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### ► To cite this version:

Timothée Bruel, Lou-Léna Vrignaud, Françoise Porrot, Isabelle Staropoli, Delphine Planas, et al.. Sotrovimab therapy elicits antiviral activities against Omicron BQ.1.1 and XBB.1.5 in sera of immunocompromised patients [letter]. *Med*, 2023, 4 (10), pp.664-667. 10.1016/j.medj.2023.07.007 . pasteur-04369632

**HAL Id: pasteur-04369632**

**<https://pasteur.hal.science/pasteur-04369632v1>**

Submitted on 10 Jan 2024

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## Sotrovimab therapy elicits antiviral activities against Omicron BQ.1.1 and XBB.1.5 in sera of immunocompromised patients.

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### Summary

Antibodies effective against the recent Omicron sublineages are missing. By taking advantage of a multi-centric prospective cohort, Bruel et al show that administration of 500 mg of sotrovimab (Xevudy) induces serum neutralization and antibody-dependent cellular cytotoxicity against BQ.1.1 and XBB.1.5 in treated individuals, suggesting that it remains a therapeutic option.

### Main text

Antiviral agents including monoclonal antibodies (mAbs) and small molecules remain of utmost importance to protect the most vulnerable against severe COVID-19. Neutralizing mAbs reduce the risk of COVID-19-related hospitalization and death in high-risk patients. However, the emergence of viral variants led to a reduction of their efficacy. This climaxed with the Omicron subvariants BQ.1.1 and XBB.1.5, which fully or partially resist neutralization by all therapeutic mAbs<sup>1</sup>. Therefore, as of June 2023, mAbs are no longer recommended as treatment of COVID-19. Small molecules such as nirmaltrevir, an inhibitor of the viral 3C-like protease (associated with ritonavir in Paxlovid), or remdesivir and molnupinavir, two nucleoside analogs, also reduce to various extents, the progression to severe COVID-19. Their efficacy is conserved across SARS-CoV-2 variants<sup>1</sup>, but their route of administration or drug-drug interactions limit their use. Therefore, there is an unmet need for direct-acting antiviral agents against the most recent Omicron sublineages.

The evaluation of mAbs mostly relies on in vitro neutralization tests. These assays are heterogenous, based on different target cells and the use of viral pseudotypes or authentic isolates<sup>2</sup>. Furthermore, in vitro evaluation does not consider variations in antibody doses and pharmacokinetics, as well as the interaction of mAbs with the immune system. Antibodies may activate effector mechanisms with their fragment crystallizable (Fc). An evaluation of both neutralizing and non-neutralizing activities of mAbs in patient samples is needed to accurately determine their efficacy against SARS-CoV-2 variants.

Here, we longitudinally evaluated neutralization and antibody-dependent cellular cytotoxicity (ADCC) in serum samples of immunocompromised patients receiving sotrovimab (Xevudy), combinations of casirivimab/imdevimab (Ronapreve) and cilgavimab/tixagevimab (Evusheld), or, as a control, nirmaltrelvir/ritonavir (Paxlovid). We used authentic viral isolates to determine neutralization titers and a reporter assay to measure ADCC.

Among the 756 patients with mild-to-moderate COVID-19 recruited in the ANRS 0003S CoCoPrev cohort study, we included all immunocompromised individuals with less than 280 BAU/mL of anti-S antibodies at inclusion having a complete longitudinal follow-up (i.e., serum sample available at day 0, day 7, month 1 and month 3; n=80). Among them, 67 were treated with mAbs (sotrovimab, n=29; imdevimab/casirivimab, n=34; cilgavimab/tixagevimab, n=4), and 13 received nirmaltrelvir/ritonavir. All patients received at least 1 dose of vaccine. Age, body mass index and COVID-19 severity were similar across all groups. A complete description of patients' characteristics is available in the **Supplementary Figure 1A**.

