Valentina Mazzotta ORCID iD: 0000-0002-0240-7504
Alessandra Vergori ORCID iD: 0000-0001-6944-0686
Pierluca Piselli ORCID iD: 0000-0002-7342-0263

Viral load decrease in SARS-CoV-2 BA.1 and BA.2 Omicron sublineages infection after treatment with monoclonal antibodies and direct antiviral agents

Mazzotta Valentina [1,2], Cozzi Lepri Alessandro [3], Colavita Francesca[4], Rosati Silvia[1], Lalle Eleonora[4], Cimaglia Claudia[5], Paulicelli Jessica[1], Mastrorosa Ilaria[1], Vita Serena[1], Fabeni Lavinia[4], Vergori Alessandra[1], Maffongelli Gaetano[1], Carletti Fabrizio[4], Lanini Simone[1], Caraffa Emanuela[1], Milozzi Eugenia[1], Libertone Raffaella[1], Piselli Pierluca[5], Girardi Enrico[6], Garbuglia AnnaRosa[4], Vaia Francesco[7], Maggi Fabrizio[4], Nicastri Emanuele[1], Antinori Andrea[1], on behalf of INMI COVID-19 Outpatient Treatment Study Group.

[1]Clinical and Research Infectious Diseases Department, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Rome, Italy;

[2]PhD course in Microbiology, Immunology, Infectious Diseases, and Transplants (MIMIT), University of Rome Tor Vergata, Rome, Italy;

[3]Centre for Clinical Research, Epidemiology, Modelling and Evaluation (CREME), Institute for Global Health, UCL, London, UK.

[4]Laboratory of Virology, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Rome, Italy;

[5]Clinical Epidemiology, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Rome, Italy;

[6]Scientific Direction, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Rome, Italy;

[7]General Direction, National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS, Rome, Italy;

Corresponding author

Valentina Mazzotta, MD

e-mail: valentina.mazzotta@inmi.it

Fax: +39 06 55170477

Clinical and Research Infectious Diseases Department

National Institute for Infectious Diseases Lazzaro Spallanzani IRCCS

Phone: +39 06 55170546

Via Portuense 292, 00149 Roma, Italy

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Shortened title

Viral load decrease with early COVID-19 therapies

Keywords: antiviral agents, monoclonal antibodies, virological efficacy, Omicron variant, BA.1, BA.2.

ABSTRACT (words=212)

Background

The efficacy on the Omicron variant of the approved early- coronavirus disease 2019 (COVID-19) therapies, especially monoclonal antibodies, has been challenged by *in vitro* neutralization data, while data on *in vivo* antiviral activity are lacking.

Materials and methods

We assessed potential decrease from day1 to day7 viral load (VL) in nasopharyngeal swabs of outpatients receiving Sotrovimab, Molnupiravir, Remdesivir, or Nirmatrelvir/ritonavir for mild-to-moderate COVID-19 due to sublineages BA.1 or BA.2, and average treatment effect (ATE) by weighted marginal linear regression models.

Results

A total of 521 patients [378 BA.1 (73%),143 (27%) BA.2] received treatments (Sotrovimab 202, Molnupiravir 117, Nirmatrelvir/ritonavir 84, and Remdesivir 118): median age 66 years, 90% vaccinated, median time from symptoms onset 3 days. Day1 mean viral load was 4.12 log2 (4.16 for BA.1 and 4.01 for BA.2). The adjusted analysis showed that Nirmatrelvir/ritonavir significantly reduced VL compared to all the other drugs, except vs. Molnupiravir in BA.2. Molnupiravir was superior to Remdesivir in both BA.1 and BA.2, and to Sotrovimab in BA.2. Sotrovimab had better activity than Remdesivir only against BA.1.

Conclusions

Nirmatrelvir/ritonavir showed the greatest antiviral activity against Omicron variant, comparable to Molnupiravir only in the BA.2 subgroup. VL decrease could be a valuable surrogate of drug activity in the context of the high prevalence of vaccinated people and low probability of hospital admission.

