Sotrovimab to Prevent Severe COVID-19 in High-Risk Patients Infected with Omicron BA.2

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Title page

Sotrovimab to prevent severe COVID-19 in high-risk patients infected with Omicron BA.2

Running title: Outcome of BA.2-infected patients treated by Sotrovimab

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Title page

Sotrovimab to prevent severe COVID-19 in high-risk patients infected with Omicron BA.2

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Text

Before the Omicron era, the neutralizing antibody targeting the SARS-CoV2 Spike protein Sotrovimab has been shown to reduce the risk of COVID-19-related hospitalization in patients who are at high risk for progression (1, 2). We recently showed that early administration of Sotrovimab in Omicron-infected patients with very high-risk for progression was associated with a low rate of COVID-19-related hospitalization within one month after treatment administration (3%), and with no death (1). However, the dominance of the Omicron sublineage BA.2 led health agencies to suspend Sotrovimab emergency use authorizations because of its lower neutralizing ability *in vitro* compared to BA.1 sublineage (3, 4). Clinical efficiency of Sotrovimab to prevent COVID-19 related complications in high-risk patients with mild-to-moderate COVID-19 Omicron BA.2 remains unknown. Our aim was to compare the clinical and virological outcomes of Omicron BA.1 and BA.2-infected patients with mild-to-moderate COVID-19 who received 500 mg of Sotrovimab IV to prevent COVID-19-related complications.

Our study is based on the ANRS 0003S CoCoPrev study (NCT04885452 (1)), an ongoing multicentric prospective cohort study that includes patients considered to be at high-risk for progression to severe COVID-19, having PCR-proven mild-to-moderate COVID-19 in the first five days of symptoms, and who are treated under an emergency use authorization (EUA) in one of the 32 participating centers. Treatment initiation, based on French Health Authorities recommendation, was left at the treating physician discretion. In this study we have included Omicron-infected patients with either the BA.1 or the BA.2 sublineages that have received 500 mg of Sotrovimab IV. The primary outcome was the proportion of patients with COVID-19-related hospitalization or death within one month of treatment administration. Secondary outcome was the slope of the change over time in the cycle threshold (Ct) value assessed by

nasopharyngeal PCR, predictive factors related to the virological response (viral genotypes, emergence of resistant strains), and genotypic and phenotypic characterization of resistance variants (supplementary methods). Mixed effect models were used to estimate the temporal dynamics of the Ct value. Written informed consent was obtained from each patient before enrolment. The protocol has been approved by the "CPP Sud-Est IV" Ethics Committee (Paris, France) and the French Regulatory Authority (ANSM).

Among 190 consecutive patients who received Sotrovimab a median of 3 days (Q1-Q3 2-4) after first symptoms, 47 (25%) were BA.2-infected, 136 (72%) were immunocompromised, 143 (77%) received ≥ 3 vaccines doses (Table 1). There was no significant difference between BA.1 and BA.2 groups with respect to comorbidities and anti-Spike IgG positivity. At the 28th day visit after treatment administration, respectively 3/125 (2.4% - 95% Confidence Interval (CI): 1-7%) and 1/42 (2.4% - 95% CI: 0-13%) BA.1 and BA.2-infected patients were hospitalized due to COVID-19, and none died. All of them were immunocompromised. The slope of Ct values did not differ between groups (p=0.87, Figure 1). Among the 86 patients who had extended nasopharyngeal virological follow-up due to persistent PCR positivity, 15/68 BA.1-infected patients (22%, 95%CI 13-34%) developed mutations in the Spike protein vs none of the 18 BA.2 infected patients (0%, 95%CI 0-19%, P=0.033) (Supplementary table 1). Emergence of these mutations was not associated with baseline characteristics, did not occur among patients who experienced COVID-19-related hospitalization, and did not significantly affect the slope of Ct values (Supplementary tables 2 and 3 and supplementary figure 1). Plasma collected at day 7 from 60 patients with negative IgG anti-Spike serology at Sotrovimab administration showed a four-fold reduction of neutralizing titers on BA.1 compared to BA.2 (Supplementary table 4). No major side effects have been reported.

In this prospective real-life cohort study that included mostly severely immunocompromised patients, administration of Sotrovimab in BA.2-infected patients was associated with a similarly low rate of COVID-19-related hospitalization, and decline of the nasopharyngeal viral load, as in BA.1-infected patients.