First, we measured the levels of anti-S IgGs in sera prior to (day 0) and after treatment initiation, at day 7, month 1 and month 3 (**Supplementary Figure 1B**). We used our standardized S-Flow assay to determine BAU/mL (**see supplemental methods**). Overall, patients treated with nirmaltrelvir/ritonavir do not display a notable increase in anti-spike antibody levels during the follow up (medians of 34 [3-50.5], 36 [4.5-107], 40 [5.5 – 1709] and 45 [15 – 1563], at day 0, day 7, month 1 and month 3, respectively). Four out of the 13 patients end the follow-up with BAU/mL above 280 (**Supplementary Figure 1B**). Administration of mAbs leads to a sharp increase of BAU/mL between day 0 and day 7 in all patients (4 [1-31.5] vs. 884 [546-1,309],  $p<0.0001$ ; 13 [2-34] vs. 1,746 [977-3,522],  $p<0.0001$ ; 14.5 [2.5-131.5] vs. 3,003 [2,582-4,982], ns; for sotrovimab, imdevimab/casirivimab and cilgavimab/tixagevimab, respectively). Peak values are reached at day 7 for sotrovimab-treated individuals and M1 for those treated with imdevimab/casirivimab and cilgavimab/tixagevimab (**Supplementary Figure 1B**). At the peak, antibody levels are lower in the sotrovimab groups as compared to imdevimab/casirivimab and cilgavimab/tixagevimab groups (884 [546-1,309] vs. 3037 [664-5,611],  $p<0.0001$ ; 884 [546-1,309] vs. 3,880 [3,788-26,273]  $p=0.012$ ; respectively). These results show that the anamnestic response to S is, as expected, impaired in our study population, but that mAb administration rescues anti-S antibody levels in the serum.

Next, we measured the neutralizing activity of sera with authentic isolates of D614G, BQ.1.1 and XBB.1.5 (**see supplemental methods**). Administration of mAbs elicits serum neutralization of D614G, which remains detectable during the entire follow-up (**Supplementary Figure 1C and D**). Median titers at day 7 are lower in individuals treated with sotrovimab as compared to those treated with imdevimab/casirivimab or cilgavimab/tixagevimab (1,115 [799-1,674] vs. 100,000 [100,000-100,000],  $p<0.0001$ ; 1,115 [799-1,674] vs. 90,644 [79,516-100,000], ns; respectively). This difference remains through the follow-up. Nirmaltrelvir/ritonavir therapy leads to a non-significant increase in neutralizing titers against all tested isolates. BQ.1.1 and XBB.1.5 omicron sub-variants dramatically reduce the neutralization provided by mAbs administration. Neither imdevimab/casirivimab nor cilgavimab/tixagevimab administration elicit serum neutralization of BQ.1.1 or XBB.1.5. Low levels of neutralization of BQ1.1 and XBB.1.5 are detectable in most sotrovimab-treated individuals, and reach significance as compared to day 0 at month 1 for BQ.1.1 ( $p=0.008$ ) and at all time points for XBB.1.5 ( $p=0.0006$ ,  $p<0.0001$ ,  $p=0.0003$ ). At day 7, BQ.1.1 and XBB.1.5 neutralizing titers are reduced by 71- and 58-fold as compared to D614G (15.6 [5-24.94] and 18.9 [13.6-56.12] vs. 1,115 [799-1,674], respectively). These results are in line with in vitro evaluation of mAbs, where only sotrovimab remains active against these variants (**Supplementary Figure 1E and 1**). These results show that mAb infusion elicits a robust neutralization of SARS-CoV-2 in the serum of treated individuals, which is evaded by BQ.1.1 and XBB.1.5 but remains detectable in individuals treated with sotrovimab.

Finally, we tested the ADCC activity of the sera (**Supplementary Figure 1C and D**). We used a reporter assay based on spike-expressing 293T cells and jurkat cells expressing CD16 and NFAT-luciferase (**see supplemental methods**). Consistent with the in vitro evaluation of ADCC (**Supplementary Figure 1E**), only sotrovimab and imdevimab/casirivimab elicit significant and substantial levels of ADCC against the D614G spike. When measuring ADCC against BQ1.1 and XBB.1.5, only sotrovimab-treated individuals remain active. Of note, fold changes are limited as compared to D614G and only significantly decreased for BQ1.1 (at day 7: 3 [2.1-3.5] vs. 4.3 [3.2-4.8],

1.4-fold,  $p=0.0075$  and 4.3 [3.1-4.6] vs. 4.3 [3.2-4.8], 1-fold, ns, respectively), again in line with the in vitro evaluation (**Supplementary Figure 1E**). Nirmaltrelvir/ritonavir-treated individuals exhibit a low and sporadically significant increase in ADCC activity. These data show that sotrovimab elicits the strongest level of ADCC activity in serum, as compared to other mAbs. This ADCC activity is only slightly evaded by BQ.1.1 and preserved against XBB.1.5.

