Supplementary Appendix

Supplement to: Hammond J, Leister-Tebbe H, Gardner A, et al. Oral nirmatrelvir for high-risk, nonhospitalized adults with Covid-19. N Engl J Med. DOI: 10.1056/NEJMoa2118542

This appendix has been provided by the authors to give readers additional information about the work.

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SUPPLEMENTARY APPENDIX

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Table does not include sites that did not screen any patients for inclusion.

Additional Inclusion and Exclusion Criteria

Patients were to have ≥1 of the following characteristics/comorbidities associated with increased risk of developing severe COVID-19 illness: ≥60 years of age; BMI >25 kg/m^2; cigarette smoking; immunosuppressive disease (including HIV infection with CD4 cell count <200 mm^3 and VL <400 copies/mL) or prolonged iatrogenic immunosuppression; chronic lung, cardiovascular, kidney, or sickle cell disease; hypertension; diabetes; cancer; neurodevelopmental disorders or other medically complex conditions; or medical-related technological dependence.

Additional exclusion criteria included pregnancy or breastfeeding; history of active liver disease; moderate to severe renal impairment; known HIV (viral load >400 copies/mL) or suspected/confirmed active systemic infection; and comorbidity requiring hospitalization and/or surgery or considered life threatening ≤7 and ≤30 days, respectively, prior to study entry.

Additional Prohibited Prior or Concomitant Therapies

Prohibited prior or concomitant therapies included medications highly dependent on CYP3A4 for clearance and that may be clinically concerning at elevated plasma concentrations (during and through 4 days following treatment), or strong inducers of CYP3A4 (≤28 days prior to and during treatment).

Blinding

The sponsor was blinded except for a small, separate, unblinded team interacting with an external data monitoring committee evaluating safety throughout the study. Select sponsor personnel were unblinded following premature study termination due to overwhelming efficacy (see Statistical Analyses section), with the remainder blinded until all patients completed, or discontinued prior to, the Day 34 visit, at which point the study was to continue in an unblinded fashion.

Ethical Conduct

All patients provided written informed consent. The study was conducted in accordance with consensus ethical principles derived from international guidelines including the Declaration of Helsinki, Council for International Organizations of Medical Sciences International Ethical Guidelines, International Council for Harmonisation Good Clinical Practice guidelines, and applicable laws and regulations. The protocol and related documents were approved by an institutional review board/ethics committee before study commencement.

Study Responsibilities

Pfizer took responsibility for study design and conduct; data collection, analysis, and interpretation; and writing of this manuscript. NMV and matching placebo were manufactured by Pfizer, while ritonavir tablets were manufactured and tested by Hetero Labs Limited (Hyderabad, India) and blinding was done by Pfizer via over-encapsulation. All data were available to all authors, who vouch for accuracy and completeness of this report as well as adherence of the study to the protocol.

Serology

Two assays were utilized for serology testing.[1] The first assay is designed to detect host immunoglobulins against the viral spike (S) protein. Elecsys® Anti-SARS-CoV-2 S. It is an electrochemiluminescence immunoassay intended for qualitative and quantitative detection of immunoglobulin (Ig) G, IgA, and IgM antibodies to the SARS-CoV-2 spike (S) protein receptor binding domain (RBD). Results are reported within a linear range spanning 0.4–250 U/mL, with <0.8 U/mL considered non-reactive (ie, negative) and ≥0.8 U/mL considered reactive (ie, positive).

The second assay is designed to detect host IgG and IgM against the viral nucleocapsid protein (N). Elecsys® Anti-SARS-CoV-2 is an immunoassay that uses a recombinant protein representing the nucleocapsid (N) antigen. The assay is qualitative and results are reported as non-reactive (cutoff index <1.0 =negative) or reactive (cutoff index ≥1.0; positive).

Viral Load Assessment

Quantitative viral load was generated using a validated Abbott RealTime Quantitative SARS-CoV-2 assay at the University of Washington Medicine Clinical Virology Laboratory. The RT-PCR assay was intended for the quantitative detection of nucleic acid from SARS-CoV-2 in nasopharyngeal or nasal swabs by detecting the RdRp and nucleocapsid (N) genes using the Abbott m2000 System. Total RNA for viral load analysis was extracted from swabs using the Roche MagnaPure LC automated platform.

Pharmacokinetic Modeling to Support Selection of NMV/r Dose for Phase 2/3

A preliminary population pharmacokinetic (PK) model was developed based on healthy adult data from first-in-human, single and multiple ascending dose studies. PK data collected from the NMV/r treatment arms (536 evaluable NMV plasma concentrations from 20 healthy subjects) were included in this population PK analysis. The PK of NMV/r following oral administration was adequately characterized by a 2-compartment disposition model with first-order absorption. The population PK model included an allometric model of baseline body weight on clearance (CL) and volume of

distribution (V) with exponents fixed to 0.75 and 1, respectively. Separate power functions were used to describe the dose effect on absorption rate constant (k_a) and relative bioavailability (F1). The parameter estimates after adjustment by F1 at a NMV dose of 300 mg were: CL 8.2 L/h, volume of distribution 111 L, and k_a 1.1 h^{-1}. This gives a population mean $t_{½}$ of approximately 15 hours (the individual post hoc $t_{½}$ ranged from 8.7 to 32.8 hours). The inter-individual variability (IIV) in CL was low at 26.4% comparing with IIV in central and peripheral volume of distribution V2 30.7%, V3 69.9%, k_a 54.3%, and inter-occasion variability IOV in k_a 60.7%.

Simulations were performed utilizing the population PK model with 1000 subjects weighing 70 kg. NMV/r doses of 100 to 500 mg given twice daily for 5 days were simulated assuming no missing dose. NMV plasma concentration profiles at a time step of 1 hour for Day 1 and Day 5 were used to calculate percentage of simulated subjects achieving a concentration at 12 hours post dose (C_{12h}) greater than or equal to the in vitro EC_{90}. The EC_{90} was derived from the antiviral activity of NMV against SARS-CoV-2 evaluated in a physiologically relevant antiviral assay of SARS-CoV-2 infection in dNHBE cells. The geometric mean EC_{90} of 0.181 µM at 3 days post infection was used and adjusted by NMV molecular weight (499.54 Daltons) and protein binding in human (69%).