Our results suggest that, although the neutralizing power of patients' sera seven days after administration of 500 mg of Sotrovimab against the Omicron sublineage BA.2 is reduced *in vitro* compared to BA.1, Sotrovimab may still be valuable in preventing COVID-19 progression in BA.2-infected patients. A recent modelization study suggested that for current monoclonal antibody regimens, doses between 7- and >1000-fold lower than currently used could still achieve around 90% of the current effectiveness (depending on the variant) (5). In that regard, the dose administered of Sotrovimab might have potentially overcome its decreased neutralizing activity on the BA.2 sublineage. The fragment crystallizable (Fc) of some monoclonal antibodies targeting the SARS-CoV2 Spike protein, such as Casirivimab and Imdevimab, is engineered in order to reduce Fc-dependent activation of immune effector cells and of the complement system, limiting the theoretical risk of antibody dependent-enhancement (6). On the contrary, although modified to enhance its half-life, the preserved ability of Sotrovimab to recruit and engage Fcγ receptor–bearing cells and complement system activator C1q may participate through Antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) to the antiviral effect of Sotrovimab *in vivo*.

Targeting a single epitope, and used as a monotherapy, the risk of developing resistance mutations of SARS-CoV-2 in Sotrovimab-treated patients is of major concern. Mutations in the spike protein at positions 337 or 340 were shown in patients infected with the Delta (7) and the Omicron lineages (8). A recent report demonstrated across a routine genomic surveillance that these mutations occurred in 24 (0.13%) of 18,882 omicron BA.1 lineages and in one (0.02%)

of 4025 omicron BA.2 lineages, affecting mostly immunocompromised patients with persistent SARS-CoV-2 excretion (9). In this work both mutations occurred in a sizeable proportion of BA.1-infected patients but did not occur among patients who experienced COVID-19-related hospitalization, and did not significantly affect the slope of Ct values. None of them were demonstrated among BA.2-infected patients.

Although our work is limited by the relatively small number of BA.2-infected patients, Sotrovimab was associated with a low incidence of COVID-19 related hospitalization or death among very high-risk patients with mild-to-moderate COVID-19 related to the BA.2 sublineage, and with no emergence of mutations.

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Contributions:
GM (guarantor) was involved in the study conception, data extraction, data analysis, interpretation of results and drafting the manuscript. AGM was involved in the study conception, data extraction, data analysis, interpretation of results and drafting the manuscript. CS was involved in the study conception, data extraction, data analysis, interpretation of results and drafting the manuscript. SK was involved in data extraction, data analysis, interpretation of results and drafting the manuscript. CLN was involved in data extraction, data analysis, interpretation of results and drafting the manuscript. CD was involved in the study conception, data extraction, data analysis, interpretation of results and revising the manuscript. LN was involved in the study conception, data extraction, data analysis, interpretation of results and revising the manuscript. AB was involved in the study conception, data extraction, data analysis, interpretation of results and revising the manuscript. CM was involved in patients inclusion and revising the manuscript. AC was involved in patients inclusion and revising the manuscript. CC was involved in patients inclusion and revising the manuscript. FC was involved in patients inclusion and revising the manuscript. JPM was involved in patients inclusion and revising the manuscript. GG was involved in patients inclusion and revising the manuscript. ATD was involved in patients inclusion and revising the manuscript. AMR was involved in patients inclusion and revising the manuscript. VPM was involved in patients inclusion and revising the manuscript. FR was involved in patients inclusion and revising the manuscript. KL was involved in patients inclusion and revising the manuscript. NPS was involved in patients inclusion and revising the manuscript. PH was involved in patients inclusion and revising the manuscript. AP was involved in patients inclusion and revising the manuscript. GP was involved in patients inclusion and revising the manuscript. AM was involved in patients inclusion and revising the manuscript. VD was involved in patients inclusion and revising the manuscript. MD was involved in patients inclusion and revising the manuscript. JF was involved in patients inclusion and revising the manuscript. CC was involved in patients inclusion and revising the manuscript. RL was involved in the study conception, interpretation of results and revising the manuscript. FC was involved in the study conception, data extraction, data analysis, interpretation of results and drafting the manuscript. YY. (guarantor) was involved in the study conception, data extraction, data analysis, interpretation of results and drafting the manuscript.

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Ethical approval: This study received the ethical approval of the Comité de Protection des Personnes SUD-EST IV.

