Journal of Infection 89 (2024) 106294

Contents lists available at ScienceDirect

Journal of Infection

journal homepage: www.elsevier.com/locate/jinf

Viruses and Viral Diseases

Pooled analysis of the MANTICO2 and MONET randomized controlled trials comparing drug efficacy for early treatment of COVID-19 during Omicron waves

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ARTICLE INFO

Article history:
Accepted 23 September 2024
Available online 27 September 2024

Keywords:
Sars-CoV2
COVID-19
Frail subjects
Antivirals
Monoclonal antibody
Pooled analyses
Clinical trial

SUMMARY

Background: The clinical effectiveness of early therapies for mild-to-moderate COVID-19, comparing antivirals and monoclonal antibodies (mAbs) during the Omicron era, has not been conclusively assessed through a post-approval comparative trial. We present a pooled analysis of two randomized clinical trials conducted during Omicron waves.

Methods: The MANTICO2/MONET trial is a pooled analysis of two multicentric, independent, phase-4, three-arm, superiority, randomized, open-label trials. Nonhospitalized patients with early mild-to-moderate COVID-19 (≤5 days after symptoms' onset) and at least one risk factor for disease progression were randomized 1:1:1 to receive 500 mg of intravenous sotrovimab (SOT) or 600 mg of intramuscular tixagevimab/cilgavimab (TGM/CGM) or oral 5-days course of nirmatrelvir/ritonavir (NMV/r) 300/100 mg BID. Primary outcome was COVID-19-related hospitalization or death within 29 days after randomization. Fisher's exact test for pooled data and incidence of failure was reported as overall and by arm with respective 95% CI. Pairwise comparisons across the arms were conducted using unadjusted exact logistic regression. An analysis by means of a doubly robust marginal model using augmented inverse probability weighting (AIPW) was also conducted to estimate the potential outcomes (Pom) in each treatment group and their difference by the average treatment effect (ATE). Analysis of symptom persistence within 30 days after randomization was performed using a 2-level hierarchical mixed-effects logistic model with a random intercept at the patient's level. Point estimates and 95% confidence intervals were adjusted for age and sex and calculated using ANOVA-like methods for the mixed effects logistic model. These trials are registered with the European Clinical Trials Database, EudraCT2021-002612-31 (MANTICO2) and EudraCT2021–004188-28 (MONET) and ClinicalTrials.gov, NCT05321394 (MANTICO2).

Findings: Between March 2022 and February 2023, 991 patients (SOT = 332, TGM/CGM = 327, NMV/r = 332) were enrolled in 15 Italian centers. The overall mean age was 66 years; 482 participants (48.80%) were male,

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https://doi.org/10.1016/j.jinf.2024.106294

and 856 were vaccinated with at least a primary course (86%). Among the 8/991 hospitalizations observed, one resulted in death. The overall estimate of failure was 0.81% (95%CI; 0.35–1.58%). The odds ratio (OR) for the primary outcome in the NMV/r arm compared to the TGM/CGM and SOT arms was 8.41 (95% CI 1.21 to infinity; p = 0.015) and 2.42 (95% CI 0.19 to infinity; p = 0.499), respectively. No significant difference was observed between SOT and TGM/CGM (OR 0.32; 95% CI 0.032–1.83; p = 0.174). Results were similar when we applied the marginal weighted model accounting for potential residual confounding bias. There was no evidence for a difference in the prevalence of symptoms between treatment groups, except for cough, which was higher in the SOT group compared to the other two groups at the 21-day follow-up (P = 0.039) and a higher prevalence of nausea at the 7-day follow-up in the NMV/r group compared to the mAbs group (p = 0.036).

Interpretation: NMV/r was superior to TGM/CGM in reducing hospital admission or death in clinically vulnerable patients with SARS-CoV-2 infection treated within 5 days of symptoms' onset. No significant difference in symptom prevalence over time across the arms was found.

Introduction

During the Omicron era, both monoclonal antibodies (mAbs) and oral antiviral drugs were recommended by several major stakeholders for the early treatment of mild-to-moderate COVID-19 in clinically vulnerable outpatients at high risk of progressing to severe disease, although most evidence supporting these treatments stem from placebo-controlled, phase-3 randomized trials (RCTs) conducted in the pre-Omicron phase.[1–4] Molnupiravir, the first approved oral antiviral drug, was suspended in February 2023 in several European countries following the negative opinion issued by the European Medicine Agency's Committee for Medicinal Products for Human Use for failure to demonstrate a clinical benefit in terms of reduced mortality and hospital admissions. The protease inhibitor nirmatrelvir, enhanced with ritonavir (NMV/r), has been shown to reduce the risk of COVID-19-related hospitalization or death by approximately 88% compared to placebo[3] and has maintained its antiviral efficacy across various Omicron sublineages.[5–7] Multiple mAbs have been shown to be effective for both prophylaxis and therapy for SARS-CoV-2 infection.[8] Sotrovimab (SOT) and the combination of tixagevimab and cilgavimab (TGM/CGM) demonstrated in RCTs a risk reduction in COVID-19 progression by approximately 85%[2] and 50%,[1] respectively. These mAbs are largely unmetabolized, have minimal drug interactions, and possess a long half-life that allows for a single administration. However, despite their favorable safety profiles, the efficacy of mAbs has been compromised by the emergence of new SARS-CoV-2 variants. The variants exhibit specific mutations in the spike protein—the binding target for mAbs—resulting in partial or complete loss of in vitro neutralizing activity.[9,10] Tixagevimab displayed no in vitro activity against recent Omicron sublineages, while cilgavimab retained efficacy against sublineage BA.2 but showed reduced neutralization against BA.4/BA.5[5] 11. Neither mAbs neutralized the latest sublineages BQ.1/BQ.1.1 and XBB.1/XBB.1.5.[12] Unlike other mAbs, sotrovimab retained partial neutralizing activity against these variants.[13,14]

Regulatory authorities responded differently to the in vitro data: the US Food and Drug Administration (FDA) revoked the authorization of in vitro ineffective mAbs,[15] while the EMA continues to authorize their use alongside antivirals, citing insufficient data on the correlation between decreased in vitro neutralization and clinical efficacy.[16] In this setting, the MANTICO trial, a non-inferiority randomized controlled trial (RCT) comparing the clinical efficacy of early treatment of COVID-19 with bamlanivimab/etesevimab, casirivimab/imdevimab, and SOT, was interrupted for possible futility after the onset of the Omicron wave. The primary analysis carried out on 319 patients showed that early SOT therapy for infection due to Omicron BA.1 and BA.1.1 reduced the time to recovery compared with other mAbs.[17]

To date, the clinical effectiveness of early therapies for mild-to-moderate COVID-19, comparing oral antivirals and mAbs during the Omicron era, has not been conclusively assessed through a post-approval comparative trial. Here, we present the findings of the integrated analysis of two 3-arm, phase 4 RCTs, MANTICO2 and MONET, financed by the Italian Medicines Agency and applying similar protocols in the Omicron era. The decision to apply same core enrolment criteria has been taken in agreement with the funder Agency to reduce the risk of RCT's interruption for possible futility due to the rapid changing of circulation of SARS-CoV-2 Variant of Concern (VoC). This study was designed to provide insights into the relative clinical efficacy of TGM/CGM, SOT, and NMV/r.