With the preliminary population PK model, NMV/r dose of 300/100 mg was projected based on simulations to have >90% of participants achieve a concentration at C_{12h} above EC_{90} of 292 ng/mL after the first dose (Table 1). The dose of NMV/r 300/100 mg BID resulted in median Day 1 and Day 5 (steady state) C_{12h} concentrations about 3–4 × EC_{90} and 5–6 × EC_{90}, respectively (Table 1).

Table 1. Predicted C_{12h} and Percentage of Simulated Subjects Achieving $C_{12h} \geq EC_{90}$ of 292 ng/mL

NMV/r dose (mg)	Dose Number	C_{12h} (ng/mL))[a]			% Subjects achieved $C_{12h} \geq EC_{90}$
		Median	10th percentile	90th percentile	
100	1st (Day 1) 9th (Day 5)	458 852	141 238	1018 2276	71.5 85.3
200	1st (Day 1) 9th (Day 5)	743 1361	228 383	1608 3575	85.0 93.4
300	1st (Day 1) 9th (Day 5)	987 1800	307 498	2124 4670	90.7 95.7
400	1st (Day 1) 9th (Day 5)	1209 2197	378 605	2565 5679	94.0 97.4
500	1st (Day 1) 9th (Day 5)	1417 2563	449 704	2979 6640	95.5 97.8

a IIV was on CL was adjusted to 60% anticipating higher variability in COVID-19 patients

These population PK analyses and simulations supported the selection of the 300/100 mg dose of NMV/r given twice daily for 5 days for the pivotal safety and efficacy study.

Additional Statistical Analyses

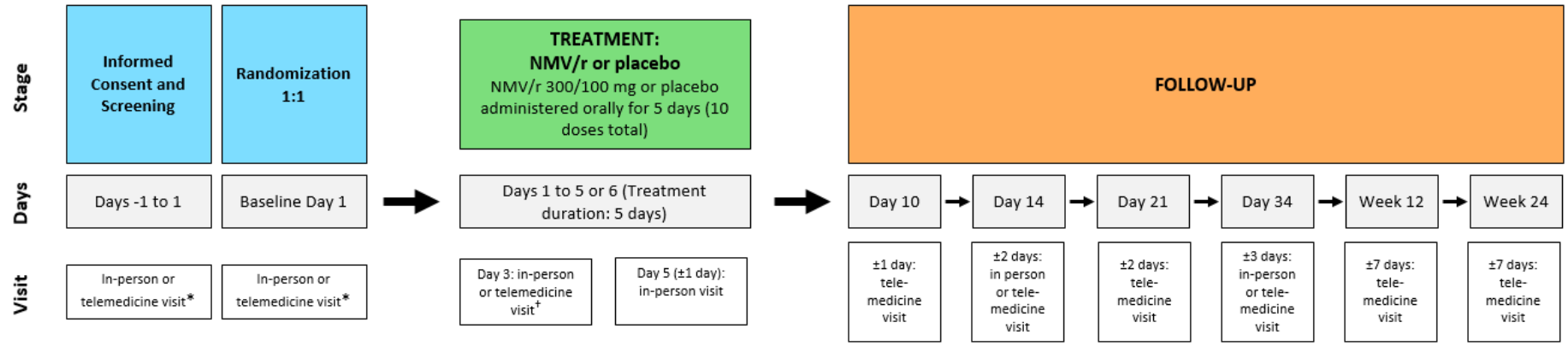
A sample size of 1717 patients was calculated using a 2-sample proportion test aiming to detect a 3.5% difference in the primary endpoint (7.0% expected rate of hospitalization/death in the placebo group based on another study performed in a similar population[2]) with 90% power at a 2-sided significance level of 5%. Allowances for patients who at baseline received or were expected to receive mAb treatment for COVID-19 (estimated at 20%, capped at 25%), symptom onset >3 days prior (estimated at 25%, capped at 1000), and dropouts (estimated at 5%) led to a total sample size of ~3000 patients.

The primary endpoint was evaluated at an overall significance level of 5%.

In an earlier stage of this study, VL was used to determine whether the study should be terminated if NMV/r had no therapeutic effect.