Transparency declaration: GM and YY (the manuscript's guarantors) affirm that the manuscript is an honest, accurate, and transparent account of the study being reported; that no

important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

Data sharing: Data available upon request for academic researchers

Tables, Figures and Legends to figures

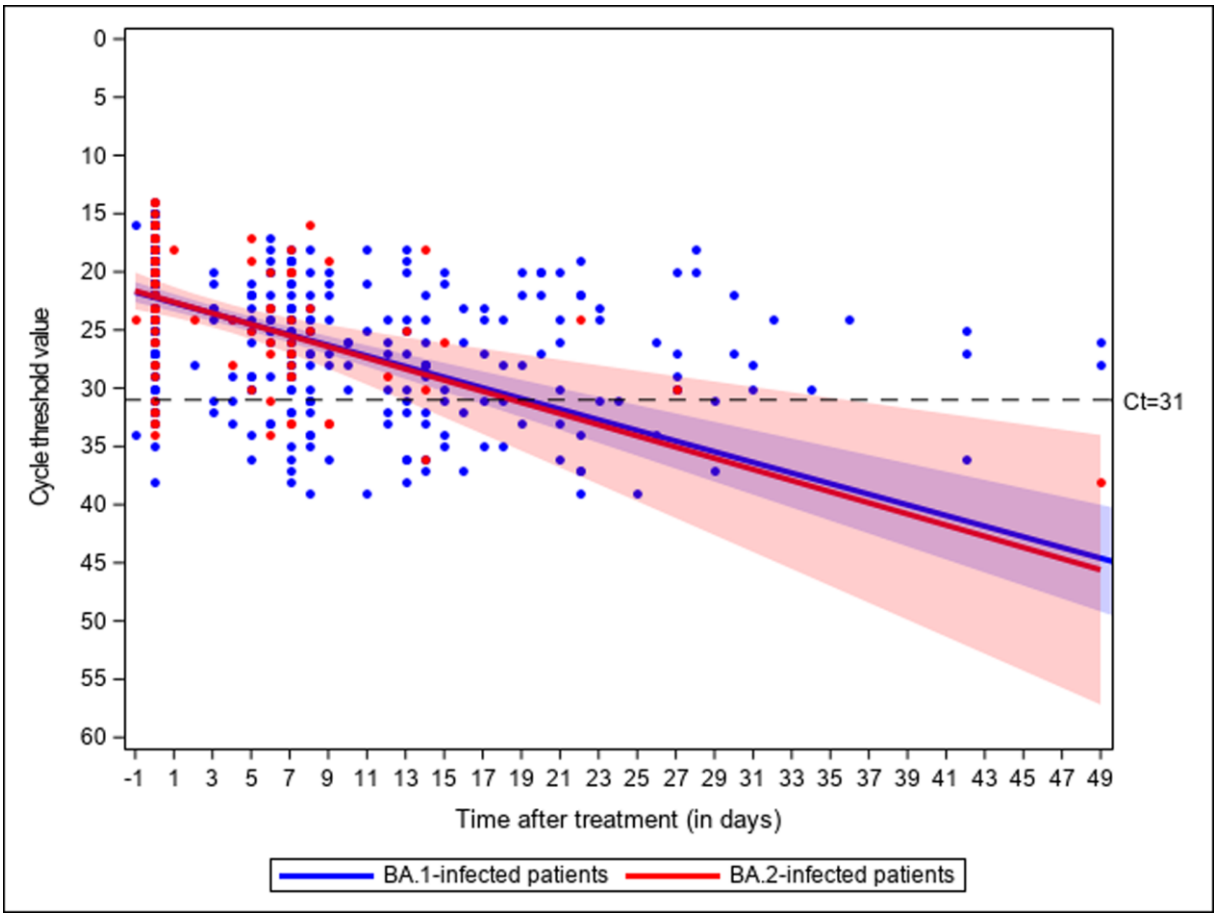
Table 1. Baseline characteristics of patients and outcomes at the 28th day visit