Our results show that sotrovimab infusion elicits an antiviral immunity against BQ.1.1 and XBB.1.5 in the sera of treated patients. This finding explains why several studies suggested a preserved efficacy of sotrovimab in real-life settings despite its limited neutralization<sup>3,4</sup>. This is consistent with the demonstration that low levels of neutralization are protective upon infusion of a polyfunctional mAbs<sup>5</sup>. It is also in line with the capacity of sotrovimab to limit viral replication in preclinical models of BQ.1.1 infection<sup>6</sup>. Sotrovimab relies on both neutralization and Fc-effector functions to limit SARS-CoV-2 replication in preclinical models<sup>7</sup>. Further work is needed to determine the relative contribution of neutralizing and non-neutralizing activities to the clinical efficacy of sotrovimab.

In vitro, spiking of sotrovimab in sera of patients with blood cancer increases neutralization in a dose-dependent manner<sup>8</sup>. Thus, increasing sotrovimab dose will likely enhance its in vivo antiviral activities, a hypothesis that is being tested at 1000 mg in the RECOVERY clinical trial (NCT04381936). Combination therapy with sotrovimab and antivirals also deserves investigation.

Our study has limitations. Our sample size is small, and, because of ethical reasons, we do not have a control group of untreated patients. We thus included patients treated with nirmaltrelvir/ritonavir as control. Their investigation confirms that our inclusion criteria selected for patients with impaired endogenous immune response. There is heterogeneity in infecting variants across groups, which are due to both changes in variant dominance and modifications in treatment recommendations during the study period. Also, as most patients included in the study do not produce antibodies, we cannot measure anti-N IgGs to determine prior SARS-CoV-2 exposures. All of these are, however, unlikely to bias our conclusion, albeit we can't rule out that it influences the results at the individuals' level. We did not directly quantify the monoclonal antibodies in the sera and restricted our analysis to BAU/mL. However, the measured BAU/mL mostly quantified the injected antibody. Our neutralization assay may be criticized because of the use of ACE2-overexpressing cells. Yet, ACE2 overexpression underestimates sotrovimab efficacy<sup>2</sup>. Using systems with endogenous ACE2 expression, would lead to higher neutralization titers, further confirming our conclusion. Our ADCC assay is a surrogate assay measuring CD16 activation rather than cell death by NK cells. However, we have previously demonstrated that it correlates with an ADCC cell killing assay<sup>9</sup>. Finally, we did not test the most recent omicron subvariant XBB.1.9 and XBB.1.16.1. However, their sequences suggest a similar efficacy of sotrovimab as compared to XBB.1.5, as already confirmed for XBB.1.16 in in vitro neutralization assays<sup>10</sup>.

In conclusion, our data supports the use of sotrovimab to treat the most recent Omicron lineages and suggest that increasing the dose may provide a clinical benefit.

## Acknowledgements

We thank members of the Virus and Immunity Unit for discussions and help in the preparation of this manuscript. We thank V.Leducq and E. Ghidaoui for their technical assistance. We thank L. Hocqueloux and T. Prazuck for providing the clinical antibodies for in vitro studies and Faustine Amara for her help with the plasmids. We thank Pr Y. Yazdanpanah and all the ANRS-MIE team for their invaluable support and help. The CoCoPrev study has been labeled as a National Research Priority by the National Orientation Committee for Therapeutic Trials and other researches on Covid-19 (CAPNET). The investigators would like to acknowledge ANRS | Emerging infectious diseases for their scientific support, the French Ministry of Health and Prevention and the French Ministry of Higher Education, Research and Innovation for their funding and support. This study would have not been possible without the teams involved in the CoCoPrev Study and designated as the CoCoPrev Study Group: M. Garcia, V. Giraud, A. Metais, F. Cazenave-Roblot, JP. Martellosio (CHU de Poitiers) ; AM. Ronchetti, T. Gabas, N. Hadjadj, C. Salanoubat, A. Chabrol, P. Housset, A. Pardon, AL. Faucon, V. Caudwell, L. Hanafi (CHU Sud Francilien, Corbeil-Essonnes) ; R. Liblau, L. Alric, G. Pugnet, M. Mourguet, E. Bories, D. Bonnet, S. Charpentier, P. Delobel, A. Debard, C. Beck, X. Boumaza, S. Rousset (CHU de Toulouse) ; F. Lanternier, C. Delage, E. Gomes Pires, M. Cheminant, N. Chavarot (Hôpital Necker, Paris) ; A. Chauvin,