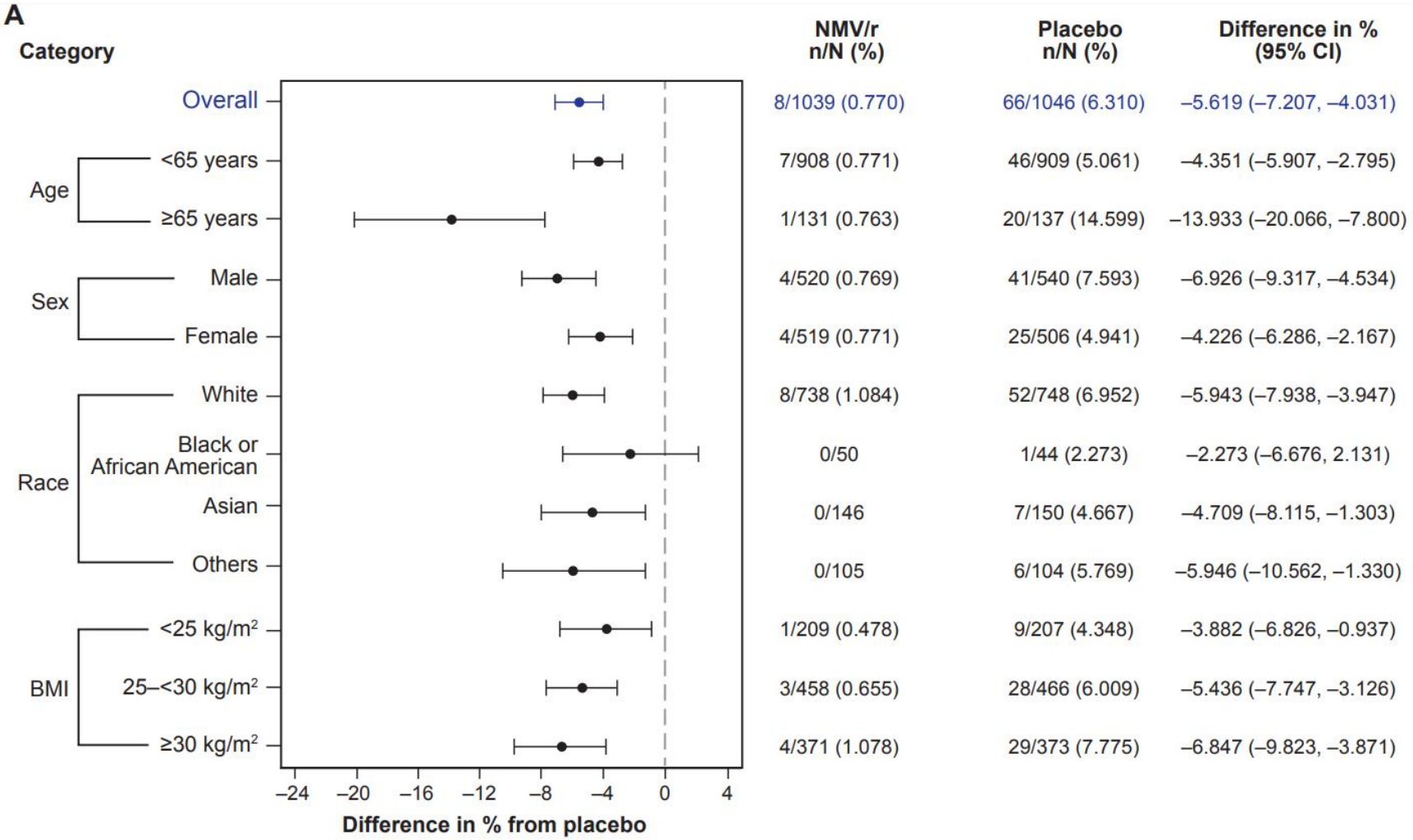
Considering the potential for missing events due to premature study discontinuation, a Kaplan-Meier model, which accounted for all patients in the analysis, was used to estimate the proportion of patients who experienced an endpoint event at 28 days.

Figure S1. Study design



***** Baseline and screening visits could be a combination of in-person and telemedicine visits. † The Day 3 visit was conducted in person for the first 68 patients (sentinel cohort) and thereafter only if a pharmacokinetic sample was collected or an electrocardiogram was required.
NMV=nirmatrelvir; r=ritonavir.

Figure S2. Participants with COVID-19-related-hospitalization or death from any cause through Day 28 – overall and by subgroups (MITT1 population)



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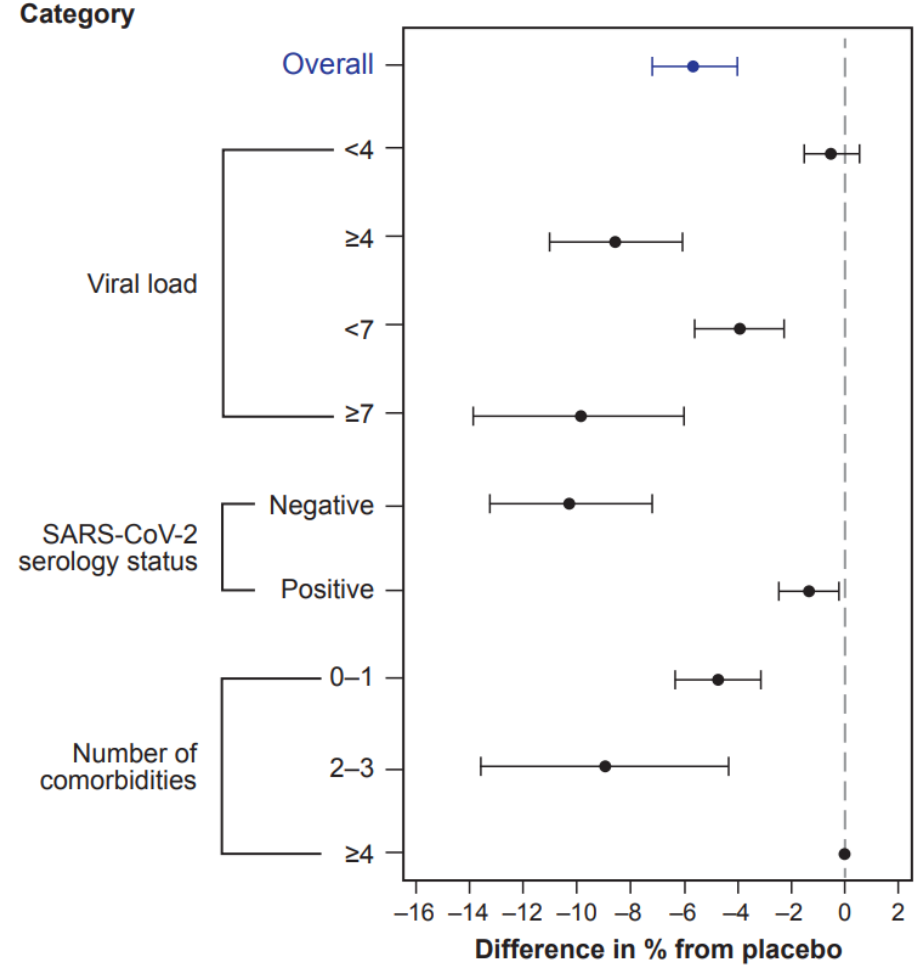


Category	NMV/r n/N (%)	Placebo n/N (%)	Difference in % (95% CI)
Overall	8/1039 (0.770)	66/1046 (6.310)	–5.619 (–7.207, –4.031)
Viral load: <4	1/382 (0.262)	3/387 (0.775)	–0.514 (–1.528, 0.500)
Viral load: ≥4	7/628 (1.115)	60/632 (9.494)	–8.543 (–11.018, –6.069)
Viral load: <7	6/734 (0.817)	36/762 (4.724)	–3.950 (–5.607, –2.292)
Viral load: ≥7	2/276 (0.725)	27/257 (10.506)	–9.929 (–13.877, –5.981)
SARS-CoV-2 serology status: Negative	7/487 (1.437)	58/505 (11.485)	–10.247 (–13.279, –7.214)
SARS-CoV-2 serology status: Positive	1/540 (0.185)	8/528 (1.515)	–1.337 (–2.445, –0.229)
Number of comorbidities: 0–1	4/829 (0.483)	43/832 (5.168)	–4.763 (–6.365, –3.160)
Number of comorbidities: 2–3	4/206 (1.942)	23/211 (10.900)	–8.958 (–13.592, –4.323)
Number of comorbidities: ≥4	0/4	0/3	0.000 (0.000, 0.000)