Baseline characteristics	**All N=190**	**BA.1-infected patients N=143 (75%)**	**BA.2-infected patients N=47 (25%)**	**p-value**
Median age (years, Q1-Q3)*	59 (45-70)	59 (44-70)	55 (50-72)	0.75
≥ 80 years old (%)	17 (9)	14 (10)	3 (6)	0.57
Median BMI (Q1-Q3)*	25 (22-29)	24 (22-29)	26 (22-30)	0.42
Male sex (%)**	98 (52)	71 (50)	27 (57)	0.38
Immunocompromised patients (%), including:	136 (72)	101 (71)	35 (75)	0.61
Solid organ transplantation	55 (40)	39 (39)	16 (46)	0.46
Immunosuppressive therapy including rituximab	53 (39)	44 (44)	9 (26)	0.06
Ongoing chemotherapy	29 (21)	20 (20)	9 (26)	0.46
Corticosteroids >10 mg/day for > 2 weeks	13 (10)	10 (10)	3 (9)	1
Allogeneic hematopoietic stem cell transplantation	7 (5)	6 (6)	1 (3)	0.68
Systemic lupus or vasculitis with immunosuppressive medications	7 (5)	5 (5)	2 (6)	1
Cancer	3 (2)	1 (1)	2 (6)	0.16
Other risk factors for severe COVID-19 (%), including:	98 (52)	75 (53%)	23 (49%)	0.68
Diabetes (type 1 and type 2)	30 (31)	22 (29)	8 (35)	0.62
High blood pressure	28 (29)	21 (28)	7 (30)	0.82
Obesity BMI>30	25 (26)	19 (25)	6 (26)	0.94
Other chronic pathologies	25 (26)	20 (27)	5 (22)	0.64
Chronic kidney disease	20 (20)	16 (21)	4 (17)	0.78
Congestive heart failure	7 (7)	7 (9)	0	0.19
COPD and chronic respiratory failure	6 (6)	3 (4)	3 (13)	0.14
Having received ≥ 3 doses of vaccine (%)***	143 (77)	102 (73)	41 (89)	0.08
Positive IgG anti-Spike serology at d0 (%)****	118 (63)	85 (61)	33 (70)	0.26
Median IgG anti-spike level at d0 (BAU/mL, Q1-Q3)	531 (120-2383)	807 (126-2500)	395 (91-1574)	0.26
Day 28 outcome (% of patients with available data)	167/190 (88)	125/143 (87)	42/47 (89)	
COVID-19–related hospitalization at d28 (%)	4 (2)	3 (2)	1 (2)	1
COVID-19-related death (%)	0	0	0	

* Age and BMI were missing in 6 BA.1-infected patients and 3 BA.2-infected patients
** Sex was missing in 1 BA.1-infected patients

*** Vaccination status was missing in 4 BA.1-infected patients and 1 BA.2-infected patients
**** IgG anti-Spike serology was missing in 4 BA.1-infected patients

Figure 1. Change in Ct value of gene N in 143 BA.1 and 47 BA.2-infected patients treated with Sotrovimab. The p-value for the slope difference is 0.87.



Sotrovimab to prevent severe COVID-19 in high-risk patients infected with Omicron BA.2

COCOPREV Study Group collaborators

Supplementary methods

Virological methods

Nasopharyngeal (NP) swabs were collected at Day 0 and 7, and repeated weekly in patients with positive SARS-CoV-2 PCR with a Cycle threshold (CT) < 31. In hospitalized patients, additional NP swabs were collected at Day 3 and 5. Blood samples were collected at Day 0 and 7, and Month 1 and 3 (for the latter, only in the first 100 patients by type of treatment). All biological samples were centralized and stored at "Centre de Ressources Biologiques ANRS-MIE, Bordeaux" and then extracted to the virological centralized unit (Pitié Salpétrière, APHP, Paris) for further analyses.

SARS-CoV-2 molecular quantification

The TaqPath™ COVID-19 RT-PCR (ThermoFisher, Waltham, USA) test was used to detect target genes of the virus (ORF1ab, N, and S).

SARS-CoV-2 serology

The qualitative detection of nucleocapsid protein (anti-N) IgG antibodies and the quantification of anti-spike RBD IgG antibodies were performed with an automated chemiluminescence assay on the Abbott Alinity i platform, in accordance with the manufacturer's instructions (SARS-CoV-2 IgG and SARS-CoV-2 IgG II Quant, Abbott, Rungis, France). An IgG index ≥ 0.8 indicates a positive serological result for anti-N antibodies. The cutoff for positivity for anti-S antibodies was 7.1 binding Ab units per milliliter (BAU/ml), as recommended by the manufacturer.

Virus neutralization test (VNT)

The neutralizing activity of Day 7 sera of patients with anti-spike RBD IgG antibodies at Day 0 was assessed with a whole virus replication assay using the two SARS-CoV-2 clinical isolates BA.1 and BA.2. The serum samples were decomplemented by heat inactivation (56°C for 30 min), subjected to serial four-fold dilution (1:10 to 1:640) in duplicate, and incubated with 50 µl of each diluted virus (2 x 10^3 $TCID_{50}$/ml) in a 96-well plate at 37°C for 60 min. We then added 100 µl of a 3 x 10^5 cells/ml Vero-TMPRSS2 cell suspension (5% CO_2 in DMEM, supplemented with 10% heat-inactivated fetal bovine serum, 1x Penicillin-Streptomycin solution and 200 µg/ml of hygromycin; kind donation from Olivier Schwartz, Virus and Immunity Unit, Institut Pasteur), to the mixture and incubated at 37°C under an atmosphere containing 5% CO_2 until the microscopy examination on day 4 to assess the cytopathic effect (CPE).