MAIN TEXT

Introduction

As of the end of 2021, the Omicron (B.1.1.529) variant of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), and its sublineages BA.1 and BA.2, have become the predominant variants responsible for coronavirus disease 2019 (COVID-19) circulating worldwide[1]. The large number of critical mutations in Spike protein of these subvariants raised concerns about the efficacy of therapies for the early phase of COVID-19, particularly of monoclonal antibodies (mAbs).[2]

Previously published *in vitro* data showed that mAbs combination Bamlanivimab/Etesevimab and Casirivimab/Imdevimab showed little neutralizing activity against BA.1 and BA.2[3 4]; conversely, Sotrovimab retained most of the activity against omicron/BA.1, but was escaped by omicron/BA.2, with a 16 to 37 fold-reduction in neutralizing activity[5 6]; finally, Tixagevimab/Cilgavimab retained most of the activity against BA.2, but it was not as effective against BA.1[7 8]. Differently from mAbs, antiviral agents, such as Remdesivir, Molnupiravir, or

Nirmatrelvir/ritonavir, which target the highly conserved protein of SARS-CoV-2, consistently retained *in vitro* activity against both BA.1 and BA.2 sublineages[9 10 11].
Analyses of *in vivo* data evaluating the clinical efficacy of these agents against the new variant are lacking. Primary endpoint in phase-3 randomized studies[12 13 14 15 16 17] in COVID-19 was typically the proportion of participants hospitalized or dead after randomization. Due to the lower risk of severe outcomes following SARS-CoV-2 Omicron infection[18], and considering the high prevalence of vaccinated people[19] during the Omicron[20] wave, a clinical outcome is not suited to the current scenario. Viral load reduction from baseline through day 7 was used as the endpoint of phase-2 studies of mAbs and may be a valuable surrogate marker of *in vivo* neutralizing or antiviral activity[21 22].
We assessed the *in vivo* viral load reduction in nasopharyngeal swab (NPS) collected on day 1 and day 7 from outpatients treated with Sotrovimab, Molnupiravir, Remdesivir, or Nirmatrelvir/ritonavir for mild-to-moderate COVID-19 due to sublineages BA.1 or BA.2.

Methods

This analysis uses the data of an observational study on the effectiveness of early treatment for outpatients with mild-to-moderate COVID-19. The study was approved by the Scientific Committee of the Italian Medicine Agency (AIFA) and by the Ethical Committee of the Lazzaro Spallanzani Institute, as National Review Board for the COVID-19 pandemic in Italy (approval number 380/2021).
All consecutive patients presenting from the 21st of December 2021 to the 15th of March 2022 to the National Institute for Infectious Diseases "L. Spallanzani" with a confirmed SARS-CoV-2 Omicron (BA.1 or BA.2) diagnosis and a mild-to-moderate COVID-19, who met AIFA criteria for eligibility for early treatment by mAbs or antiviral agents were enrolled. Treatment allocation was subject to drug availability, time from symptoms onset, and presence of comorbidities as defined by AIFA criteria.
Outpatients visits, with a medical evaluation, vital signs recording, and laboratory tests, were scheduled at baseline (day of treatment, day1) and after seven days (day7). Patients were followed-up for the occurrence of clinical events through day 30 after starting treatment through a telephone visit.
SARS-CoV-2 load in NPS was assessed using Abbott Alinity m RealTime System (Abbott Laboratories, Wiesbaden, Germany) on day1 and day7, and expressed as log2 of cycle threshold (CT) values[23]. Identification of SARS-CoV-2 variants was performed by Sanger sequencing of the Spike coding gene on samples collected on day1 using the ABI 3500 analyzer (Applied Biosystem, Waltham, United States)[24].
SARS-COV-2 serology was performed by two chemiluminescence microparticle assays (CMIA) detecting anti-Nucleoprotein and anti-Spike/RBD IgG (ARCHITECT SARS-CoV-2 IgG, and ARCHITECT SARS-CoV-2 IgG II Quantitative; Abbott Laboratories, Wiesbaden, Germany, respectively)[25 26]. According to the manufacturer's instructions, for the two CMIA, Index >1.4 and Binding Antibody Units (BAU)/mL ≥7.1 are considered positive for anti-N and anti-Spike/RBD IgG, respectively.