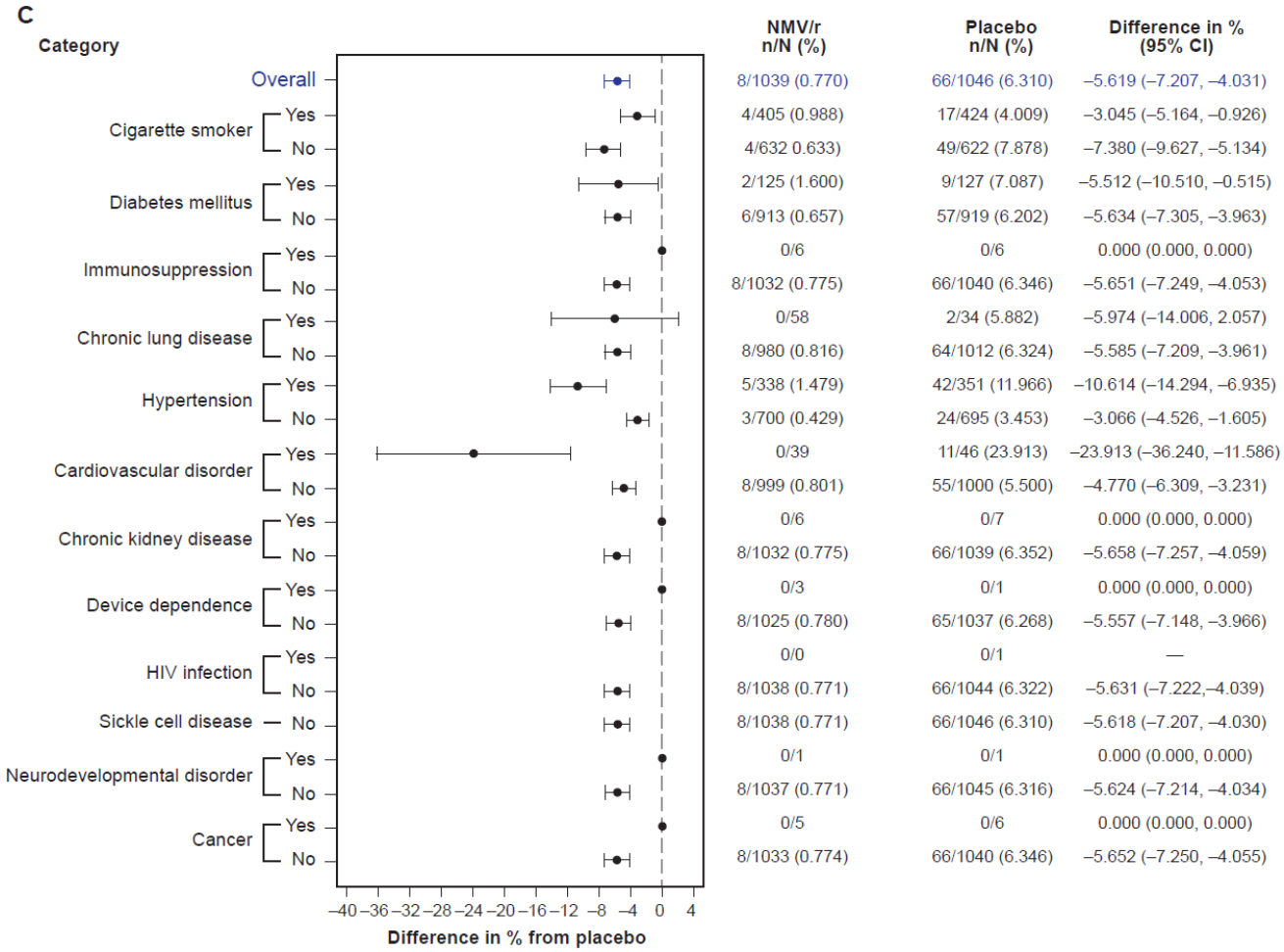


Figure S2 shows subgroup analysis of the differences of the proportions (95% confidence intervals) of patients treated ≤5 days from symptom onset with COVID-19–related hospitalization or death from any cause through Day 28 estimated for each treatment group using the Kaplan-Meier method (A) by subgroup of age, gender, race and BMI; (B) by subgroup of viral load, serology, and number of baseline comorbidities; and (C) by subgroup of baseline comorbidities. All patients randomly assigned to study intervention who took ≥1 dose of study intervention, had ≥1 postbaseline visit through Day 28 visit, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment, and were treated ≤5 days following COVID-19 onset. *P*-values are based on normal data approximation. BMI=body mass index; COVID-19=coronavirus disease 2019; mITT1=modified intent-to-treat 1; NMV/r=nirmatrelvir 300 mg + ritonavir 100 mg.