An infectivity score has been assigned on each well: 0, no cytopathic effect; 1, less than 25% cells were affected; 2, 25%-50% of cells affected; 3, 50%-75% of cells affected and 4, more than 75% cells affected. The addition of the scores in each duplicate was then transformed in percentage of the maximal scoring (ex. Score of 8 considered as 100%). Neutralizing antibody (NAb) titers are expressed as the serum dilution displaying 90% (NT_{90}) or 50% (NT_{50})

inhibition of the CPE. NT_{90} and NT_{50} were analyzed by nonlinear regression using a four-parameter dosage-response variable slope model with the GraphPad Prism 8.0.2 software (GraphPad Software, USA).

Whole genome sequencing

Whole genome sequencing was performed using the xGen™ ARTIC nCoV-2019 Amplicon Panel v4.1 according to the Eco PCR tiling of SARS-CoV-2 virus with native barcoding Nanopore protocol on the Gridion Oxford Nanopore device. Sequencing data were both base-called and demultiplexed using Guppy v6.0.7. Consensus sequences were generated with the ARTIC SARS-CoV-2 Workflow v0.3.12 from the nf-core framework and EPI2ME labs (https://doi.org/10.1038/s41587-020-0439-x). Briefly, sequenced reads are mapped against the Wuhan-Hu-1 reference genome (MN908947.3) with Minimap2. Alignment files are used to prepare a consensus sequence that is then polished using Medaka. Consensus sequences are annotated for virus clade information using NextClade and a strain assignment is performed using Pangolin. The analyses of resistance mutations were performed on S gene.

Supplementary tables and figures

Supplementary table 1: Emergence of mutations of the Spike protein according to variant and time

Patient	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Variant	BA.1.1.14	BA.1.1	BA.1.1	BA.1.18	BA.1.1.1	BA.1.1	BA.1.1.1	BA.1.1.1	BA.1.1	BA.1.1.1	BA.1.1.1	BA.1.15	BA.1.1	BA.1.17.2	BA.1.1
Day 0															
Day 7	N164T			E340A								E340K	E340K		
Day 14						E340D	E340D	E340D						E340K	
Day 21					E340D				E340K		E340K			E340K	T588A
Day 28		P337L	P337S		E340D				E340K	E340K			E340K		
Day 35					E340D										
Day 42					E340D								E340K		
Day 49					E340D								E340K		

Supplementary table 2: Baseline characteristics according to the emergence of mutations of the Spike protein

	ALL N=86	**With mutation N=15 (17%)**	**Without mutation N=71 (83%)**	**p-value**
Follow-up time in days*– median (Q1-Q3)	7 (6-14)	14 (7-22)	7 (6-9)	**0.001**
Number of timepoints** – median (Q1-Q3)	2 (2-3)	3 (2-3)	2 (2-3)	**0.003**
Age in years – median (Q1-Q3)	63 (50-73)	58 (42-73)	64 (50-73)	0.31
BMI – median (Q1-Q3)	25 (23-29)	24 (22-26)	27 (22-29)	0.23
Missing	2	0	2	
Variant – N (%)				**0.03**
BA.1	68 (79%)	15 (100%)	53 (75%)	
BA.2**	18 (21%)	0 (0%)	18 (25%)	
Gender – N (%)				0.58
Male	40 (47%)	6 (40%)	34 (48%)	
Female	46 (53%)	9 (60%)	37 (52%)	
Risk exposure – N (%)				
Immunocompromised patients including:	66 (77%)	14 (93%)	52 (73%)	0.18
Solid organ transplantation	26 (39%)	4 (29%)	22 (42%)	0.35
Immunosuppressive therapy including rituximab	26 (39%)	8 (57%)	18 (35%)	0.13
Ongoing chemotherapy	15 (23%)	2 (14%)	13 (25%)	0.49
Corticosteroids >10 mg/day for > 2 weeks	6 (9%)	1 (7%)	5 (10%)	1
Allogeneic hematopoietic stem cell transplantation	4 (6%)	1 (7%)	3 (6%)	1
Systemic lupus or vasculitis with immunosuppressive medications	3 (5%)	0 (0%)	3 (6%)	1
Cancer	1 (2%)	0 (0%)	1 (2%)	1
Other risk factors for severe COVID-19 including:	42 (49%)	7 (47%)	35 (49%)	0.85
Diabetes (type 1 and type 2)	14 (33%)	0 (0%)	14 (40%)	0.08
High blood pressure	14 (33%)	2 (29%)	12 (34%)	1
Other chronic pathologies	14 (33%)	2 (29%)	12 (34%)	1
Obesity BMI>30	11 (26%)	2 (29%)	9 (26%)	1
Chronic kidney disease	6 (14%)	1 (14%)	5 (14%)	1
Congestive heart failure	4 (10%)	1 (14%)	3 (9%)	0.53
COPD and chronic respiratory failure	1 (2%)	0 (0%)	1 (3%)	1
≥ 80 years old	7 (8%)	1 (7%)	6 (8%)	1
Severity of Covid-19 – N (%)				1
Mild	77 (92%)	14 (93%)	63 (91%)	
Moderate	7 (9%)	1 (7%)	6 (9%)	
Missing	2	0	2	
Symptoms– N (%)				1
Yes	81 (98%)	15 (100%)	66 (97%)	