Primary endpoint was log2 viral load variation from day1 to day7. We adopted the log transformation because the distribution of the viral load change in the raw scale was positively skewed and significantly deviating from the normal distribution. Secondary endpoints were the proportion of negative NPS at day7 and the proportion of patients who experienced COVID-related clinical failure, defined as hospitalization due to development of severe COVID-19 or death from any cause over days 0-30.

Because of the observed large between-patients variability in day 1 value, we have also performed a sensitivity analysis using the percentage variation at day 7 as an alternative endpoint. This was calculated as the difference between the value at day 7 minus the value at day 1 divided by the value at day 1 (all values in the log2 scale).

Main characteristics of the participants, assessed on day1, were compared by treatment strategy using Chi-square (categorical variables) and Kruskal-Wallis (continuous variable) tests. We estimated potential outcomes and the average treatment effect (ATE) of treatment on viral load change on day7. Because we had 4 drugs to compare this led to 6 possible 2-by-2 comparisons in separate parallel trials. We controlled for confounding by modeling the treatment assignment (via inverse probability of weighting) or the outcome (via regression adjustment) or both (doubly robust methods). The latter provides unbiased estimates for the treatment effect even if one of the models is mis-specified. According to our assumptions, we identified the following key confounding factors: calendar month of infusion, immunodeficiency at time of infusion, and duration of symptoms. All analyses were controlled for these factors.

Proportion of participants who experienced the secondary endpoints was shown by treatment group and compared using a Chi-square test. All analyses were stratified by type of Omicron variant detected (BA.1 vs BA.2).

Results

Of 568 participants enrolled, 521 had a viral load measured at day7: 202 received Sotrovimab, 117 Molnupiravir, 84 Nirmatrelvir/ritonavir, and 118 Remdesivir. Overall, 250 (48%) were female, 469 (90%) were vaccinated and 81 (15%) had negative baseline serology. Median age was 66 years (IQR 55-76) and median time from symptoms onset to day1 was 3 days (2-4). BA.1 and BA.2 were detected in 378 (73%) and 143 (27%), respectively. A higher proportion of chronic respiratory disease (chi-square, p<0·001), liver disease (p<0·001), and immunodeficiency (p=0·01) was observed on day1 among participants receiving Sotrovimab. The baseline mean viral load was 4·12 (SD 0·27) $\log_2$ CT [4·16 for BA.1 and 4·01 for BA.2]. Detailed characteristics according to treatment groups are reported in Table 1. Linear regression analysis calculating the average treatment effect of therapies when compared to each other in separately emulated parallel trials showed that Nirmatrelvir/ritonavir significantly reduced viral load compared to other drugs both in the BA.1 and BA.2 subgroups. In contrast, there was no difference in activity between Molnupiravir and Nirmatrelvir/ritonavir against BA.2.

No evidence for a difference was also found against BA.1 between Sotrovimab and Molnupiravir.

Sotrovimab had better activity than Remdesivir only against BA.1 (Figure 1a and 1b).

Detailed results of potential decrease in viral load and average treatment effect for all possible 2-by-2 treatment comparisons separately for BA.1 and BA.2 are also shown in Supplementary Tables 1 and 2.

All variations of SARS-CoV-2 RNA levels from day1 to day7 according to treatment groups are reported in Supplementary Figure 1.

Results were similar when we used the alternative endpoint of percentage variation at day 7 (Supplementary Table 3)

Proportion of participants with CT≤40 at day7 was 6·7% (35/521, 31 infected with BA.1 and 4 with BA.2). See details in Table 2.

COVID-19-related hospitalization or death from any cause through day 30 was assessed in 568 patients: 9 patients [7/226 (3·1%) Sotrovimab (5 BA.1) and 2/87 (2·3%) Nirmatrelvir/ritonavir (2 BA.1)] experienced clinical failure.

Discussion

Our study showed that considering the reduction of viral load as a marker of antiviral activity in vivo, Nirmatrelvir/ritonavir had the strongest activity in all face-to-face treatment comparisons in patients infected with BA.1 and BA.2, with the only exception of no evidence for a difference versus Molnupiravir for BA.2 infected. Molnupiravir had better activity against Remdesivir in both BA.1 and BA.2, comparable activity against BA.1, and better activity in BA.2 than Sotrovimab. Sotrovimab had better activity than Remdesivir against BA.1 but there was no significant difference between Sotrovimab and Remdesivir for BA.2.

