48
Mean (SD), mg/L	14.29 (21.72)	12.65 (15.97)	17.19 (31.07)	12.87 (12.55)

infected with Delta, were more likely to present with symptoms limited to the upper respiratory tract and to have pre-existing immunity, considering that Omicron is better equipped than Delta to infect people with pre-existing immunity (Nyberg et al., 2022).

Considering the time to symptom resolution, no differences in the effect between treatment groups were found in Delta infections, whereas sotrovimab seems to show a benefit in patients infected with Omicron BA.1 and BA.1.1. This benefit was consistent across all Omicron subgroups, regardless of the SARS-CoV-2 serology and vaccination status, confirming the preliminary in-vitro evidence on the mAbs activity against Omicron BA.1 and BA.1.1 (Cao et al., 2022; Planas et al., 2022; Dejnirattisai et al., 2022).

The COVID-19 progression was recorded in two patients infected with Omicron, who were both randomised to receive bamlanivimab/etesevimab. On the one hand, these findings seem consistent with recent in-vitro data showing that all study treatments were active against Delta, and both casirivimab/imdevimab and sotrovimab retained a residual neutralising activity against Omicron BA.1/BA.1.1, whereas bamlanivimab/etesevimab did not neutralise Omicron (Takashita et al., 2022b; Iketani et al., 2022; Takashita et al., 2022a; Arora et al., 2022). Nevertheless, the above-mentioned results are severely limited by the early discontinuation of the trial, and firm conclusions on the primary outcome parameters cannot be drawn. Furthermore, the observed rate of COVID-19 progression (2/319, 0.6%) was lower than the one used to inform the sample size calculation (5% in the casirivimab/imdevimab arm, reference standard; NCT05205759). This overestimation of the primary outcome could be influenced by the lower intrinsic-severity of Omicron, the high vaccination rate in Italy, and the prioritisation of the booster vaccination for the elderly (Bhattacharyya and Hanage, 2022). Another limitation of this study is the lack of data on the clinical efficacy of the study mAbs, as well as other commercially available early COVID-19 treatments (mAbs, such as tixagevimab/cilgavimab

**Table 6.** Efficacy outcomes of the study population infected with Omicron by type of treatment with the exclusion of time to sustained patient-reported symptom resolution.

Outcome	Total N=170	Sotrovimab N=61	Bamlanivimab/ etesevimab N=57	Casirivimab/ imdevimab N=52
<b>Composite primary outcome – n (%)</b>	2 (1.18)	0	2 (3.51)	0
Hospitalisation	2 (1.18)	0	2 (3.51)	0
Need of supplemental oxygen therapy	2 (1.18)	0	2 (3.51)	0
Death from any cause through day 14	1 (0.59)	0	1 (1.75)	0
<b>Secondary outcomes</b>				
Emergency department visits through day 28 – n (%)	1 (0.59)	0	1 (1.75)	0
All-cause mortality through day 28 – n (%)	2 (1.18)	0	2 (3.51)	0
Duration of supplemental oxygen therapy – days	4 (patient 1) 22 (patient 2)	0	4 (patient 1) 22 (patient 2)	0
Rate of non-invasive ventilation – n (%)	2 (1.18)	0	2 (3.51)	0
Duration of non-invasive ventilation – days	4 (patient 1) 13 (patient 2)	0	4 (patient 1) 13 (patient 2)	0
Rate of mechanical ventilation – n (%)	0	0	0	0
Duration of mechanical ventilation – days	0	0	0	0

**Table 7.** Cox regression to assess the difference between treatment effects upon the time to symptom resolution in selected subgroups of interest in the study population infected with Omicron.

Subgroup	Sotrovimab	Bamlanivimab/etesevimab	p value	Casirivimab/imdevimab	p value
	HR	HR (95% CI)		HR (95% CI)	
<b>SARS-CoV-2 serological status</b>					
Antibody-negative	1	0.34 (0.16–0.75)	<b>0.008</b>	0.41 (0.18–0.97)	<b>0.043</b>
Antibody-positive	1	0.40 (0.22–0.71)	<b>0.002</b>	0.32 (0.18–0.57)	<b>&lt;0.001</b>
<b>Anti-SARS-CoV-2 vaccination status</b>					
1 or 2 doses ≥120 days or not vaccinated	1	0.47 (0.30–0.77)	<b>0.003</b>	0.49 (0.30–0.82)	<b>0.006</b>
3 doses or 2 doses ≤120 days	1	0.50 (0.28–0.89)	<b>0.019</b>	0.35 (0.19–0.62)	<b>&lt;0.001</b>

and bebtelovimab, and antiviral drugs, such as remdesivir, nirmatrelvir/ritonavir, and molnupiravir, against the currently circulating VOC (BA.2 subvariants, BA.4, or BA.5; **CoVariants, 2022**). Following an adaptive design in a real-life setting, the MANTICO trial is actively recruiting to compare the clinical efficacy of commercially available early COVID-19 treatments against the currently circulating VOC (tixagevimab/cilgavimab, nirmatrelvir/ritonavir, and sotrovimab; NCT05321394).