No	2 (2%)	0 (0%)	2 (3%)	
Missing	3	0	3	
Time between administration and appearance of symptoms in days – median (IQR)	3 (2-4)	3 (2-4)	3 (2-4)	0.46
Missing	2	0	2	
Vaccination status – N (%)				0.41
Complete (≥ 3 doses)	68 (81%)	11 (74%)	57 (83%)	
Incomplete (≤2 doses)	10 (12%)	2 (13%)	8 (12%)	
Unvaccinated	6 (7%)	2 (13%)	4 (6%)	
Missing	2	0	2	
Time between last injection and inclusion in days – median (IQR)	117 (47-207)	132 (56-272)	110 (47-200)	0.29
Missing	20	4	16	
Previous treatment – N (%)				
-For prevention				
Ronapreve (Casirivimab/Imdevimab)	1 (2%)	0 (0%)	1 (2%)	
Evusheld (tixagévimab/cilgavimab)	2 (4%)	0 (0%)	2 (5%)	
-For treatment				
Ronapreve (Casirivimab/Imdevimab)	1 (2%)	0 (%)	1 (2%)	
Paxlovid (Nirmatrelvir/Ritonavir)	1 (2%)	0 (0%)	1 (2%)	
None	45 (83%)	10 (91%)	35 (81%)	
Unknown	5 (9%)	1 (9%)	4 (9%)	
Missing	32	4	28	

3 patients without mutations are hospitalised before day 7.

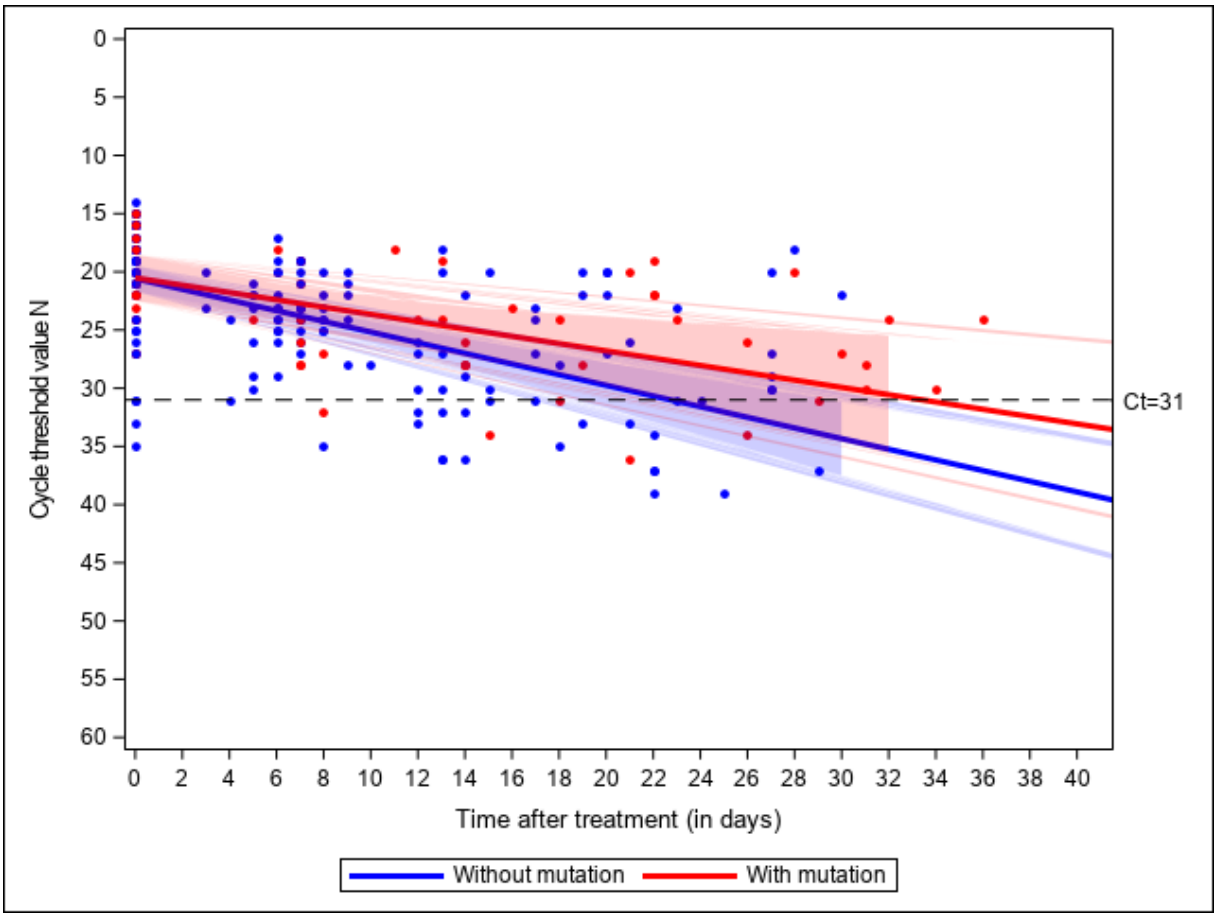
* Until the visit that the mutation was observed for the mutated patients and until the last visit for the non-mutated