Methods

Trial design

The MANTICO2/MONET trial represents a pooled analysis of two multicentric, independent, phase-4, three-arm, superiority, randomized, open-label trials conducted in Italy—MANTICO2 (EudraCT 2021-002612-31; NCT05321394) and MONET (EudraCT 2021-004188-28) financed by the Italian Agency of Drug (AIFA) in 2021. This analysis aimed to assess the clinical efficacy of three treatments (TGM/CGM, SOT, and NMV/r) available for managing mild-to-moderate COVID-19 during the Omicron era. Both trials enrolled patients at high risk for progression to severe COVID-19 and shared treatment arms and outcomes, thus providing a unique opportunity to pool the data to enhance the statistical power of the analysis. This pooling was particularly pertinent given the premature termination of both trials due to emerging in vitro evidence suggesting that TGM/CGM was ineffective against the Omicron sublineages circulating during the study period. Consequently, this analysis employs a pragmatic approach to leverage randomized data from two separate but similar studies to maximize inferential power.

Participants and setting

Patients were enrolled across 15 COVID-19 outpatient clinics throughout Italy (8 clinical centers in MANTICO2 and 7 centers in MONET). Eligible participants included adult (aged > 18 years) outpatients with laboratory-confirmed SARS-CoV-2 infection—detected either via direct antigen or nucleic acid tests—and assessed within five days of the onset of mild-to-moderate COVID-19 symptoms according to the WHO definition.[18] To qualify for inclusion, patients were required to meet the AIFA criteria for individuals at high risk for severe COVID-19 progression: being aged 65 years or older or having one or more of the following risk factors: a body mass index (BMI) above 30, chronic kidney or liver disease, uncontrolled or complicated diabetes mellitus, any immunocompromising condition, cardio-cerebrovascular disease, oncologic and hematologic conditions, chronic obstructive pulmonary disease (COPD), hemoglobinopathies, and neurodevelopmental or neurodegenerative diseases.[19]

Intervention

Participants were randomized in a 1:1:1 ratio to receive one of three treatment regimens: a single intravenous infusion of 500 mg of SOT (Arm 1), two separate intramuscular injections of TGM/CGM at 300 mg each (Arm 2), or a five-day course of NMV/r, dosed either as 300 mg/100 mg twice daily (BID) for those with a creatinine clearance > 60 mL/min, or 150 mg/100 mg BID for those with a creatinine clearance of 30–60 mL/min. Since this is a phase 4 trial, the assessed treatments were commercial compounds provided to the recruiting sites by the AIFA and administered according to AIFA recommendation guidance.

Outcome

The primary outcome was clinical failure within 30 days of randomization, defined as any-cause mortality, hospitalization, or progression to severe COVID-19 (scoring five or more on the WHO severity scale).[18] Project-dedicated personnel performed the clinical assessment of patients at the respective centers. Participants were scheduled for three visits: Visit 1 at enrolment, Visit 2 between days 7 and 9, and Visit 3 between days 28 and 30 of randomization. For patients unable to attend their final visit, vital status, hospitalization, and disease progression were assessed via telephone calls made by hospital clinical staff. This procedure mirrored the routine practice used for non-study patients required to complete the AIFA form for outcome assessment post-treatment for the study drugs. Whole-genome Sequencing was performed on nasopharyngeal swabs (NPS) samples collected at baseline for patients who experienced failure. Nucleic acid extraction was performed by QiaSymphony automatic extractor (QIAGEN, Hilden, Germany) with DSP Virus/Pathogen Kit (QIAGEN). Sequencing libraries were prepared by using Ion AmpliSeq SARS-CoV-2 Insight Research Assay, and Next Generation Sequencing (NGS) was carried out Ion Torrent Gene Studio S5 Prime (GSS5 Prime) platform, following the manufacturer's instructions (ThermoFisher, Waltham, MA, USA). SARS-CoV-2 genomes were assembled using the Easy-to-use SARS-CoV-2 Assembler pipeline (ESCA).[20]

Additionally, COVID-19 symptoms were recorded using a self-reported standardized paper log diary, which was distributed at Visit 1. Recorded symptoms included cough, nasal congestion, sore throat, feeling hot or feverish, myalgia, fatigue, headache, anosmia/ageusia, nausea, vomiting, and diarrhea.[21] The prespecified time points for the symptom collection were days 7–14-21–30.

Secondary outcomes focused on the duration of symptoms within 30 days after randomization. For patients missing any follow-up visits, missing symptom data were managed using a mixed regression model designed to accommodate incomplete datasets.

Sample size

This analysis constitutes a pragmatic review of pooled data from two trials initially designed to detect an improvement in overall survival from 93% to 97%. However, as the epidemiology of SARS-CoV-2 has significantly and rapidly evolved and being the treatments effectiveness susceptible to the VoC, neither trial achieved the requisite number of events needed to conclusively demonstrate the superiority of any one intervention. The analysis encompasses all patients who were enrolled in both trials.

Blinding and randomization

In each of the trials, the random allocation sequence was generated using a central online random sequence generator specifically designed for each study. MONET utilized a simple randomization method without restrictions or stratification, while the randomization list in MANTICO2 was prepared using permuted blocks of 6 and stratified by site to ensure balanced patient assignment across sites and arms. An independent statistician, not involved in participant enrolment or assignment, created the sequence. The random allocation was administered via a centralized web-based system, accessible to authorized personnel only after recruitment was complete to ensure concealment of allocation. At the screening, all participants provided informed consent, and their relevant data were entered into the system.

Due to the nature of the interventions and their differing routes of administration, this was an open-label trial. Consequently, both participants, care providers and staff in charge of assessing the outcome were all aware of the intervention assignments.

Statistical analysis

Descriptive analysis was conducted to examine patient characteristics distribution and identify any potential imbalances across treatment arms.

For the primary endpoint, the comparison was analyzed using the Fisher exact test for both individual trial data and pooled data. Additionally, pairwise comparisons across the arms were conducted using unadjusted exact logistic regression, which is robust for modeling data that may have zero events in any individual group. This model measures effect in term of odd-ratio (OR) and relative 95% CI and p-values. Although only small imbalances in important predictors of the outcome between treatment groups were observed, in order to account for potential residual confounding bias, we also conducted an analysis by means of a doubly robust marginal model using augmented inverse probability weighting (AIPW) to estimate the potential outcomes (Pom) in each treatment group and their difference by the average treatment effect (ATE). This also allowed the estimation of the risks in the additive scale instead of odds ratios. Identified predictors of outcome used to construct the weights included gender, age, cardiovascular disease, diabetes, COPD, timing of therapy initiation from symptoms' onset, BMI, hematological malignancies, any other immunodeficiencies, and chronic renal failure. The same linear predictor was used for both the propensity and outcome model.

Analysis of symptom persistence was performed using a 2-level hierarchical mixed-effects logistic model with a random intercept at the patient's level. All estimates were adjusted for age and gender. This approach allowed for the comparison of symptom prevalence across the arms at enrolment and during follow-ups (on days 7, 14, 21, and 30). Point estimates and 95% confidence intervals were adjusted for age and sex and calculated using ANOVA-like methods for the mixed-effects logistic model.

All analyses were carried out using Stata Statistical Software: Release 18, produced by StataCorp LLC in College Station, TX.

Role of the funding source

MANTICO2 and MONET trials were funded by the Italian Medicines Agency (Agenzia Italiana del Farmaco, AIFA). The funder had no role in study design, data collection, data analysis, data interpretation, or writing of the report. EudraCT 2021–002612-31; NCT05321394 (MANTICO); EudraCT 2021–004188-28 (MONET).