Figure S3. Change from baseline in log_{10} transformed viral load (copies/mL) over time (MITT1 population)

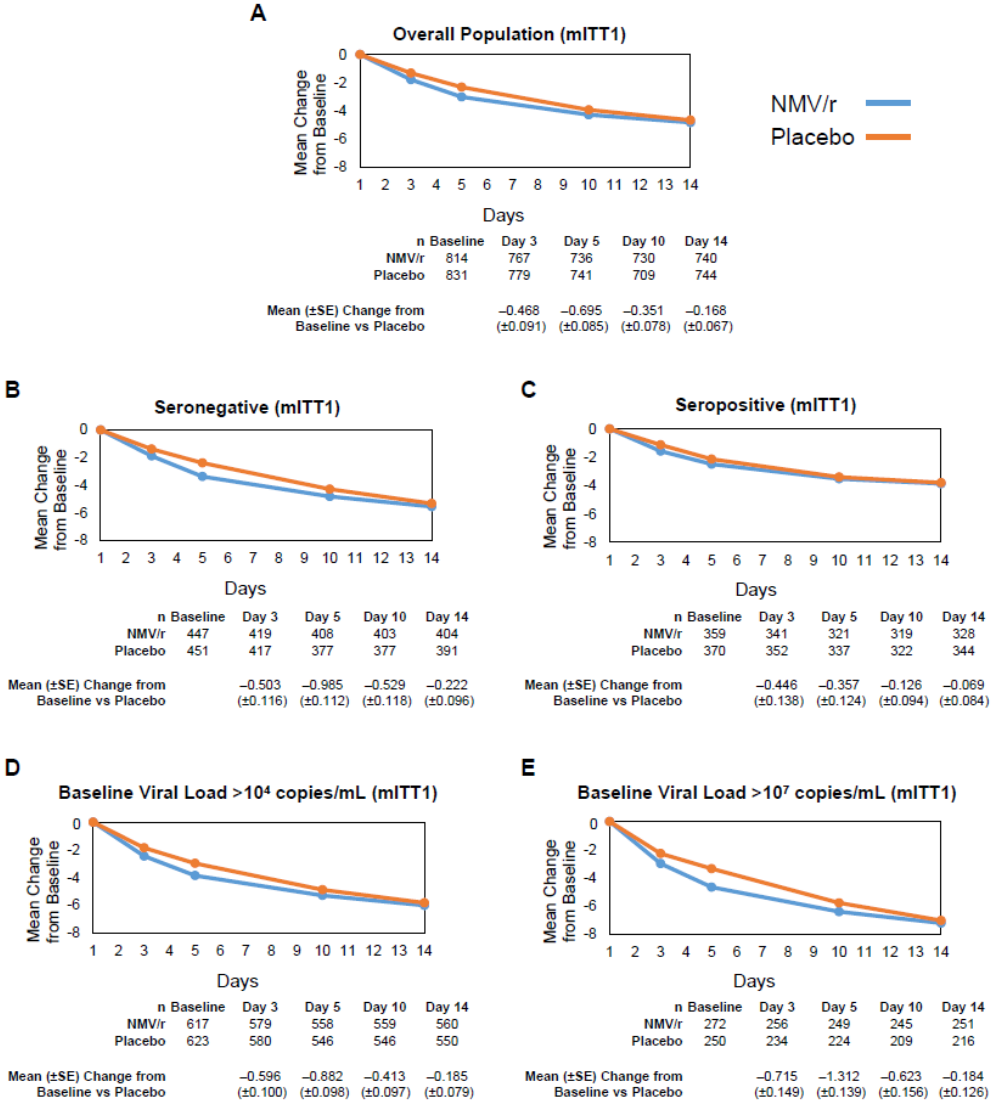
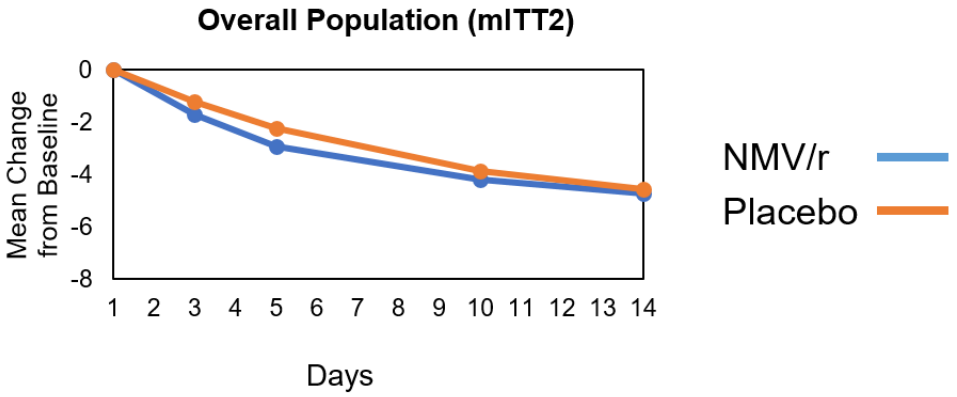


Figure S3 shows the adjusted mean change in viral load from baseline (A) overall: all patients randomly assigned to study intervention who took ≥1 dose of study intervention, had ≥1 postbaseline visit through Day 28 visit, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment, and were treated ≤5 days following COVID-19 onset (mITT1); (B) by subgroup of baseline SARS-CoV-2 serology status negative; (C) by subgroup of baseline SARS-CoV-2 serology status positive; (D) by subgroup of baseline viral load $>10^4$ copies/mL; and (E) by subgroup of baseline viral load $>10^7$ copies/mL. Patients excluded from the analysis for reasons of not detected or missing baseline viral load result. Results obtained using unvalidated swabs also excluded. Results were obtained from a mixed effects repeated measures (MMRM) analysis of covariance model. Treatment visit, visit by treatment interaction were fixed effects. Geographic region, symptom onset duration, baseline SARS-CoV-2 serology status, baseline viral load and nasopharyngeal sample site were covariates along with participant as a random effect. mAb=monoclonal antibody; mITT1=modified intent-to-treat 1; NMV/r=nirmatrelvir 300 mg + ritonavir 100 mg; SE=standard error.

Figure S4. Change from baseline in log_{10} transformed viral load (copies/mL) over time (MITT2 population)



n	Baseline	Day 3	Day 5	Day 10	Day 14
NMV/r	873	821	789	782	794
Placebo	888	829	792	760	800
Mean (±SE) Change from Baseline vs Placebo		–0.493 (±0.085)	–0.689 (±0.082)	–0.356 (±0.075)	–0.163 (±0.065)

Shown is the adjusted mean change in viral load from baseline. Results were obtained from a mixed effects repeated measures (MMRM) analysis of covariance model. Treatment visit, visit by treatment interaction were fixed effects. Geographic region, symptom onset duration, baseline SARS-CoV-2 serology status, baseline viral load and nasopharyngeal sample site were covariates along with participant as a random effect. mAb=monoclonal antibody; mITT2=modified intent-to-treat 2; NMV/r=nirmatrelvir 300 mg + ritonavir 100 mg; SE=standard error.