** The 18 BA.2 patients that did not present a mutation have a median follow-up of 2 timepoints (Q1-Q3: 2-2) and 7 days (Q1-Q3 : 6-8)

Supplementary table 3: Mixed models for the Ct of the gene N according to the emergence of mutations of the Spike protein of BA.1-infected patients

	Coefficient (beta) from univariable analysis 95%CI	p-value
Variables at baseline		
Without mutation vs mutation	0.07 (-2.20-2.34)	0.95
Variables through time		
Without mutation vs mutation	0.14 (-0.09-0.38)	0.22

Supplementary figure 1: Mixed model for Ct of the gene N according to the emergence of mutations of the Spike of the BA.1 subvariant



The Ct of the nasopharyngeal PCR of the gene N were displayed according to time for 53 BA.1 patients without emergence of mutations of the Spike protein and 15 BA.1 patients with. The p-value for the slope is 0.26

Supplementary table 4: Neutralizing titles of plasma collected at day 7 from 60 patients having a negative IgG anti-Spike serology at baseline

	BA.1	**BA.2**	**p-value**
NT 50-median (Q1-Q3)	42.19 (37.55-67.82)	10.64 (10.17-18.35)	**<0.0001**
NT 90-median (Q1-Q3)	32.69 (12.59-36.93)	9.27 (8.43-9.87)	**<0.0001**

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Tables, Figures and Legends to figures

Table 1. Baseline characteristics of patients and outcomes at the 28th day visit

Baseline characteristics	**All N=190**	**BA.1-infected patients N=143 (75%)**	**BA.2-infected patients N=47 (25%)**	**p-value**
Median age (years, Q1-Q3)*	59 (45-70)	59 (44-70)	55 (50-72)	0.75
≥ 80 years old (%)	17 (9)	14 (10)	3 (6)	0.57
Median BMI (Q1-Q3)*	25 (22-29)	24 (22-29)	26 (22-30)	0.42
Male sex (%)**	98 (52)	71 (50)	27 (57)	0.38
Immunocompromised patients (%), including:	136 (72)	101 (71)	35 (75)	0.61
Solid organ transplantation	55 (40)	39 (39)	16 (46)	0.46
Immunosuppressive therapy including rituximab	53 (39)	44 (44)	9 (26)	0.06
Ongoing chemotherapy	29 (21)	20 (20)	9 (26)	0.46
Corticosteroids >10 mg/day for > 2 weeks	13 (10)	10 (10)	3 (9)	1
Allogeneic hematopoietic stem cell transplantation	7 (5)	6 (6)	1 (3)	0.68
Systemic lupus or vasculitis with immunosuppressive medications	7 (5)	5 (5)	2 (6)	1
Cancer	3 (2)	1 (1)	2 (6)	0.16
Other risk factors for severe COVID-19 (%), including:	98 (52)	75 (53%)	23 (49%)	0.68
Diabetes (type 1 and type 2)	30 (31)	22 (29)	8 (35)	0.62
High blood pressure	28 (29)	21 (28)	7 (30)	0.82
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Day 28 outcome (% of patients with available data)	167/190 (88)	125/143 (87)	42/47 (89)	
COVID-19–related hospitalization at d28 (%)	4 (2)	3 (2)	1 (2)	1
COVID-19-related death (%)	0	0	0	