Results

Descriptive analysis

Between March 4, 2022, and February 1, 2023, a total of 991 patients were enrolled in 15 different clinical centers across Italy, with 536 participants in the MANTICO2 trial and 455 in the MONET study (Fig. 1). The overall mean age was 66 years, and 48.80% (482)

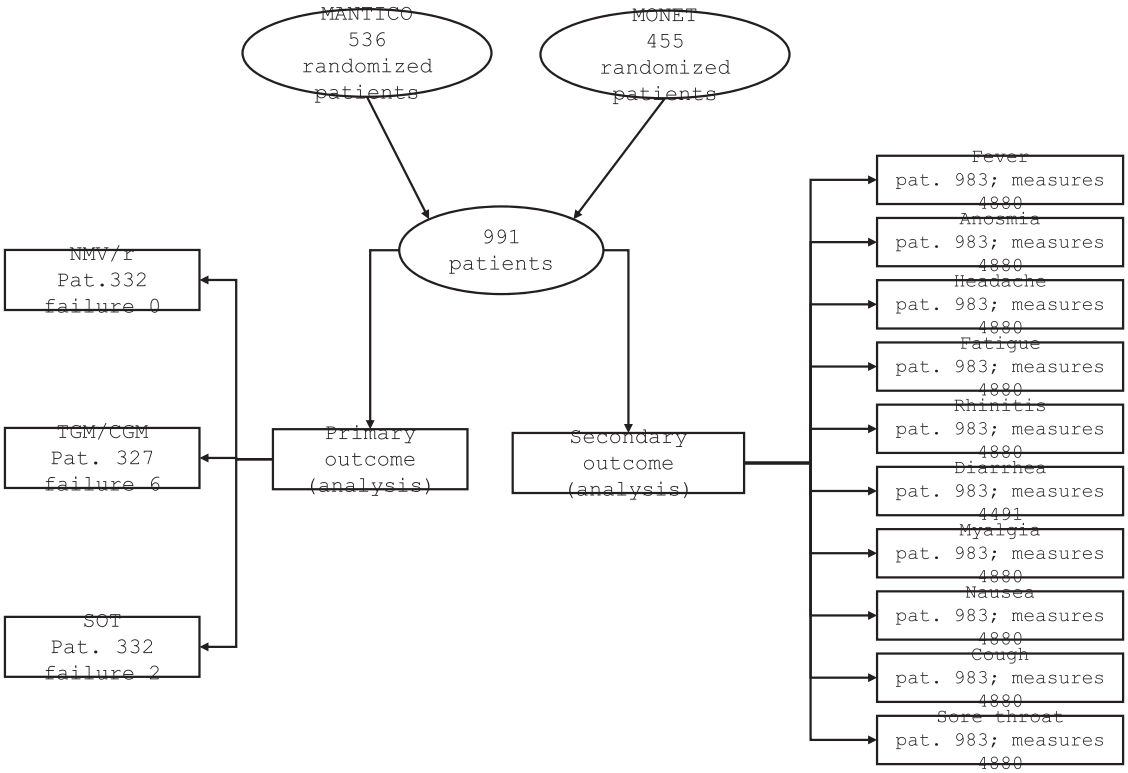

Fig. 1. Flowchart of the analyses illustrates patients and the number of events for primary analyses and patients and the number of measures for secondary analyses.

of the participants were male. The average time from symptom onset to randomization was 2.70 days (median 3, SD 1.06). The number of patients enrolled in each center is reported in Table S1.

Baseline characteristics of the study population, stratified by treatment arms, are detailed in Table 1. Participants appeared balanced across study arms with respect to most key predictors of outcome. Two differences in the case-mix of the population enrolled in the two trials were detected: MANTICO2 patients were more likely to be older and enrolled slightly earlier after symptom onset compared to those in MONET (difference, 2.73 years, 95% CI 1.17–4.28, p < 0.001; difference, 0.60 days, 95% CI 0.73 to −0.47; p < 0.001, respectively).

None of the variables examined showed an imbalance > 10% by the study arm. A descriptive analysis of potential imbalance is reported in Supplementary Table S2.

Analyses of primary outcome

Among the 991 patients enrolled across two studies, the overall cumulative incidence risk of clinical failure was 0.81% (95% CI 0.35–1.58%). The breakdown by study arm was as follows: 6/327 (1.83%) in the TGM/CGM arm (2 in MANTICO2 and 4 in MONET), 2/332 (0.86%) in the SOT arm (1 in MANTICO2 and 1 in MONET trial), and none in the NMV/r arm. Notably, there was only one death, which was recorded in the SOT arm. Comprehensive details of the failure events, including comorbidities and vaccination status, are reported in Table 2.

Separate analyses in each trial showed Fisher's exact p-value of 0.777 for MANTICO2 (536 patients; failure = 3) and a p-value of 0.030 for the MONET trial (455 patients, failure =5). The pooled data indicated a significant difference in the risk of the primary outcome by study arm (p = 0.015; 991 patients; failure=8).

Primary outcome analyses are reported in Table 3. The analysis by exact logistic regression model confirmed the crude findings and estimated an odds ratio (OR) for the primary outcome in the NMV/r arm compared to the TGM/CGM and SOT arms of 8.41 (95% CI 1.21 to infinity; p = 0.015) and 2.42 (95% CI 0.19 to infinity; p = 0.499), respectively. No significant difference was observed between SOT and TGM/CGM (OR 0.32; 95% CI 0.032–1.83; p = 0.174).

Results were similar when we applied the marginal weighted model accounting for potential residual confounding bias. In particular, the potential outcome means (Pom, the day-30 risk of hospitalization/severe disease/death) was null for NMV/r, 0.57% (95% CI 0.21–1.35%) for SOT and 1.84% (0.39%–3.28%) in the TGM/CGM arm. The weighted model estimated a difference in risk of developing the primary outcome between TGM/CGM and NMV/r of 1.84% (95% CI 0.39–3.28). Data also suggested superiority of NMV/r vs SOT and of SOT vs. TGM/CGM although results were inconclusive for these comparisons.

Analyses of symptom prevalence over time

The most common symptoms at enrolment were respiratory symptoms (cough, rhinitis, and sore throat) and fever, reported by over 60% of participants. Prevalence rates for headache, myalgia, and fatigue were between 40% and 60% at baseline. Nausea and diarrhea were reported less frequently at baseline but exhibited increased rates after 7 days among participants who received NMV/r (from 12.54% to 18.17% p < 0.005 for nausea, and from 8.79% to 19.43% for diarrhea, p = 0.001). Fatigue, myalgia, and anosmia persisted at over 10% prevalence at the 30-day follow-up. In particular, anosmia was present in approximately 27% of participants, with no evidence for a change in frequency between the time of enrolment and the end of the 30-day follow-up. There was no evidence for a difference in the prevalence of symptoms between treatment groups, except for cough, which was higher in the SOT group compared to the other two groups at the 21-day follow-up (p = 0.039) and a higher prevalence of nausea at the 7-day follow-up in the NMV/r group compared to the mAbs group (p = 0.036). Fig. 2 reports the analyses of symptoms prevalence over time.

Table 1
Baseline characteristics of the study population.