Table S1. Signs and symptoms attributable to COVID-19

Daily Sign and Symptom Collection	Targeted (Used for Study Entry)
Cough	×
Shortness of breath or difficulty breathing	×
Fever (documented temperature >38˚C [100.4˚F]) or feeling feverish	×
Feeling feverish	
Chills or shivering	×
Fatigue	×
Muscle or body aches	×
Diarrhea	×
Nausea	×
Vomiting	×
Headache	×
Sore throat	×
Stuffy or runny nose	×
Loss of smell	
Loss of taste	

COVID-19=coronavirus disease 2019.

Table S2. Study populations

Population	Description
Full Analysis Set (FAS)	All patients randomly assigned to study intervention regardless of whether or not study intervention was administered.
Safety Analysis Set (SAS)	All patients randomly assigned to study intervention who received ≥1 dose of study intervention.
Modified Intent-to-Treat (mITT)	All patients randomly assigned to study intervention who took ≥1 dose of study intervention, had ≥1 postbaseline visit through Day 28 visit, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment, and were treated ≤3 days following COVID-19 symptom onset.
Modified Intent-to-Treat 1 (mITT1)	All patients randomly assigned to study intervention who took ≥1 dose of study intervention, had ≥1 post-baseline visit through Day 28 visit, who at baseline did not receive nor were expected to receive COVID-19 therapeutic mAb treatment.
Modified Intent-to-Treat 2 (mITT2)	All patients randomly assigned to study intervention who took ≥1 dose of study intervention, had ≥1 post-baseline visit through Day 28.

COVID-19=coronavirus disease 2019; mAb=monoclonal antibody.

Table S3. Representativeness of trial patients

Disease Under Investigation	COVID-19
Special considerations related to	
Sex and gender	COVID-19 affects both men and women with similar frequency. Men appear have increased risk for progressing to severe disease, with somewhat higher rates of hospitalization and death reported in men compared to women. Data on gender identity and COVID-19 are limited; currently, there is no known impact on COVID-19 case rates or poor outcomes.
Age	Prevalence of COVID-19 cases is generally similar across age groups of adults ≥18 years of age, the target population of this present trial. Older adults are more likely to progress to severe illness from COVID-19, including hospitalization and death. Risk of severe disease increases with age.
Race or ethnicity	COVID-19 affects people of all race and ethnicity. In the United States, Black/African American, Hispanic/Latinx, and American Indian/Alaska Native persons have experienced a disproportionate burden of COVID-19 in terms of number of cases, hospitalizations and deaths. In contrast, non-Hispanic White and Asian persons make up a lower share of cases and deaths compared to their population share.
Geography	COVID-19 is a pandemic with global impact, with varying case rates, hospitalizations and mortality rates by global region, by country and even by region within a given country. Factors influencing spread and disease outcome include prevalence of risk factors in the patient population, healthcare infrastructure, access to healthcare systems, availability of treatment options, vaccination rates, SARS-CoV-2 variants in circulation, population density, and country- and local-level control strategies and intervention measures to control spread of disease.
Other considerations	There are several established medical conditions and comorbidities that increase risk of progressing to severe COVID-19, including hospitalization and death. Such conditions include, but are not limited to: obesity, cancer, chronic kidney disease, chronic liver disease, chronic lung disease, smoker, diabetes mellitus, heart conditions, hypertension, immunosuppressive disease, HIV, sickle cell disease, and medical-related technological dependence.
Overall representativeness of this trial	The present trial was designed to enroll adult patients with SARS-CoV-2 infection with at least 1 risk factor for progressing to severe COVID-19. The patients in the present trial demonstrated the expected ratio of men to women; with slightly more males versus females enrolled. Biologic sex, based on sex at birth, was reported by the patient; options were female and male. Gender was not collected due to local restrictions to collect such data. The study design included only adult participants ≥18 years of age. The median (range) age for study patients was 46.0 (18.0, 88.0) years. Patients ≥65 years of age were somewhat underrepresented in the study (12.8%). Patients <60 years of age must have had another risk factor for progressing to severe COVID-19. Race and ethnicity were self-reported. Most patients were White (71.5%); 14% patients were Asian. Black/African American patients (5%) were underrepresented in the study.

	Hispanic/Latinx patients were highly represented, comprising 45% of randomized patients in the study. Study patients were enrolled at centers globally, with most patients enrolled from centers in the United States (41%), Europe (30%), South America (12.3%) and India (9%). Enrollment in Asia (5%) and Africa (0.6%) was underrepresented. Eligible patients must have had at least 1 well-established risk factor, including predefined comorbidity or medical condition, for progressing to COVID-19. Most (80.5%) patients had a baseline BMI ≥25 kg/m^2. The mean BMI was 29.17 kg/m^2. Other common comorbidities included cigarette smoker (39%), hypertension (33%), and diabetes mellitus (12.2%). Risk factors that were least represented in enrolled patients (<1%) included: chronic kidney disease, immunosuppressive disease, neurodevelopmental disorder, sickle cell disease, HIV infection, device dependence. Patients with severe renal impairment, active liver disease and pregnant or lactating woman were excluded from the study for safety purposes and are not represented in the patient population. As data on risk factors for progression to severe COVID-19 has evolved since the start of the trial, there are some risk factors that were not included in the eligibility criteria (eg, dementia and neurological conditions, mental health conditions).

Table S4. Percentage of patients who were treated ≤5 days from symptom onset and regardless of mAb status (mITT2 population*) with COVID-19–related hospitalization or death from any cause through Day 28†

	NMV/r (N=1109)	Placebo (N=1115)
Patients with event, n (%)	9 (0.812)	68 (6.099)
Patients with COVID-19 hospitalization	9 (0.812)	67 (6.009)
Patients with death‡	0	12 (1.076)
Average time at risk for event, days§	27.057	26.040
Average study follow-up, days‖	27.216	27.083
Estimated percentage (95% CI), %	0.822 (0.429, 1.574)	6.185 (4.909, 7.779)
Difference from placebo (SE)	−5.363 (0.776)	
95% CI of difference	−6.884, –3.842	
P-value	<0.0001	

COVID-19=coronavirus disease 2019; mAb=monoclonal antibody; mITT2=modified intent-to-treat 2; NMV/r=nirmatrelvir 300 mg + ritonavir 100 mg; SE=standard error.