We evaluated the decrease in viral load in the nasopharyngeal swab as a surrogate for drug activity that could reflect the clinical response to treatment. Due to the low rate of hospitalization and death in persons infected with Omicron variants, it has become increasingly difficult to design clinical studies with adequate statistical power. Therefore, in the absence of clinical events, the change in viral load could be a candidate surrogate endpoint for clinical response.

More studies are needed to test whether early viral load decrease is a strong and consistent surrogate or whether it might be subject to what is known as the 'surrogate paradox'[27 28]

Anyway, our results showed concordance of viral load decrease from day 1 to day 7 with known data on early COVID-19 therapies and reflected previously *in vitro* published data: the virologic efficacy of Nirmatrelvir/ritonavir was the counterpart to the high clinical efficacy demonstrated in the registrative trials[15] and real-life data[29]. The lower change in viral load in patients with BA.2 compared with BA.1 during Sotrovimab therapy was also in agreement with the lower neutralizing activity observed *in vitro* for this monoclonal antibody[9]. Likewise, the poor activity on viral load reduction of Remdesivir with both BA.1 and BA.2 subvariants agreed with the data from the Pinetree study[16]. Molnupiravir activity toward both variants, with a better profile on BA.2 also seemed to agree with recent *in vitro* data[10].

The main limitations of our analysis are the observational nature of the study and the lack of a randomized design, which does not allow to rule out confounding bias. These limitations are partially mitigated by the use of weighted marginal linear regression models and appropriate control of measured confounding factors. Our

results are however important as, to the best of our knowledge, this is the first analysis to evaluate the *in vivo* efficacy of currently available treatments against the Omicron BA.1 and BA.2 variants.

Even if the evolution of Sars-Cov-2 variants is faster than the generation of data on drug efficacy and the current epidemiological scenario is dominated by new sublineages, data such as ours can still contribute to the classification of the disease, especially in light of the direct correlation with BA.2 of some sublineages (e.g. BA.2.75[30] in India) and the resulting similar susceptibility. Furthermore, we do not know whether future variants will reoccur with similar mutations to previous ones (as has already happened, for example, with the reappearance in BA.4 and BA.5 of the mutation at position 425, already seen in the Delta variant).

In conclusion, according to our viral load change dynamic model and assumptions, in outpatients with mild-to-moderate COVID-19, Nirmatrelvir/ritonavir appears to be the option with the strongest *in vivo* antiviral activity against the Omicron variant among all other treatment options examined. Only for Molnupiravir and limited to the BA.2 sublineage, the antiviral effect appeared to be comparable to that observed with Nirmatrelvir/ritonavir. Because of the low incidence of hospital admissions in the Omicron era, the emulation of trials with surrogate endpoints such as *in vivo* neutralizing activity can provide useful information for treatment decisions of early COVID-19.