Patients' characteristics		ARM						Overall	
		NMV/r		TGM/CGM		SOT			
		N	%	N	%	N	%	N	%
age > 65	no	160	48.19	178	54.43	155	46.69	493	49.75
	yes	172	51.81	149	45.57	177	53.31	498	50.25
Gender	female	159	47.89	180	55.05	170	51.20	509	51.36
	male	173	52.11	147	44.95	162	48.80	482	48.64
Time between symptoms and randomization	≤2 day	139	41.87	117	35.78	132	39.76	388	39.15
	3 days	121	36.45	134	40.98	131	39.46	386	38.95
	4–5 days	72	21.69	76	23.24	69	20.78	217	21.90
Body max index	< 30	276	83.13	268	81.96	269	81.02	813	82.04
	≥30	56	16.87	59	18.04	63	18.98	178	17.96
Diabetes	no	284	85.54	288	88.07	274	82.53	846	85.37
	yes	48	14.46	39	11.93	58	17.47	145	14.63
CVD	no	183	55.12	172	52.60	160	48.19	515	51.97
	yes	149	44.88	155	47.40	172	51.81	476	48.03
COPD	no	281	84.64	263	80.43	286	86.14	830	83.75
	yes	51	15.36	64	19.57	46	13.86	161	16.25
Liver disease	no	327	98.49	321	98.17	328	98.80	976	98.49
	yes	5	1.51	6	1.83	4	1.20	15	1.51
Renal impairment	no	313	94.28	315	96.33	316	95.18	944	95.26
	yes	19	5.72	12	3.67	16	4.82	47	4.74
Immunocompromised status	no	270	81.33	278	85.02	282	84.94	830	83.75
	yes	62	18.67	49	14.98	50	15.06	161	16.25
Neurological disease	no	315	94.88	302	92.35	319	96.08	936	94.45
	yes	17	5.12	25	7.65	13	3.92	55	5.55
At least primary vaccinal course completed	no	36	10.84	53	16.21	35	10.54	124	12.51
	yes, last < 120 d	80	24.10	83	25.38	90	27.11	253	25.53
	yes, last ≥120 d	213	64.16	188	57.49	202	60.84	603	60.85
	yes last unknown	3	0.90	3	0.92	5	1.51	11	1.11
Positive anti-Spike IgG at baseline	negative	14	4.22	28	8.43	29	8.73	71	7.16
	positive	283	85.24	263	79.22	266	80.12	812	81.94
	not available	35	10.54	36	10.84	37	11.14	108	10.90
Overall		332	100.00	327	100.00	332	100.00	991	100.00

NMV/r: nirmatrelvir and ritonavir; SOT: sotrovimab; TGM/CGM: tixagevimab, cilgavimab; N: number; % percentage; CVD: Cardiovascular disease; COPD: Chronic obstructive pulmonary diseases.

Discussion

The integrated MANTICO2/MONET analysis shows a cumulative risk of clinical failure of 0.8% in high-risk patients for moderate to severe COVID-19, treated within the first five days of symptoms' onset with either NMV/r, SOT, or TGM/CGM. The study also demonstrates that NMV/r is more effective than TGM/CGM in reducing the risk of hospital admission or death by day 30. These data are particularly valuable as MANTICO2/MONET represents the first randomized comparison of these drugs during the Omicron wave. The cumulative risk of clinical failure (0.8%) aligns with real-world studies from the same period,[22–26] suggesting that our sample is representative of the wider population and that our results can be well generalized. Although vaccination has significantly reduced the risk of severe COVID-19 and evidence suggests that the Omicron variant may be less pathogenic than its predecessors,[27,28] clinically vulnerable populations remain at higher risk of severe COVID-19 than the general population. Notably, compared to early phase 3 registration studies, our study included a higher proportion of immunocompromised patients, supporting the generalizability and transferability of results to the case-mix currently at higher risk for severe disease, regardless of the vaccination status.

From the data of this pooled analysis, NMV/r resulted as more effective than TGM/CGM in reducing the risk of hospital admission or death by day 30. The present study represents the sole randomized comparison of these treatments in this context, as, in the Omicron era, in vitro efficacy studies and a lower number of outcomes than expected have significantly influenced the completion rates of clinical trials. Our findings may serve as the in vivo counterpart to previously published in vitro data,[5–7] which had shown that the neutralizing activity of TGM/CGM diminished progressively against BA.1/BA.2/BA.4/5 and was entirely lost against BQ.1 and XBB.1/XBB.1.5[10,29–31]. Our trials spanned from March 2022 to February 2023, tracking the evolution of the Omicron variant from BA.2 to BA.4/BA.5 and then to BQ.1/BQ.1.1 and XBB.1/XBB.1.5. Notably, of the eight clinical failures in the TGM/CGM group, three participants were infected with BA.2, two with BA.4/5, and one with BQ.1.

Given the discontinuation of mAbs use in the USA and its continued use in the UK and Europe, robust evidence is urgently needed to inform treatment guidelines for clinically vulnerable outpatients at high risk to progress to severe disease in the Omicron era. Some real-world data comparisons of drug effectiveness have been conducted but they typically rely on the assumption of no unmeasured confounding. Therefore, our study provides the highest level of epidemiological evidence currently available for comparing these interventions, suggesting that NMV/r significantly reduces the risk of hospitalization or death within 30 days by more than eight times compared to TGM/CGM. By converting the estimated difference in risk in the number needed to treat (NNT), our data suggest that 55 individuals at high risk of severe COVID-19 disease need to be treated with NMV/r instead of TGM/CGM in order to prevent 1 case of severe disease/death.

The efficacy of SOT against Omicron variants is less surprising, given its design to recognize a conserved RBD epitope across all Sarbecoviruses, possibly explaining its retained binding and neutralizing activity against the BA.2 subvariants.[11,32] Additionally, SOT-preserved effector functions may account for its effective promotion of antibody-dependent cellular toxicity (ADCC) and phagocytosis (ADCP).[33,34] Real-world studies have shown the benefit of SOT compared to no treatment in high-risk patients,[35,36] and its effectiveness is comparable to that of NMV/r.[37] Both EMA and NICE continue to recommend SOT for COVID-19 treatment in Europe.

Table 2
Description of the 8 patients who experienced treatment's failure.

Study	Arm	Gender, Age (yrs)	Days from symptoms' onset	VOC	Underlying conditions	Vaccination status	Outcome	Treatment after failure	Reason for hospitalization
MONET	TGM/CGM	Male, 69	3	BA.2	Previous vein thrombosis, hypertension	COMINARTY 3 doses	Hospitalization	No	Pulmonary thromboembolism
MONET	SOT	Female, 20	1	BA.2.44	NHL	COMINARTY 3 doses	Hospitalization	Remdesivir	SARS-COV-2 pneumonia
MONET	TGM/CGM	Female, 72	4	BA.4/BA.5	Multiple myeloma, hypertension	SPIKEVAX 4 doses	Hospitalization	Remdesivir	SARS-COV-2 pneumonia
MONET	TGM/CGM	Male, 78	4	BA.2	Schonlein-Henoch, hypertension	COMINARTY 3 doses	Hospitalization	No	Persistent fever
MONET	TGM/CGM	Female, 74	3	BQ.1.1.1	COPD	no	Hospitalization	Remdesivir	SARS-CoV-2 pneumonia
MANTICO2	SOT	Female, 88	3	BA.2.9	COPD, giant cell arteritis	COMINARTY 3 doses	Hospitalization, death	No	SARS-CoV-2 pneumonia
MANTICO2	TGM/CGM	Male, 80	1	BA.2	COPD (restrictive lung disease), hypertension	COMINARTY 3 doses	Supplemental oxygen therapy	No	SARS-CoV-2 pneumonia
MANTICO2	TGM/CGM	Female, 88	2	BA.5.2	COPD, hypertension	COMINARTY 3 doses	Supplemental oxygen therapy	No	SARS-CoV-2 pneumonia

NMV/r: nirmatrelvir and ritonavir; SOT: sotrovimab; TGM/CGM: tixagevimab, cilgavimab; VOC: variant of concern; NHL: non-Hodgkin Lymphoma; COPD: Chronic obstructive pulmonary diseases.