* All patients randomly assigned to study intervention who took ≥1 dose of study intervention, had ≥1 post-baseline visit through Day 28, and were treated ≤5 days following COVID-19 onset, regardless of mAb treatment status.

† The cumulative percentage of patients hospitalized for the treatment of COVID-19 or death during the first 28 days of the study was estimated for each treatment group using the Kaplan-Meier method.

‡ All reported deaths were related to COVID-19 and included COVID-19 pneumonia (n=5), COVID-19 (n=2), hypoxia (n=1), acute respiratory distress syndrome (n=1), and acute respiratory failure (n=1).

§ Average time at risk for event is computed as time to first event, or time to last day of participation, or Day 28, whichever is earlier.

‖ Average study follow-up is computed as time to last day of participation, or Day 28, whichever is earlier.

Table S5. Treatment-emergent adverse events by system organ class, preferred term, and grade (all causalities; SAS population*)†

System Organ Class Preferred Term‡	NMV/r (N=1109) n (%)						Placebo (N=1115) n (%)					
	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total	Grade 1	Grade 2	Grade 3	Grade 4	Grade 5	Total
Participants with event	138 (12.4)	68 (6.1)	34 (3.1)	11 (1.0)	0	251 (22.6)	88 (7.9)	72 (6.5)	75 (6.7)	18 (1.6)	13 (1.2)	266 (23.9)
Blood and lymphatic system disorders	3 (0.3)	2 (0.2)	0	0	0	5 (0.5)	4 (0.4)	2 (0.2)	1 (0.1)	2 (0.2)	0	9 (0.8)
Anemia	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	1 (0.1)	0	1 (0.1)
Leukocytosis	2 (0.2)	0	0	0	0	2 (0.2)	0	0	0	0	0	0
Leukopenia	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)	2 (0.2)	0	0	0	0	2 (0.2)
Lymphadenopathy mediastinal	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Microcytic anemia	0	0	0	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)
Neutropenia	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)	0	0	2 (0.2)
Thrombocytopenia	0	0	0	0	0	0	1 (0.1)	2 (0.2)	0	0	0	3 (0.3)
Cardiac disorders	0	1 (0.1)	1 (0.1)	0	0	2 (0.2)	5 (0.4)	0	1 (0.1)	0	0	6 (0.5)
Palpitations	0	1 (0.1)	1 (0.1)	0	0	2 (0.2)	2 (0.2)	0	0	0	0	2 (0.2)
Pericardial effusion	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Sinus bradycardia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Sinus tachycardia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Ventricular arrhythmia	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Ear and labyrinth disorders	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.2)	0	0	0	0	2 (0.2)
Hyperacusis	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Vertigo	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Eye disorders	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Eye pain	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Gastrointestinal disorders	53 (4.8)	13 (1.2)	0	0	0	66 (6.0)	35 (3.1)	16 (1.4)	2 (0.2)	0	0	53 (4.8)
Abdominal pain	2 (0.2)	0	0	0	0	2 (0.2)	2 (0.2)	1 (0.1)	0	0	0	3 (0.3)
Abdominal pain lower	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Abdominal pain upper	3 (0.3)	0	0	0	0	3 (0.3)	2 (0.2)	0	0	0	0	2 (0.2)
Aphthous ulcer	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Colitis	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Constipation	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.2)	1 (0.1)	0	0	0	3 (0.3)
Diarrhea	29 (2.6)	5 (0.5)	0	0	0	34 (3.1)	13 (1.2)	5 (0.4)	0	0	0	18 (1.6)

Dry mouth	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Dyspepsia	4 (0.4)	2 (0.2)	0	0	0	6 (0.5)	5 (0.4)	0	0	0	0	5 (0.4)
Feces soft	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Gastritis	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Gastroesophageal reflux disease	3 (0.3)	0	0	0	0	3 (0.3)	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)
Hiatus hernia	0	0	0	0	0	0	2 (0.2)	0	0	0	0	2 (0.2)
Hyperchlorhydria	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Large intestine polyp	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Nausea	12 (1.1)	4 (0.4)	0	0	0	16 (1.4)	10 (0.9)	7 (0.6)	2 (0.2)	0	0	19 (1.7)
Rectal hemorrhage	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Vomiting	8 (0.7)	4 (0.4)	0	0	0	12 (1.1)	6 (0.5)	3 (0.3)	0	0	0	9 (0.8)
General disorders and administration site conditions	15 (1.4)	2 (0.2)	0	0	0	17 (1.5)	12 (1.1)	3 (0.3)	1 (0.1)	0	0	16 (1.4)
Asthenia	3 (0.3)	0	0	0	0	3 (0.3)	2 (0.2)	0	1 (0.1)	0	0	3 (0.3)
Catheter site pain	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Chest discomfort	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)	0	0	0	0	0	0
Chest pain	2 (0.2)	0	0	0	0	2 (0.2)	1 (0.1)	0	0	0	0	1 (0.1)
Chills	4 (0.4)	1 (0.1)	0	0	0	5 (0.5)	0	0	0	0	0	0
Fatigue	2 (0.2)	0	0	0	0	2 (0.2)	5 (0.4)	0	0	0	0	5 (0.4)
Non-cardiac chest pain	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Edema due to cardiac disease	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Pain	0	0	0	0	0	0	1 (0.1)	2 (0.2)	0	0	0	3 (0.3)
Peripheral swelling	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Pyrexia	8 (0.7)	0	0	0	0	8 (0.7)	5 (0.4)	2 (0.2)	0	0	0	7 (0.6)
Hepatobiliary disorders	1 (0.1)	2 (0.2)	1 (0.1)	0	0	4 (0.4)	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)
Cholestasis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Hepatic function abnormal	0	1 (0.1)	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	1 (0.1)
Hepatitis toxic	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Hyperbilirubinemia	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Liver injury	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Immune system disorders	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)	0	0	0	0	0	0
Mycotic allergy	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Seasonal allergy	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Infections and infestations	6 (0.5)	8 (0.7)	7 (0.6)	2 (0.2)	0	23 (2.1)	7 (0.6)	15 (1.3)	36 (3.2)	7 (0.6)	11 (1.0)	76 (6.8)
Abscess	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Atypical pneumonia	0	0	0	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)
Bronchitis	0	1 (0.1)	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	1 (0.1)