* Age and BMI were missing in 6 BA.1-infected patients and 3 BA.2-infected patients
** Sex was missing in 1 BA.1-infected patients

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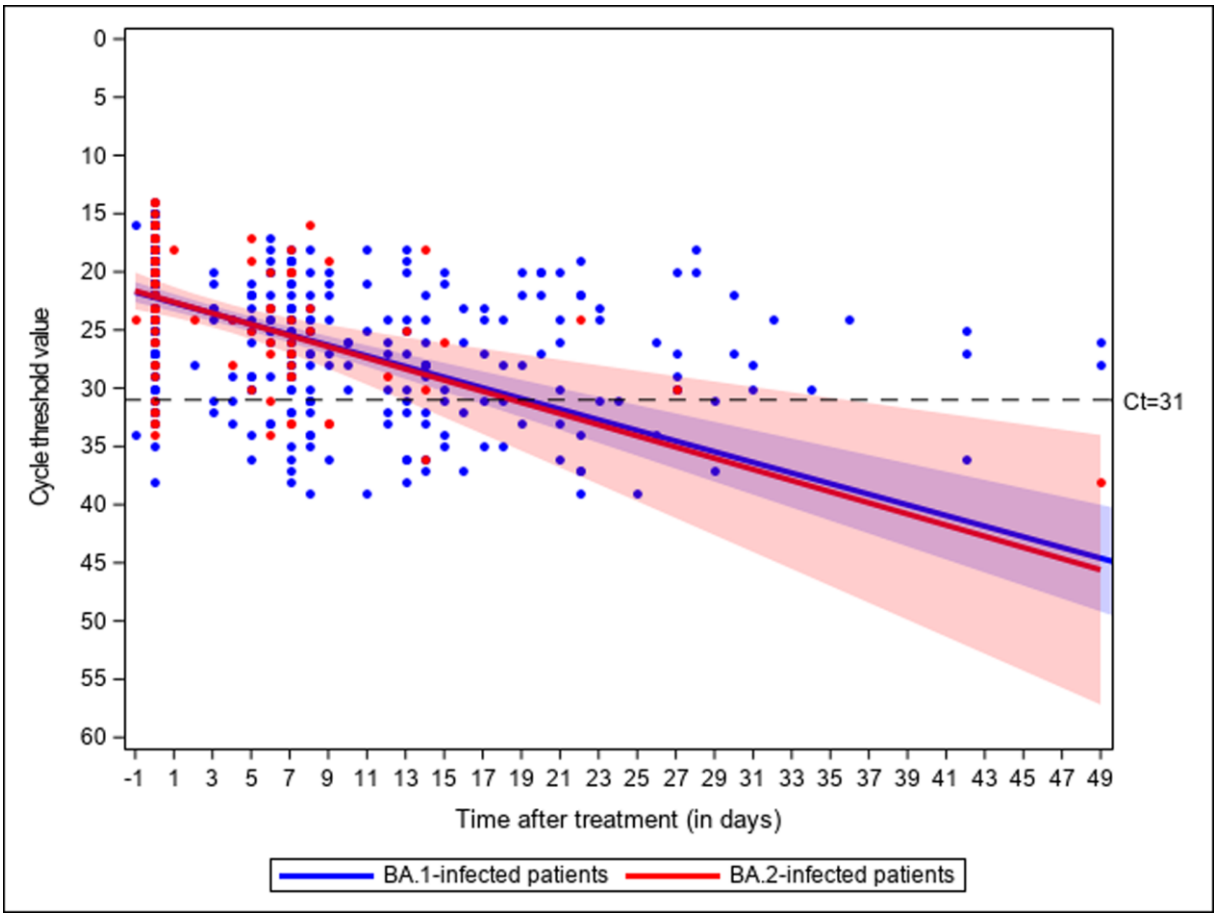
Figure 1. Change in Ct value of gene N in 143 BA.1 and 47 BA.2-infected patients treated with Sotrovimab. The p-value for the slope difference is 0.87.



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