Notably, 70% of high-risk patients receive medications that interact with NMV/r, and 4% present contraindications against its use,[38] underscoring the importance of alternative treatment options.

Because of the low risk of hospitalization/death in the Omicron era, recent phase 3 trials have included symptom resolution time as the primary outcome for assessing drug efficacy.[39,40] Our study found no significant difference by treatment arm in achieving sustained alleviation of most targeted COVID-19 symptoms by day 30. However, participants in the NMV/r arm experienced higher rates of nausea and diarrhea, consistently with known adverse effects of ritonavir. Symptoms typically associated with early disease phases declined within the first two weeks across all three arms, whereas those indicative of post-COVID-19 syndrome (PCS), such as fatigue, cough, myalgia, and alterations in taste and smell, often persisted beyond the first month.[41]

This integrated analysis of the MANTICO2/MONET RCTs underscores the crucial importance of pooling data from individual clinical trials during pandemics. As countries and stakeholders formulate pandemic preparedness plans, incorporating specific definitions and requirements for data harmonization within RCTs becomes paramount. In a disease characterized by the dramatic and rapid changing in the epidemiological scenario of the VoC circulation, harmonization of data and outcomes among RCTs assessing new therapeutics is of utmost importance. The lessons learned from the COVID-19 pandemic should guide the development of pandemic preparedness plans. These plans should include specific actions to support the development of sharable electronic case report forms (eCRFs) and coordination mechanisms, such as the Trial Coordination Board of RCTs, supporting successful implementation and development of European adaptive platform trials for treatment of infectious diseases with pandemic potential.[42] Harmonization of data and outcomes among RCTs would be essential not only to facilitate the pooling of data and data sharing but also to promote transparency and accountability in clinical research during the pandemic time. Several European projects and stakeholders (e.g., IDDO, Recodid, ORCHESTRA, COMECT, CONTAGIO) are actively engaged in data harmonization processes for both trials and cohorts. However, a cohesive European strategy for automated and harmonized eCRFs remains lacking. By defining processes and dictionaries for infectious diseases with epidemic and pandemic potential during interpandemic periods, we can ensure that data from different RCTs targeting the same new drugs can be readily analyzed. This would have a substantial impact on decision-making, especially in the face of changing epidemiological scenarios.

Our analysis has several limitations. First, the low event rate, particularly in some study arms, is a significant limitation. The unexpectedly mild severity of Omicron, high vaccination coverage, and targeted booster campaigns for the elderly in Italy likely contributed to the low risk of disease progression. The logistical challenges posed by the pandemic's dynamics prevented our trials from reaching the planned scale in terms of event occurrence and patient enrolment, thus preventing us from drawing definitive conclusions for the primary outcome due to a lack of statistical power. Additionally, the study design did not track clinical progression beyond 30 days, and the underrepresentation of certain high-risk groups could limit the generalizability of our conclusions. These challenges underscore the need for adaptable and resilient trial designs. Finally, the results of pooled analyses might be biased due to heterogeneity in study design, inclusion criteria, and study conduct. Nevertheless, we believe this issue minimally impacts our estimates, as the study considered an identical set of interventions carried out in the same setting (i.e., Italian COVID outpatient clinics), and because our unadjusted estimates of effect were also confirmed by means of a counterfactual analysis to correct for potential residual confounding.

In conclusion, our analysis provides evidence of the superiority of NMV/r over TGM/CGM in reducing the risk of hospital admission or

Table 3
Pair-wise comparisons according to exact logistic and doubly robust marginal model.

Pair-wise comparison	Unadjusted analysis			Adjusted analysis[a]					
	Exact Logistic analysis			Potential outcomes mean		Augmented inverse-probability weight Risk difference			
	OR	95% CI	p-value	Pom	95% CI	ATE	95% CI		p-value
NMV/r	Ref			0.00		Ref			
SOT	2.41	0.19-inf	0.499	0.57	0.00–1.34	+0.57%	−0.21%	+1.35%	0.15
NMV/r	Ref			0.00		Ref			
TGM/CGM	8.41	1.21-inf	0.015	1.84	0.39–3.28	+1.84%	+0.39%	+3.28%	0.01
TGM/CGM	Ref			1.84	0.39–3.28	Ref			
SOT	0.32	0.03–1.83	0.174	0.57	0.00–1.34	−1.27%	−2.91%	+0.37%	0.13

[a] Adjusted for variables that are potentially associated with outcome (i.e. gender, age, cardiovascular disease, diabetes, chronic obstructive pulmonary disease-, timing of therapy initiation, Body max index, hematological malignancies, other immunodeficiencies, and chronic renal failure); NMV/r: nirmatrelvir and ritonavir; SOT: sotrovimab; TGM/CGM: tixagevimab, cilgavimab.