X. Eyer ; V. Delcey (Hôpital Lariboisière, Paris) ; S. Bessis, M. Cresta, R. Gueneau (Hôpital du Kremlin Bicêtre) ; P. Thibaut, M. Nadal, M. Siguier, M. Bachir, C. Palacios (Hôpital Tenon, Paris) ; V. Pourcher, C. Melenotte, A. Faycal, V. Berot, C. Brin, S. Djebara, K. Zafilaza, S. Marot, S. Sayon, V. Leducq, I. Malet, E. Teyssou, A. Gothland (Hôpital de la Pitié Salpêtrière, Paris) ; K. Lacombe, Y. Abi Aad, T. Chiarabini, R. Feliho, N. Valin, F. Brigant, J. Boize, PC. Thiébaud, M. Moreau, C. Billard (Hôpital St Antoine, Paris), N. De Castro, G. Liégeon, B. Denis, JM. Molina, L. Etheve (Hôpital Saint Louis, Paris) ; A. Cabié, S. Abel, O. Cabras, K. Guitteaud, S. Pierre-François (CHU de Martinique) ; V. Dubee, D. Ndiaye, J. Pehlivan, M. Phelippeau, R. Mahieu (CHU d'Angers) ; A. Duvignaud, T. Piston, A. Desclaux, D. Neau, C. Cazanave (CHU de Bordeaux) ; JF. Faucher, B. Festou, M. Dupuy-Grasset, V. Loustaud-Ratti, D. Chainier (CHU de Limoges) ; N. Peiffer-Smadja, C. Choquet, O. Da Conceicao, M. Thy , L. Collas, C. Godard, D. Bouzid, Vittiaroat Ing, L. Pereira, T. Pavlowsky, C. Ravaut (Hôpital Bichat, Paris) ; A. Asquier-Khati, D. Boutoille, M. Chauveau, C. Deschanvres, F. Raffi (CHU de Nantes) ; A. Le Bot, M. Cailleaux, F. Benezit, A. Maillard, B. Hue, P. Tattevin (CHU de Rennes) ; F. Coustilleres, C. Carvalho-Schneider, S. Jamard, L. Petit, K. Stefic (CHU de Tours) ; N. Mrozek, C. Theis, M. Vidal , L. Sauvat, D. Martineau (CHU de Clermond-Ferrand) ; B. Lefèvre, G. Baronnet, A. Didier (CHRU de Nancy) ; F. Ader, T. Perpoint, A. Conrad, P. Chabert, P. Chauvelot (CHU de Lyon) ; A. Martin, P. Loubet, J. Mazet, R. Larcher, D. Laureillard (CHU de Nîmes) ; M. Devaux (Hôpital de Poissy) ; J. Frey, A. Woerlen, A. Remillon, L. Absensur-Vuillaume, P. Bouquet (CHU de Metz) ; A. Trinh-Duc, P. Rispal (Hôpital d'Agen) ; P. Petua, J. Carillo (Hôpital de Tarbes) ; A. Perrot, K. Delavigne, P. Cougoul, J. Dion, O. Rauzy (Oncopole, Toulouse), M. Blot, T. Sixt, F. Moretto, C. Charles, L. Piroth (CHU de Dijon) ; S. Circosta, L. Leger, A. Arulananthan, C. Lascoux, P. Valérie, L. Becam (Team Biobanque ANRS-INSERM US19, Villejuif) ; Y. Yazdanpanah, V. Petrov-Sanchez, A. Diallo, S. Le Mestre, G. Le Meut (ANRS-MIE) ; I. Goderel, F. Chau, B. Soltana, J. Chane Tang (IPLESP), J. Guedj (Université de Paris, IAME, INSERM, Paris), Y. Caille (Renaloo).

Work in TB and OS lab is funded by Institut Pasteur, Urgence COVID-19 Fundraising Campaign of Institut Pasteur, Fondation pour la Recherche Médicale (FRM), ANRS-MIE, the Vaccine Research Institute (ANR-10-LABX-77), Labex IBEID (ANR-10-LABX-62-IBEID), ANR / FRM Flash Covid PROTEO-SARS-CoV-2, ANR Programme Hubert Curien Maimonide, Coronamito, HERA european funding, Sanofi and IDISCOVER. The E.S.-L. laboratory receives funding from Institut Pasteur, the INCEPTION program (Investissements d'Avenir grant ANR-16-CONV-0005) and NIH PICREID program (Award Number U01AI151758).