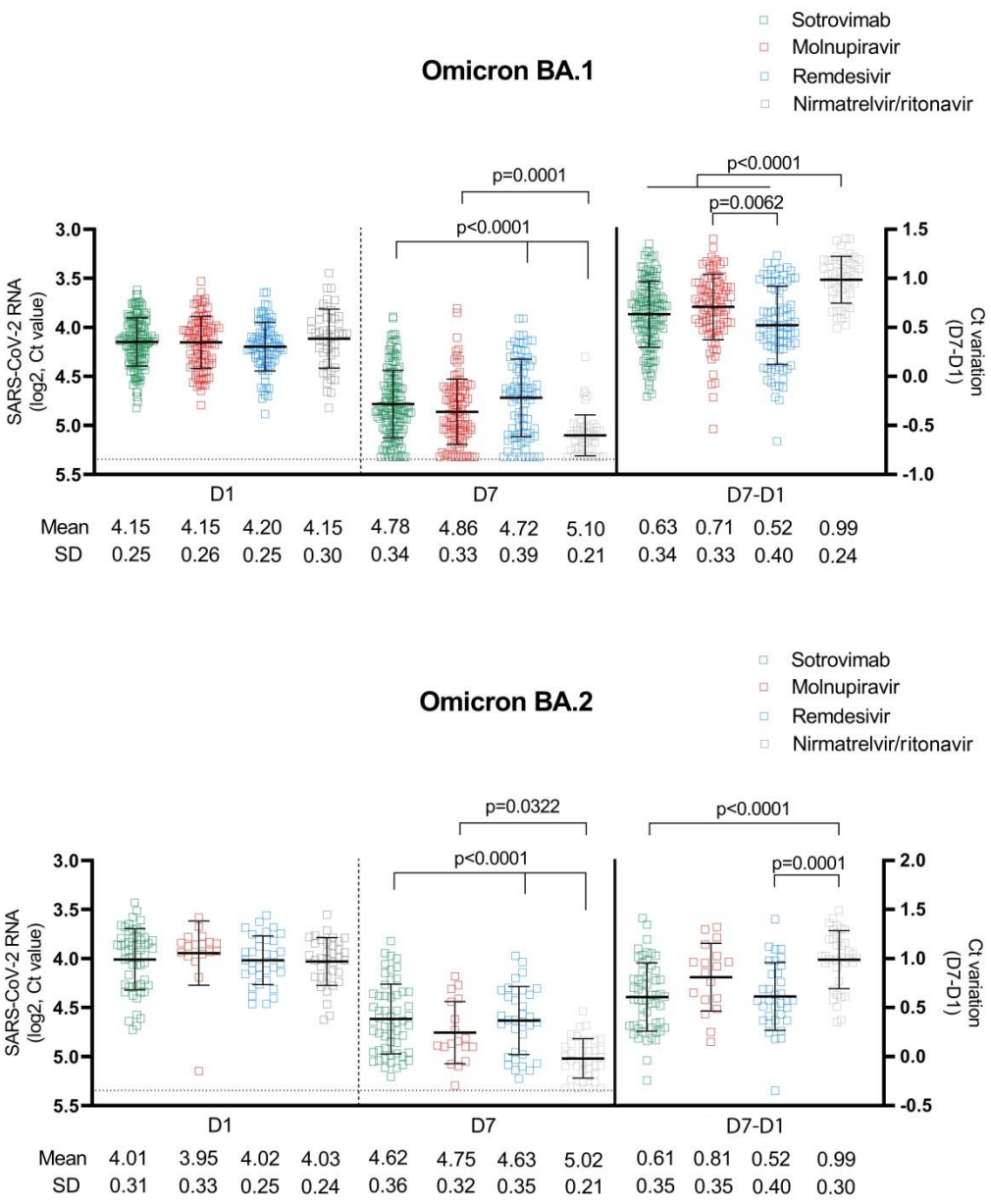

Figure 1. SARS-CoV-2 RNA levels at D1 and D7 in patients treated with Sotrovimab, Molnupiravir, Remdesivir and Nirmatrelvir/ritonavir

Dot-plots showing the comparison of viral loads detected at D1 and D7 and the variation of RNA levels observed between the two time-points by intervention in **(A)** patients with Omicron BA.1 infection treated with Sotrovimab (n=146), or Molnupiravir (n=99), or Remdesivir (n=84), or Nirmatrelvir/ritonavir (n=49); **(B)** patients with Omicron BA.2 infection treated with Sotrovimab (n=56), or Molnupiravir (n=18), or Remdesivir (n=34), or Nirmatrelvir/ritonavir (n=35). Viral RNA levels are expressed as log2 CT values. Mean of log2 CT values and SD are shown. Statistical analysis of the comparisons between treatment groups was performed by Kruskal-Wallis test, adjusted with Dunn's multiple comparisons test. Horizontal dashed line represents the limit of detection (CT: 40.0), values ≥40 are considered negative.

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Data statement

Anonymized participant data will be made available upon reasonable requests directed to the corresponding author. Proposals will be reviewed and approved by investigator, and collaborators on the basis of scientific merit. After approval of a proposal, data can be shared through a secure online platform after signing a data access agreement.