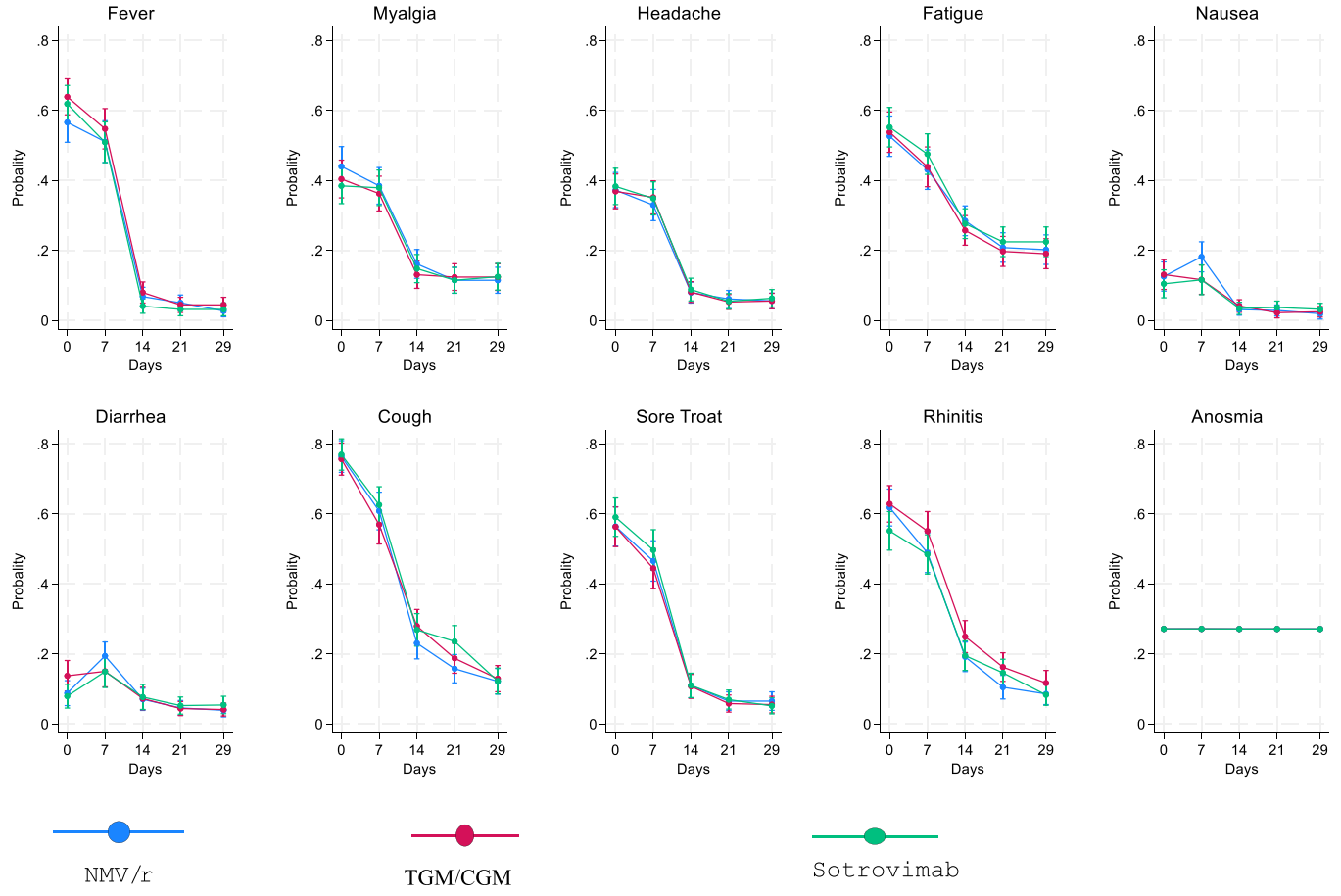

Fig. 2. Analyses of persistence of symptoms. The analyses have been carried out with an effect logistic model with random intercept at the patient level and adjusted for age and gender. X-axes indicate an adjusted proportion of patients with a specific symptom; Y-axes indicate time of follow-up; blue lines indicate estimates for patients receiving nirmatrelvir and ritonavir (NMV/r); Red lines indicate estimates for patients receiving tixagevimab, cilgavimab (TGM/CGM); Green lines indicate estimates for patients receiving sotrovimab (SOT).

mortality by day 30. Despite the limitations related to the epidemiological scenario, our data offer the highest level of evidence for this comparison among vaccinated clinically vulnerable outpatients at high risk of progressing to severe disease, including a significant proportion of immunocompromised individuals, all infected with Omicron variants The results from these trials are pivotal in the ongoing efforts to refine and optimize COVID-19 treatment guidelines. The findings will be instrumental in supporting healthcare professionals in making informed decisions regarding the management of COVID-19 patients at risk for severe disease and further support recommendations for early antiviral therapy to minimize the risk of complications and mortality associated with SARS-CoV-2 infection.

Further research is crucial to exploring the broader benefits of NMV/r, including its potential role in preventing post-COVID syndrome and other complications through an extending participant follow-up. Additionally, adequately powered studies are required to evaluate the efficacy of SOT in this patient population in the evolving scenario of SARS-CoV-2 subvariants, particularly as an alternative for those unable to use NMV/r.

A significant contribution of our analysis is its emphasis on the vital role of independent research. Establishing autonomous collaborative networks and conducting independent studies are essential due to the lack of comparative randomized analyses with the different available options and considering the complexities of the COVID-19 pandemic. Such efforts are key to deepening our

understanding of both laboratory and real-world comparative studies. This approach not only enriches our knowledge but also reinforces the importance of independent research in improving patient care amidst evolving global health challenges.

Funding

The trials were funded by the Italian Agency of Drugs (AIFA) in 2021 and Ministero della Salute (Rome) Ricerca Corrente Linea 1 INMI Lazzaro Spallanzani IRCCS (Rome).

Author contributions

AA and ET conceived the study. VM and FM wrote the study protocols; SL performed the statistical analysis; MM contributed to the statistical analysis; ACL supervised the statistical analyses and validated the results; VM and FM wrote the first draft of the manuscript; SL, ACL, AA and ET contributed to reviewing and editing the manuscript; AV, AS, AS, GM, IM, OS FDZ, GR, LT, LR enrolled the participants, observed the study procedures and followed-up the patients; LS, CT, EG, CAM revised the final version of the manuscript. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Data availability

Anonymised data sharing will occur as per Institutes's policy statement on data sharing.

Declaration of Competing Interest

1. Valentina Mazzotta (VM): she received support for participation in conference from AstraZeneca and GSK, has served as a paid consultant to GSK, Viatris, Pfizer, Gilead Science, ViiV Healthcare and AstraZeneca and received research institutional funding from Gilead Sciences
2. Fulvia Mazzaferri (FM): she declares no conflict of interests
3. Simone Lanini (SL): he received grants for consultancies and travel from Gilead Sciences, ViiV Healthcare, GSK and MSD. He also acts as a paid expert for European Union in the framework of HORIZON programme.
4. Massimo Mirandola (MM): he declares no conflict of interests
5. Alessandro Cozzi-Lepri (ACL): his work was funded from EU (EuCARE project funded by the EU under the HORIZON Europe programme GA n. 101046016).
6. Alessandra Vergori (AV): she received fees for consultancy from Astra Zeneca, Gilead Sciences, ViiV Healthcare
7. Alessia Savoldi (AlS): she declares no conflict of interests
8. Andrea Santoro (AnS): he declares no conflict of interests
9. Gaia Maccarrone (GM): she declares no conflict of interests
10. Ilaria Mastrorosa (IM): she declares no conflict of interests
11. Omar Simonetti (OS): he declares no conflict of interests
12. Federico De Zottis (FDZ): he declares no conflict of interests
13. Emanuele Nicastri (EN): received travel grant from Gilead Sciences and PharmaMar, is part of Valneva and Takeda advisory board, received presentation and consultation fees from Gilead Sciences and Roche
14. Giulia Rosini (GR): she declares no conflict of interests
15. Laura Rovigo (LR): she declares no conflict of interests
16. Lorenzo Tavernaro (LT): he declares no conflict of interests
17. Loredana Sarmati (LS): she received Travel grants from Gilead, Merck, Pfizer and Fee for lectures and expertise from Merck, Gilead, Abbvie, Angelini, Astra Zeneca, GSK
18. Carlo Tascini (CT): he received unconditional grants from Angelini, Menarini, Merck, Gilead, Astra, Pfizer, Shionogi, Advanz, ThermoFischer, Biomerieux, Hikma, Beckman, Glaxo and Diasorin
19. Enrico Girardi (EG): he declares no conflict of interests
20. Anna Maria Cattelan (AMC): she received fees for Advisory Boards and travel grants from Gilead Sciences, Angelini, Janssen, MSD, and ViiV Healthcare
21. Andrea Antinori (AA): he received fees for consultancy from Astra Zeneca, Bavarian Nordic, Gilead Sciences, GSK, Janssen-Cilag, Merck, Moderna, Pfizer, and ViiV Healthcare; institutional research grants from Astra Zeneca, Gilead Sciences and ViiV Healthcare.
22. Evelina Tacconelli (ET): she declares no conflict of interests