### **Author contributions**

T.B., O.S., A.G.M. and G.M.B. designed the overall experiments, wrote the article, and had unrestricted access to all data. T.B., L.L.V, F.P, I.S, D.P, F.G., O.S. performed the experiments. C.S., K.Z., C.L.N, M.L.M., C.D., D.M., Y.Y., F. C., A.G.M., G.M.B., & C.S.G. managed the cohort. J.P., M.P., S.M., H.P., E.S.L., & D.V. provided key reagents and/or viral strains. T.B., C.L.N., M.L.N., O.S., A.G.M. & G.M.B. performed statistical analyses. All authors read and approved the final article and take responsibility for its content.

### **Declaration of interest**

T.B. and O.S. have a pending patent application for an anti-RBD mAb not used in this study (PCT/FR2021/070522). All other authors declare no conflicts of interest.

### **Inclusion and diversity**

We support inclusive, diverse, and equitable conduct of research.

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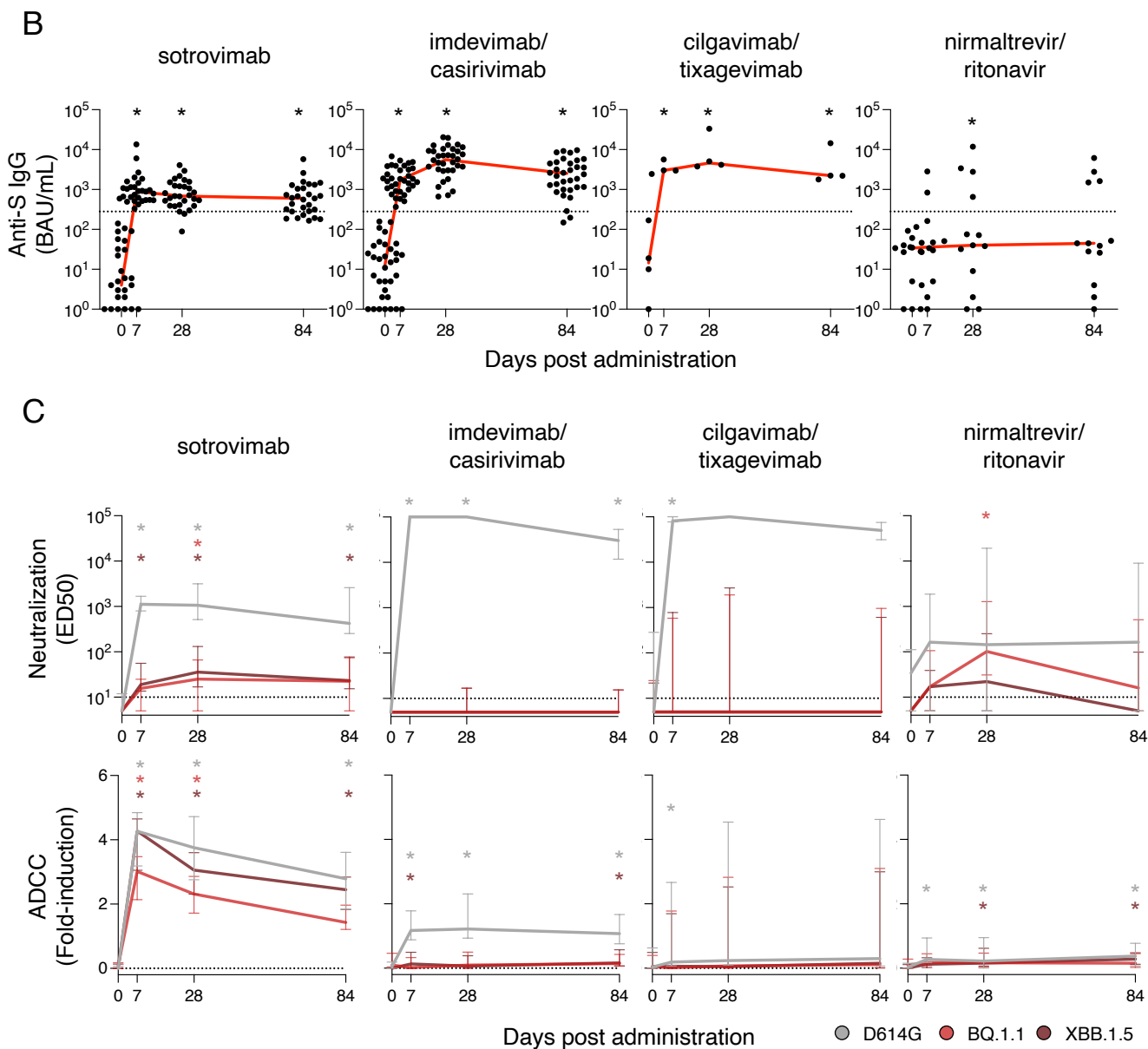
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	Total N=80	Casirivimab/ Imdevimab (1200 and 600 mg) N=34	Sotrovimab N=29	Nirmatrelvir/r N=13	Tixagévimab/ Cilgavimab N= 4	p-value
<b>SARS-CoV-2 variant (n, %)</b>						<b>&lt;0.001</b>
Delta	33 (42%)	33 (100%)	0	0	0	
Omicron	45 (58%)	0	29 (100%)	12 (92%)	4 (100%)	
Omicron BA.1	27 (33%)	0	26 (90%)	1 (8%)	0	<b>&lt;0.001</b>
Omicron BA.2	14 (17%)	0	3 (10%)	11 (84%)	0	
Omicron BA.5	4 (5%)	0	0	0	4 (100%)	
Missing	2	1	0	1	0	
<b>Age (years, median, Q1-Q3)</b>	59 (45-70)	54 (45-64)	64.5 (42.5-70.5)	65 (55-73)	47.5 (32 – 62.5)	0.16
≥ 80 years old	6 (8%)	3 (9%)	2 (7%)	1 (8%)	0	1.0
Missing	1	0	1	0	0	
<b>BMI (median, Q1-Q3)</b>	25 (23-28)	26 (21.5-30.5)	24 (23-28)	25 (22-27.5)	25 (22 - 31)	0.96
Missing	9	6	2	1	0	
<b>Male sex (n, %)</b>	37 (46%)	16 (47%)	14 (48%)	7 (54%)	0	<b>0.003</b>