Additional clinical studies with an adequate sample size are required to determine whether casirivimab/imdevimab and sotrovimab are indeed effective in preventing COVID-19 progression due to Omicron infection. Should the role of casirivimab/imdevimab in preventing severe COVID-19 due to Omicron infections be confirmed, this mAb could represent a readily available and well-tolerated treatment option in case of shortages of mAbs supplies and contraindication to other early COVID-19 treatments.

The MANTICO trial provides the first data on the clinical efficacy of bamlanivimab/etesevimab, casirivimab/imdevimab, and sotrovimab against Omicron VOC. There is an urgent need for adaptive clinical trials comparing anti-SARS-CoV-2 treatments by the currently circulating VOC to promptly inform recommendations for the management of early COVID-19.

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### Competing interests

Lolita Sasset: Lolita Sasset has served as a paid consultant to Abbvie, Janssen, MSD, Gilead Sciences, Janssen, MSD and ViiV Healthcare; she does not have any financial competing interests with this study. Annamaria Cattelan: Annamaria Cattelan has served as a paid consultant to Abbvie, Janssen, MSD, and received research fundings from Gilead Sciences, Janssen, MSD and ViiV Healthcare; she does not have any financial competing interests with this study. Carlo Tascini: Carlo Tascini has received grants from Correvio, Biotest, Biomerieux, Gilead, Angelini, MSD, Pfizer, Thermofisher, Zambon, Shionogi, Avir Pharma and Hikma outside the submitted work in the last two years. MANTICO Working Group: The other authors declare that no competing interests exist.

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### Author contributions

Fulvia Mazzaferri, Conceptualization, Data curation, Software, Formal analysis, Supervision, Methodology, Writing - original draft, Writing - review and editing; Massimo Mirandola, Conceptualization, Data curation, Software, Formal analysis, Supervision, Validation, Visualization, Methodology, Writing - original draft, Writing - review and editing; Alessia Savoldi, Pasquale De Nardo, Resources, Data curation, Software, Formal analysis, Supervision, Validation, Investigation, Visualization, Methodology, Writing - original draft, Writing - review and editing; Matteo Morra, Data curation, Software, Supervision, Validation, Investigation, Project administration, Writing - review and editing; Maela Tebon, Data curation, Software, Supervision, Validation, Investigation, Project administration; Maddalena Armellini, Data curation, Validation, Investigation, Project administration; Giulia De Luca, Data curation, Validation, Investigation; Lucrezia Calandrino, Lolita Sasset, Data curation, Supervision, Investigation; Denise D'Elia, Resources, Data curation, Supervision, Investigation; Emanuela Sozio, Resources, Data

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#### Ethics

Clinical trial registration NCT05205759.

All recruited subjects provided the informed consent to participate to the MANTICO trial. The IRB approval was provided by the Ethics Committee of the National Institute for Infectious Diseases "Lazzaro Spallanzani" (468\_2021) and by the Scientific Technical Committee of the Italian Medicines Agency (28 OCT 2021).

#### Decision letter and Author response

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## Additional files

#### Supplementary files

- MDAR checklist
- Reporting standard 1. CONSORT checklist.

#### Data availability

The trial dataset has been uploaded to the Dryad repository (<https://doi.org/10.5061/dryad.tdz08kq2w>). As per predefined protocol, personally identifiable information (such as gender, date of birth, age, and weight) has been removed from the dataset to keep the records completely anonymous. In addition, the dataset record order was randomised so the resulting dataset is a file very similar in terms of length, fields and content to the original version, except for row order which is now completely random and the record id variable deleted.

The following dataset was generated:

Author(s)	Year	Dataset title	Dataset URL	Database and Identifier
Tacconelli E	2022	Adaptive, Randomized, Non-inferiority Trial to Evaluate the Efficacy of Monoclonal Antibodies in Outpatients With Mild or Moderate COVID-19	<a href="https://dx.doi.org/10.5061/dryad.tdz08kq2w">https://dx.doi.org/10.5061/dryad.tdz08kq2w</a>	Dryad Digital Repository, 10.5061/dryad.tdz08kq2w

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