Author contributions statement

AA and VM conceptualized and designed the study. VM, FC and ACL wrote the first draft of the manuscript and referred to appropriate literature. ACL was also the main responsible person for formal data analysis. AA, ACL, VM, FC, FM and EN conceived, supervised the study and contributed to data interpretation. JP, CC and PP were responsible for data collection and curation. FV, EG, PP, AGR, FM, IM, AV revised the manuscript content, reviewed and edited the manuscript. FC, LF, EL, AGR, FC and FM performed all virological test. VM, IM, AV, SV, EC, EM, RL, GM and SR enrolled participants. All authors agreed with and approved the final version of the manuscript.

Conflict of Interest Statement

A.A. declares consultancy fees from Gilead Sciences, Merck, GSK, Pfizer, Astra Zeneca, and research institutional grants from Gilead Sciences and the Italian Medicine Agency (AIFA).

EN declares consultancy fees from Gilead Sciences, Eli-lilly, Roche and Sobi.

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Table 1. Main characteristics at enrolment by intervention

	Regimen started					
Characteristics	**Sotrovimab**	**Molnupiravir**	**Remdesivir**	**Nirmatrelvir/ritonavir**	***p*-value***	**Total**
	N= 202	N= 117	N= 118	N= 84		N= 521
Gender, n(%)					0.454	
Female	105 (52.0%)	52 (44.4%)	52 (44.1%)	41 (48.8%)		250 (48.0%)
Age, years					0.092	
Median (IQR)	63 (52, 75)	68 (57, 75)	70 (57, 78)	63 (55, 76)		66 (55, 76)
Older than 65, n(%)	93 (46.0%)	65 (55.6%)	71 (60.2%)	36 (42.9%)	0.028	265 (50.9%)
Days from sypmtoms onset to MAbs infusion					0.003	
Median (IQR)	3 (2, 5)	3 (2, 4)	4 (2, 5)	3 (2, 4)		3 (2, 4)
Comorbidities/risk factors, n(%)						
Diabetes	28 (13.9%)	24 (20.5%)	23 (19.5%)	19 (22.6%)	0.239	94 (18.0%)
Obesity (BMI>30)	93 (46.0%)	64 (54.7%)	73 (61.9%)	53 (63.1%)	0.012	283 (54.3%)
CVD	31 (15.3%)	27 (23.1%)	24 (20.3%)	17 (20.2%)	0.357	99 (19.0%)
Chronic respiratory disease	22 (10.9%)	2 (1.7%)	1 (0.8%)	1 (1.2%)	<.001	26 (5.0%)
Renal impairment	7 (3.5%)	1 (0.9%)	2 (1.7%)	0 (0.0%)	0.174	10 (1.9%)
Hepatic Disease	61 (30.2%)	20 (17.1%)	21 (17.8%)	9 (10.7%)	<.001	111 (21.3%)
Cancer	32 (15.8%)	15 (12.8%)	16 (13.6%)	17 (20.2%)	0.485	80 (15.4%)
Primary/secondary immunodeficiency	52 (25.7%)	17 (14.5%)	18 (15.3%)	10 (11.9%)	0.010	97 (18.6%)
Neurologic disease	16 (7.9%)	6 (5.1%)	3 (2.5%)	4 (4.8%)	0.229	29 (5.6%)
Vital signs at baseline						
SpO2, median (IQR)	98 (97, 99)	98 (97, 99)	98 (97, 98)	98 (97, 99)	0.173	98 (97, 99)
Fever (>37.5°C), n(%)	8 (4.2%)	0 (0.0%)	2 (1.8%)	0 (0.0%)	0.036	10 (2.0%)
BMI, median (IQR)	24.65 (22.20, 28.57)	25.26 (23.23, 29.40)	26.19 (23.23, 29.02)	26.06 (23.44, 29.48)	0.093	25.31 (22.99, 29.05)
Laboratory values, median (IQR)						
Ferritin, ng/ml	99.00 (39.00, 181.0)	89.00 (48.00, 173.0)	84.00 (44.00, 155.0)	94.00 (55.00, 145.0)	0.885	91.00 (47.00, 171.0)
C-reactive protein, mg/dl	0.95 (0.32, 2.48)	0.93 (0.29, 1.91)	0.88 (0.34, 1.67)	0.99 (0.37, 1.98)	0.793	0.93 (0.32, 2.09)
Lymphocytes, /uL	1270 (870.0, 1670)	1460 (1145,	1470 (1100,	1500 (1120, 1940)	<.001	1400 (1010,