<b>Immunocompromised patients (n, %)</b>	80 (100%)	34 (100%)	29 (100%)	13 (100%)	4 (100%)	-
Ongoing chemotherapy	26 (33%)	8 (24%)	9 (31%)	9 (69%)	0	<b>0.01</b>
Solid organ transplantation	23 (29%)	9 (26%)	12 (41%)	1 (8%)	1 (25 %)	0.14
Hematopoietic stem cell transplant	3 (4%)	0	2 (7%)	1 (8%)	0	0.31
Corticosteroids	9 (11%)	7 (21%)	2 (7%)	0	0	0.19
Systemic lupus or vasculitis with immunosuppressive medications	3 (4%)	1 (3%)	2 (7%)	0	0	0.80
Immunosuppressive therapy including rituximab	38 (48%)	18 (53%)	15 (52%)	2 (15%)	3 (75 %)	0.05
Cancer	7 (9%)	0	5 (17%)	2 (15%)	0	<b>0.04</b>
<b>Other non-immunosuppressive comorbidities (n, %)</b>	27 (34%)	13 (38%)	10 (34%)	2 (15%)	2 (50 %)	0.41
<b>Covid-19 severity (n, %)</b>						0.92
Mild	70 (90%)	31 (91%)	24 (86%)	11 (91%)	4 (100 %)	
Moderate	8 (10%)	3 (9%)	4 (14%)	1 (8%)	0	
Missing	2	0	1	1	0	
<b>Median time between symptoms onset and initiation of treatment (days, median, Q1-Q3)</b>	3 (2-4)	3 (2-4)	3 (2-4)	2.5 (1-4)	3 (2 – 6)	1.0
Missing	7	1	2	3	1	
<b>Vaccination status (n, %)</b>						<b>0.02</b>
Having received ≥ 3 doses of vaccine	61 (76%)	20 (60%)	25 (86%)	12 (92%)	4 (100 %)	
Having received ≤ 2 doses of vaccine	19 (24%)	14 (40%)	4 (14%)	1 (8%)	0	
Median time between last vaccine shot and initiation of treatment (days, median, Q1-Q3)	122.5 (64.5-175)	132 (67-155)	126.5 (54-234)	102.5 (73-126)	209(107-271)	0.32
Missing	8	3	3	1	1	
<b>Covid-19-related hospitalization at day 28 (%; 95% Clopper-Pearson CI)</b>	2 (3, 0-9)	0	2 (7, 1-23)	0	0	0.37

**Supplementary Figure 1: Anti-S IgG levels, neutralization, and antibody-dependent cellular cytotoxicity in sera of COVID-19 patients receiving antiviral therapies.**

(A) Clinical characteristics of the patients included in the study. Quantitative and categorical variables were compared with Kruskal-Wallis and Fisher's exact tests, respectively.