Acknowledgments

MANTICO2/MONET working group: Alessandro Castelli, Ilaria Dalla Vecchia, Chiara Konishi De Toffoli, Enrico Gibbin, Marco Meroi, Matteo Morra, Chiara Perlini, Pasquale De Nardo, Elisa Danese, Martina Montagnana, Davide Negrini, Giuseppe Lippi, Davide Gibellini (University of Verona); Emanuela Sozio, Luca Martini, Denise D′Elia, Francesca Prataviera, Tosca Semenzin, Dario Carloni (University of Udine and Azienda Sanitaria Universitaria Friuli Centrale); Roberto Luzzati, Riccardo Pol (Azienda Sanitaria Universitaria Giuliano Isontina, Trieste); Lolita Sasset, Lucrezia Calandrino, Elena Agostini, Carla Benfatto, Nicola Bonadiman, Marco Canova, Giuseppe Lombardo, Daniele Mengato, Danilo Puntrello (Padova University Hospital); Marco Anselmo, Federica Briano (Ospedale San Paolo, Savona); Daniela Francisci, Giuseppe De Socio (University of Perugia); Roberto Cauda, Valentina Siciliano (Fondazione Policlinico Universitario Agostino Gemelli, Rome); Silvia Corcione (University of Turin); Samir Al Moghazi, Elisa Biliotti, Emanuela Caraffa, Carlotta Cerva, Alessandra D′Abramo, Francesca Faraglia, Francesca Gavaruzzi, Raffaella Libertone, Laura Loiacono, Eugenia Milozzi, Maria Maddalena Plazzi, Silvia Rosati, Laura Scorzolini, Serena Vita, Pietro Vittozzi (National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Rome); Massimo Andreoni, Luigi Coppola (Infectious Diseases Unit, Tor Vergata University Hospital, Rome); Pierluigi Blanc (S. Jacopo hospital Pistoia), Antonella d′Arminio Monforte, Giulia Marchetti (San Paolo University Hospital, Milan); Chiara Iaria (Cristina Benfratelli Civic hospital, Palermo); Carlo Torti (Policlinico Universitario Mater Domini, Catanzaro).

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jinf.2024.106294.

References

1. Montgomery H, Hobbs FDR, Padilla F, Arbetter D, Templeton A, Seegobin S, et al. *Efficacy and safety of intramuscular administration of tixagevimab-cilgavimab for early outpatient treatment of COVID-19 (TACKLE): a phase 3, randomised, double-blind, placebo-controlled trial. Lancet Respir Med* 2022;**10**(10):985–96. https://doi.org/10.1016/S2213-2600(22)00180-1
2. Gupta A, Gonzalez-Rojas Y, Juarez E, COMET-ICE Investigators. *Early treatment for Covid-19 with SARS-CoV-2 neutralizing antibody sotrovimab. N Engl J Med* 2021 Nov 18;**385**(21):1941–50. https://doi.org/10.1056/NEJMoa2107934
3. Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, et al. *Oral nirmatrelvir for high-risk, non-hospitalized adults with Covid-19. N Engl J Med* 2022;**386**(15):1397–408. https://doi.org/10.1056/NEJMoa2118542
4. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, et al. *Molnupiravir for oral treatment of COVID-19 in non hospitalized patients. N Engl J Med* 2022;**386**:509–20.
5. Takashita E, Yamayoshi S, Simon V, van Bakel H, Sordillo EM, Pekosz A, et al. *Efficacy of antibodies and antiviral drugs against Omicron BA.2.12.1, BA.4, and BA.5 subvariants. N Engl J Med* 2022;**387**(5):468–70. https://doi.org/10.1056/NEJMc2207519
6. Takashita E, Yamayoshi S, Halfmann P, Wilson N, Ries H, Richardson A, et al. *In vitro efficacy of antiviral agents against Omicron subvariant BA.4.6. N Engl J Med* 2022;**387**(22):2094–7. https://doi.org/10.1056/NEJMc2211845