		2045)	1790)			1840)
Baseline SARS-COV-2 Serology, n(%)					0.006	
Anti-N positive	4 (2.0%)	3 (2.6%)	3 (2.5%)	3 (3.6%)		13 (2.5%)
Anti-S Positive	138 (68.3%)	90 (76.9%)	97 (82.2%)	72 (85.7%)		397 (76.2%)
Negative	43 (21.3%)	16 (13.7%)	15 (12.7%)	7 (8.3%)		81 (15.5%)
Unknown	17 (8.4%)	8 (6.8%)	3 (2.5%)	2 (2.4%)		30 (5.8%)
Vaccination, n(%)					0.185	
Yes (partly or fully)	182 (91.0%)	108 (93.1%)	101 (85.6%)	78 (92.9%)		469 (90.5%)
Vaccine type, n(%)					0.463	
BNT162b2	87 (73.7%)	50 (75.8%)	38 (74.5%)	39 (75.0%)		214 (74.6%)
mRNA-1273	22 (18.6%)	10 (15.2%)	10 (19.6%)	6 (11.5%)		48 (16.7%)
ChAdOx1	9 (7.6%)	6 (9.1%)	3 (5.9%)	7 (13.5%)		25 (8.7%)
Ad26.COV2.S	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)		0 (0.0%)
Other/unknown	64 (35.2%)	42 (38.9%)	50 (49.5%)	26 (33.3%)		182 (38.8%)
SARS-COV-2 variant, n(%)						
Omicron BA1	146 (72.3%)	99 (84.6%)	84 (71.2%)	49 (58.3%)	<.001	378 (72.6%)
Omicron BA2	56 (27.7%)	18 (15.4%)	34 (28.8%)	35 (41.7%)	<.001	143 (27.4%)
Baseline CT						
Mean (SD)	17.57 ± 3.39	17.75 ± 3.72	17.99 ± 3.31	17.23 ± 3.49	0.283	17.65 ± 3.46
log2 scale Mean (SD)	4.11 ± 0.27	4.12 ± 0.28	4.15 ± 0.26	4.08 ± 0.28	0.283	4.12 ± 0.27
Less than 25, n(%)	195 (96.5%)	114 (97.4%)	113 (95.8%)	81 (96.4%)	0.919	503 (96.5%)
MASS score, median (IQR)	3 (0, 5)	3 (2, 5)	3 (2, 5)	3 (1, 4)	0.444	3 (1, 5)
Baseline symptoms score, median (IQR)	11 (6, 14)	11 (7, 16)	8 (4, 15)	12 (8, 16)	0.172	10 (6, 15)

*Chi-square or Kruskal-Wallis test as appropriate

IQR, interquartile range; BMI, body mass index; SpO2, peripheral oxygen saturation; MASS score, Monoclonal Antibody Screening Score.

Table 2. Proportion of participants with undetectable Sars-CoV-2 in nasopharyngeal swab collected at day 7 (defined as cycle threshold, CT≤40) by intervention.

	Regimen started					
	Sotrovimab n (%)	**Molnupiravir n (%)**	**Remdesivir n (%)**	**Nirmatrelvir/ritonavir n (%)**	**Total n (%)**	***p*-value***
Omicron (BA.1 + BA.2)						
Day7 CT > 40	8 (3.96)	9 (7.69)	7 (5.93)	11 (13.10)	35 (6.72)	0.0001
Day7 CT ≤ 40	194 (96.04)	108 (92.31)	111 (94.07)	73 (86.90)	486 (93.28)	
Omicron BA.1						
Day7 CT > 40	8 (5.48)	9 (9.09)	7 (8.33)	7 (14.29)	31 (8.20)	0.0010
Day7 CT ≤ 40	138 (94.52)	90 (90.91)	77 (91.67)	42 (85.71)	347 (91.80)	
Omicron BA.2						
Day7 CT > 40	0 (0)	0 (0)	0 (0)	4 (11.43)	4 (2.80)	0.0031
Day7 CT ≤ 40	56 (100)	18 (100)	34 (100)	31(88.57)	139 (97.20)	

*Fisher's exact test

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