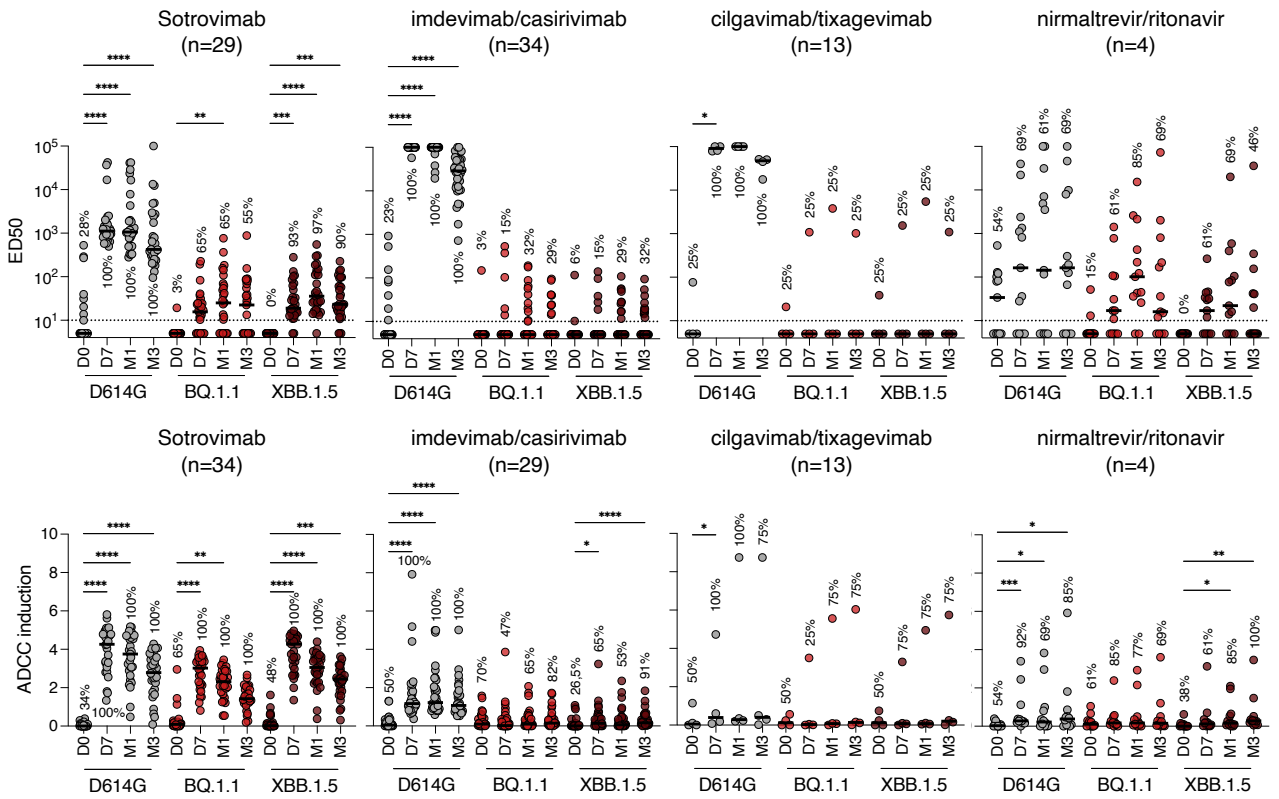
**Supplementary Figure 1 (continued): Anti-S IgG levels, neutralization, and antibody-dependent cellular cytotoxicity in sera of COVID-19 patients receiving antiviral therapies.**

(B) Anti-S IgGs were measured using the flow cytometry-based S-Flow assay in sera of individuals before and after treatment initiation. sotrovimab,  $n=29$ ; imdevimab/casirivimab,  $n=34$ ; tixagevimab/cilgavimab,  $n=4$ ; nirmaltrevir/ritonavir,  $n=13$ . Indicated are the binding antibody units (BAUs) per mL (BAU/mL) of anti-S IgGs. Stars indicate statistical significance according to a two-sided Friedman test with a Dunn's multiple comparison correction. Each dot is an individual. Red lines indicate medians. Dashed lines indicate 280 BAU/mL.