7. Imai M, Ito M, Kiso M, Yamayoshi S, Uraki R, Fukushi S, et al. *Efficacy of antiviral agents against Omicron subvariants BQ.1.1 and XBB. N Engl J Med* 2023;**388**(1):89–91. https://doi.org/10.1056/NEJMc2214302
8. Focosi D, McConnell S, Casadevall A, Cappello E, Valdiserra G, Tuccori M. *Monoclonal antibody therapies against SARS-CoV-2. Lancet Infect Dis* 2022 Nov;**22**(11):e311–26. https://doi.org/10.1016/S1473-3099(22)00311-5. Epub 2022 Jul 5.
9. Planas D, Saunders N, Maes P, Guivel-Benhassine F, Planchais C, Buchrieser J, et al. *Considerable escape of SARS-CoV-2 Omicron to antibody neutralization. Nature* 2022;**602**(7898):671–5. https://doi.org/10.1038/s41586-021-04389-z
10. Cao Y, Wang J, Jian F, Xiao T, Song W, Yisimayi A, et al. *Omicron escapes the majority of existing SARS-CoV-2 neutralizing antibodies. Nature* 2022;**602**(7898):657–63. https://doi.org/10.1038/s41586-021-04385-3
11. Yamasoba D, Kosugi Y, Kimura I, Fujita S, Uriu K, Ito J. *Neutralisation sensitivity of SARS-CoV-2 omicron subvariants to therapeutic monoclonal antibodies. Lancet Infect Dis* 2022;**22**(7):942–3. https://doi.org/10.1016/S1473-3099(22)00365-6
12. Convertino I, Ferraro S, Cappello E, Valdiserra G, Bonaso M, Tuccori M, et al. *Tixagevimab + cilgavimab against SARS-CoV-2: the preclinical and clinical development and real-world evidence. Expert Opin Drug Discov* 2023;**18**(3):231–45. https://doi.org/10.1080/17460441.2023.2170348
13. Touret F, Giraud E, Bourret J, Donati F, Tran-Rajau J, Chiaravalli J, et al. *Enhanced neutralization escape to therapeutic monoclonal antibodies by SARS-CoV-2 omicron sub-lineages. iScience* 2023;**26**(4):106413. https://doi.org/10.1016/j.isci.2023.106413
14. Bruel T, Vrignaud LL, Porrot F, Staropoli I, Planas D, Guivel-Benhassine F, et al. *Sotrovimab therapy elicits antiviral activities against Omicron BQ.1.1 and XBB.1.5 in sera of immunocompromised patients. Med* 2023;**4**(10):664–7. https://doi.org/10.1016/j.medj.2023.07.007
15. U.S. Food and Drug Administration. FDA updates on Sotrovimab emergency use authorization. Available from: ⟨https://www.fda.gov/drugs/drug-safety-and-availability/fda-updates-sotrovimab-emergency-use-authorization⟩. Accessed on 10 May 2024.
16. European Medicines Agency. COVID-19 medicines. Available from: ⟨https://www.ema.europa.eu/en/human-regulatory-overview/public-health-threats/coronavirus-disease-covid-19/covid-19-medicines#authorised-covid-19-treatments-section⟩. Accessed on 10 May 2024.
17. Mazzaferri F, Mirandola M, Savoldi A, De Nardo P, Morra M, Tebon M, et al. *Exploratory data on the clinical efficacy of monoclonal antibodies against SARS-CoV-2 Omicron variant of concern. Elife* 2022;**11**:e79639. https://doi.org/10.7554/eLife.79639
18. WHO Working Group on the Clinical Characterisation and Management of COVID-19 infection. *A minimal common outcome measure set for COVID-19 clinical research. Lancet Infect Dis* 2020 Aug;**20**:e192–7. https://doi.org/10.1016/S1473-3099(20)30483-7
19. Rubio-Rivas M, Mora-Luján JM, Formiga F, Arévalo-Cañas C, LebrónRamos JM, VillalbaGarcía M, et al. *WHO ordinal scale and inflammation risk categories in COVID-19. Comparative study of the severity scales. J Gen Intern Med* 2022:1980–7. https://doi.org/10.1007/s11606-022-07511-7
20. Rueca M, Giombini E, Messina F, Bartolini B, Di Caro A, Capobianchi MR, Gruber CE. *The easy-to-use SARS-CoV-2 assembler for genome sequencing: development study. JMIR Bioinform Biotechnol* 2022;**3**(1):e31536. https://doi.org/10.2196/31536
21. U.S. Department of Health and Human Services. Food and Drug Administration. Assessing COVID-19-related symptoms in outpatient adult and adolescent subjects in clinical trials of drugs and biological products for COVID-19 prevention or treatment. Available from: ⟨https://www.fda.gov/regulatory-information/search-fda-guidance-documents/assessing-covid-19-related-symptoms-outpatient-adult-and-adolescent-subjects-clinical-trials-drugs⟩. Accessed 23 March 2024.
22. Aggarwal NR, Molina KC, Beaty LE, Bennett TD, Carlson NE, Mayer DA, et al. *Real-world use of nirmatrelvir– ritonavir in outpatients with COVID-19 during the era of omicron variants including BA.4 and BA.5 in Colorado, USA: a retrospective cohort study. Lancet Infect Dis* 2023. https://doi.org/10.1016/S1473-3099(23)00011-7
23. Wong CKH, Au ICH, Lau KTK, Lau EHY, Cowling BJ, Leung GM. *Real-world effectiveness of early molnupiravir or nirmatrelvir-ritonavir in hospitalised patients with COVID-19 without supplemental oxygen requirement on admission during Hong Kong's omicron BA.2 wave: a retrospective cohort study [published correction appears in Lancet Infect Dis. 2024 Feb;24(2):e83. doi: 10.1016/S1473-3099(23)00755-7]. Lancet Infect Dis* 2022;**22**(12):1681–93.
24. Dormuth CR, Kim JD, Fisher A, Piszczek J, Kuo IF. *Nirmatrelvir-ritonavir and COVID-19 mortality and hospitalization among patients with vulnerability to COVID-19 complications. JAMA Netw Open* 2023 Oct 2;**6**(10):e2336678. https://doi.org/10.1001/jamanetworkopen.2023.36678
25. Xie Y, Bowe B, Al-Aly Z. *Nirmatrelvir and risk of hospital admission or death in adults with covid-19: emulation of a randomized target trial using electronic health records. BMJ* 2023;**381**:e073312. https://doi.org/10.1136/bmj-2022-073312
26. Arbel R, Wolff Sagy Y, Hoshen M, Battat E, Lavie G, Sergienko R, et al. *Nirmatrelvir use and severe Covid-19 outcomes during the omicron surge. N Engl J Med* 2022;**387**:790–8.
27. Chavda VP, Bezbaruah R, Deka K, Nongrang L, Kalita T, et al. *The Delta and Omicron variants of SARS-CoV-2: what we know so far. Vaccines* 2022 Nov 14;**10**(11):1926. https://doi.org/10.3390/vaccines10111926
28. Hedberg P, Parczewski M, Serwin K, Marchetti G, Bai F, Ole Jensen BE, et al. *In-hospital mortality during the wild-type, alpha, delta, and omicron SARS-CoV-2 waves: a multinational cohort study in the EuCARE project. Lancet Reg Health Eur* 2024;**38**:100855. https://doi.org/10.1016/j.lanepe.2024.100855
29. Akerman A, Milogiannakis V, Jean T, Esneau C, Silva MR, Ison T, et al. *Emergence and antibody evasion of BQ, BA.2.75 and SARS-CoV-2 recombinant sub-lineages in the face of maturing antibody breadth at the population level. EBioMedicine* 2023;**90**:104545. https://doi.org/10.1016/j.ebiom.2023.104545
30. Arora P, Cossmann A, Schulz SR, Ramos GM, Stankov MV, Jäck HM, et al. *Neutralisation sensitivity of the SARS-CoV-2 XBB.1 lineage. Lancet Infect Dis* 2023;**23**(2):147–8. https://doi.org/10.1016/S1473-3099(22)00831-3
31. Arora P, Kempf A, Nehlmeier I, Schulz SR, Jäck HM, Pöhlmann S, et al. *Omicron sublineage BQ.1.1 resistance to monoclonal antibodies. Lancet Infect Dis* 2023;**23**(1):22–3. https://doi.org/10.1016/S1473-3099(22)00733-2
32. Planas D, Bruel T, Staropoli I, Guivel-Benhassine F, Porrot F, Maes P, et al. *Resistance of Omicron subvariants BA.2.75.2, BA.4.6, and BQ.1.1 to neutralizing antibodies. Nat Commun* 2023;**14**(1):824. https://doi.org/10.1038/s41467-023-36561-6
33. Corti D, Purcell LA, Snell G, Veesler D. *Tackling COVID-19 with neutralizing monoclonal antibodies. Cell* 2021;**184**(17):4593–5. https://doi.org/10.1016/j.cell.2021.07.027
34. Addetia A, Piccoli L, Case JB, Park YJ, Beltramello M, Guarino B, et al. *Neutralization, effector function and immune imprinting of Omicron variants. Nature* 2023;**621**(7979):592–601. https://doi.org/10.1038/s41586-023-06487-6
35. Evans A, Qi C, Adebayo JO, Underwood J, Coulson J, Bailey R, et al. *Real-world effectiveness of molnupiravir, nirmatrelvir-ritonavir, and sotrovimab on preventing hospital admission among higher-risk patients with COVID-19 in Wales: a retrospective cohort study. J Infect* 2023 Apr;**86**(4):352–60. https://doi.org/10.1016/j.jinf.2023.02.012
36. Zaqout A, Almaslamani MA, Chemaitelly H, Hashim SA, Ittaman A, Alimam A, et al. *Effectiveness of the neutralizing antibody sotrovimab among high-risk patients with mild-to-moderate SARS-CoV-2 in Qatar. Int J Infect Dis* 2022;**124**:96–103. https://doi.org/10.1016/j.ijid.2022.09.023
37. Zheng B, Tazare J, Nab L, OpenSAFELY Collaborative. *Comparative effectiveness of nirmatrelvir/ritonavir versus sotrovimab and molnupiravir for preventing severe COVID-19 outcomes in non-hospitalised high-risk patients during Omicron waves: observational cohort study using the OpenSAFELY platform. Lancet Reg Health Eur* 2023 Oct 8;**34**:100741. https://doi.org/10.1016/j.lanepe.2023.100741
38. Ross SB, Bortolussi-Courval É, Hanula R, Lee TC, Goodwin Wilson M, McDonald EG. *Drug interactions with nirmatrelvir-ritonavir in older adults using multiple medications. JAMA Netw Open* 2022;**5**(7):e2220184. https://doi.org/10.1001/jamanetworkopen.2022.20184
39. Cao B, Wang Y, Lu H, Huang C, Yang Y, Shang L, et al. *Oral Simnotrelvir for adult patients with mild-to-moderate Covid-19. N Engl J Med* 2024;**390**(3):230–41. https://doi.org/10.1056/NEJMoa2301425
40. Yotsuyanagi H, Ohmagari N, Doi Y, Imamura T, Sonoyama T, Ichihashi G, et al. *A phase 2/3 study of S-217622 in participants with SARS-CoV-2 infection (Phase 3 part). Medicine* 2023;**102**(8):e33024. https://doi.org/10.1097/MD.0000000000033024
41. Gentilotti E, Górska A, Tami A, Gusinow R, Mirandola M, Rodríguez Baño J, et al. *Clinical phenotypes and quality of life to define post-COVID-19 syndrome: a cluster analysis of the multinational, prospective ORCHESTRA cohort. EClinicalMedicine* 2023 Jul 21;**62**:102107. https://doi.org/10.1016/j.eclinm.2023.102107
42. CoMeCT. The Trial Coordination Board (TCB). Available from: ⟨https://comectproject.org/tcb⟩.