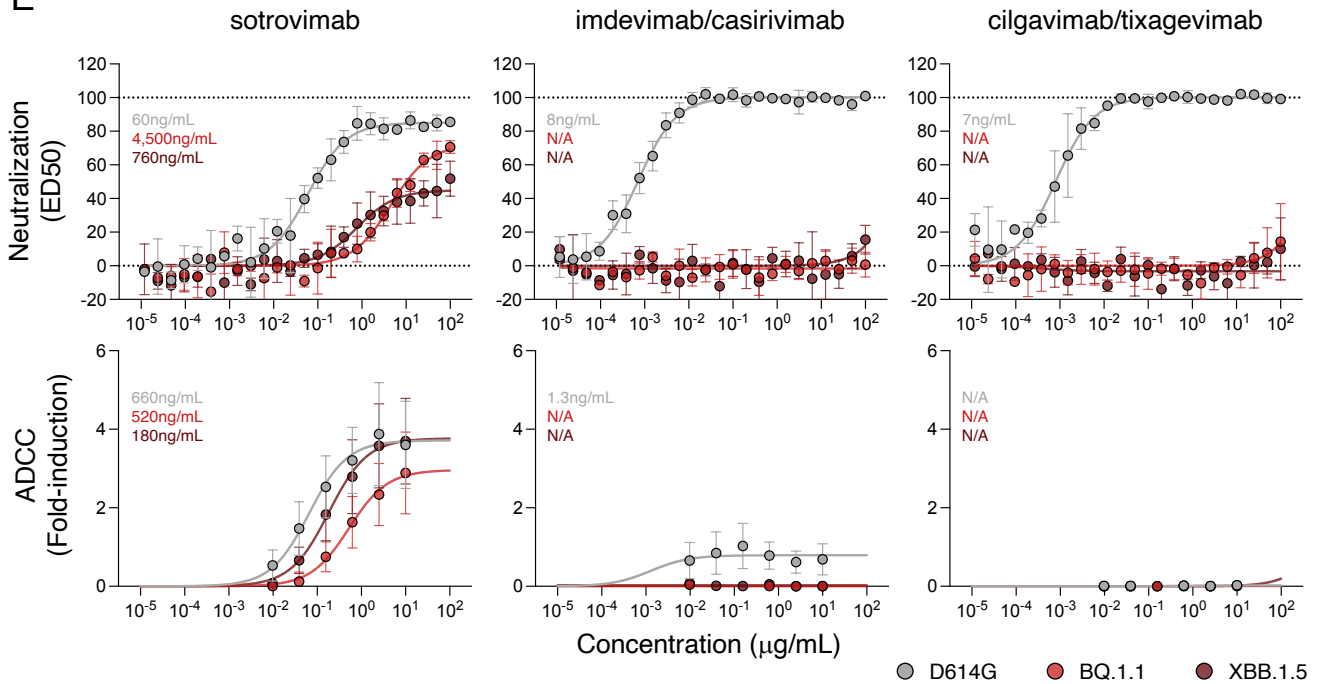
(C) Serum neutralization (upper panels) and ADCC activity (lower panels) of D614G and Omicron BQ.1.1 and XBB.1.5 in sera of individuals before and after treatment initiation. sotrovimab,  $n=29$ ; imdevimab/casirivimab,  $n=34$ ; tixagevimab/cilgavimab,  $n=4$ ; nirmaltrevir/ritonavir,  $n=13$ . Indicated are either effective dilution 50% (ED50; titers) as calculated with the S-Fuse assay (A) or fold-induction of the CD16 pathway in the ADCC reporter assay (B). Stars indicate statistical significance according to a two-sided Friedman test with a Dunn's multiple comparison correction. Colored lines indicate medians and error bars inter-quartile range. Dashed lines indicate the limits of detection.



D



E



**Supplementary Figure 1 (continued): Anti-S IgG levels, neutralization, and antibody-dependent cellular cytotoxicity in sera of COVID-19 patients receiving antiviral therapies.**

(D) Individual data points of panel C. Serum neutralization (upper panels) and ADCC activity (lower panels). The percentage of patients above the limit of detection is indicated.

(E) Dose-response analysis of the neutralization by the indicated antibodies (upper panels). Data are mean  $\pm$  SD of 3 independent experiments. The dashed lines indicate no inhibition (0%) and full inhibition (100%). Dose-response analysis of the ADCC activity by the indicated antibodies (lower panels). The y-axis indicates the fold-increase in CD16 induction, calculated using the condition without target cells and with target cells transfected with a empty plasmid. Data are mean  $\pm$  s.d. of 2-5 independent experiments.