Bronchopulmonary aspergillosis	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
COVID-19	0	2 (0.2)	1 (0.1)	0	0	3 (0.3)	1 (0.1)	4 (0.4)	5 (0.4)	1 (0.1)	3 (0.3)	14 (1.3)
COVID-19 pneumonia	0	2 (0.2)	5 (0.5)	0	0	7 (0.6)	1 (0.1)	5 (0.4)	22 (2.0)	5 (0.4)	8 (0.7)	41 (3.7)
Gastroenteritis viral	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Influenza	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Mumps	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Nasopharyngitis	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)	0	0	0	0	0	0
Oral candidiasis	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Oral herpes	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.2)	0	0	0	0	2 (0.2)
Oropharyngeal candidiasis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Pharyngitis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Pneumonia	1 (0.1)	0	1 (0.1)	0	0	2 (0.2)	0	5 (0.4)	9 (0.8)	1 (0.1)	0	15 (1.3)
Pneumonia viral	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Pyelonephritis chronic	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	0	0	0
Respiratory tract infection bacterial	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Respiratory tract infection viral	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)	0	0	0	0	0	0
Sepsis	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	0	0	0
Staphylococcal bacteremia	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Tonsillitis	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Upper respiratory tract infection	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Urinary tract infection	0	1 (0.1)	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Viral rhinitis	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Viral sepsis	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Vulvovaginal candidiasis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Injury, poisoning and procedural complications	0	0	0	0	0	0	1 (0.1)	2 (0.2)	0	1 (0.1)	0	4 (0.4)
Craniocerebral injury	0	0	0	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)
Eye injury	0	0	0	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)
Fall	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Hand fracture	0	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)	0	2 (0.2)
Meniscus injury	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Road traffic accident	0	0	0	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)
Wrist fracture	0	0	0	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)

Investigations	26 (2.3)	32 (2.9)	23 (2.1)	8 (0.7)	0	89 (8.0)	27 (2.4)	41 (3.7)	30 (2.7)	6 (0.5)	0	104 (9.3)
Activated partial thromboplastin time prolonged	5 (0.5)	3 (0.3)	1 (0.1)	0	0	9 (0.8)	10 (0.9)	0	2 (0.2)	0	0	12 (1.1)
Alanine aminotransferase increased	2 (0.2)	13 (1.2)	2 (0.2)	0	0	17 (1.5)	4 (0.4)	18 (1.6)	5 (0.4)	0	0	27 (2.4)
Aspartate aminotransferase increased	4 (0.4)	5 (0.5)	1 (0.1)	0	0	10 (0.9)	4 (0.4)	6 (0.5)	3 (0.3)	1 (0.1)	0	14 (1.3)
Blood albumin decreased	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Blood alkaline phosphatase increased	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Blood bicarbonate decreased	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Blood calcium decreased	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Blood creatine phosphokinase increased	1 (0.1)	0	0	1 (0.1)	0	2 (0.2)	3 (0.3)	0	2 (0.2)	0	0	5 (0.4)
Blood creatinine decreased	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Blood creatinine increased	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Blood fibrinogen decreased	1 (0.1)	1 (0.1)	2 (0.2)	0	0	4 (0.4)	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)
Blood glucose decreased	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Blood glucose increased	0	1 (0.1)	0	1 (0.1)	0	2 (0.2)	0	3 (0.3)	3 (0.3)	1 (0.1)	0	7 (0.6)
Blood lactate dehydrogenase increased	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Blood potassium decreased	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Blood potassium increased	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Blood pressure increased	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Blood sodium decreased	0	0	0	0	0	0	2 (0.2)	0	0	0	0	2 (0.2)

Blood thyroid stimulating hormone decreased	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Blood thyroid stimulating hormone increased	6 (0.5)	0	0	0	0	6 (0.5)	5 (0.4)	2 (0.2)	0	0	0	7 (0.6)
Blood urea increased	0	1 (0.1)	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Breath sounds abnormal	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
C-reactive protein	2 (0.2)	0	0	0	0	2 (0.2)	1 (0.1)	0	0	0	0	1 (0.1)
C-reactive protein increased	6 (0.5)	1 (0.1)	2 (0.2)	0	0	9 (0.8)	11 (1.0)	1 (0.1)	1 (0.1)	0	0	13 (1.2)
Creatinine renal clearance abnormal	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Creatinine renal clearance decreased	0	5 (0.5)	9 (0.8)	2 (0.2)	0	16 (1.4)	0	6 (0.5)	10 (0.9)	2 (0.2)	0	18 (1.6)
Creatinine renal clearance increased	0	0	1 (0.1)	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Differential white blood cell count abnormal	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Fibrin D dimer	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)	0	0	0	0	0	0
Fibrin D dimer increased	11 (1.0)	6 (0.5)	4 (0.4)	0	0	21 (1.9)	14 (1.3)	11 (1.0)	4 (0.4)	2 (0.2)	0	31 (2.8)
Glomerular filtration rate abnormal	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Glomerular filtration rate decreased	0	0	3 (0.3)	0	0	3 (0.3)	0	0	1 (0.1)	1 (0.1)	0	2 (0.2)
Glycosylated hemoglobin increased	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Hematocrit increased	1 (0.1)	0	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	1 (0.1)
Hemoglobin decreased	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	0	0	0
Hemoglobin increased	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Haptoglobin	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Haptoglobin increased	3 (0.3)	0	0	0	0	3 (0.3)	3 (0.3)	0	0	0	0	3 (0.3)
Hepatic enzyme abnormal	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Hepatic enzyme increased	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)	0	1 (0.1)	2 (0.2)	0	0	3 (0.3)

International normalized ratio abnormal	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	0	0	0
International normalized ratio increased	1 (0.1)	0	0	2 (0.2)	0	3 (0.3)	3 (0.3)	1 (0.1)	1 (0.1)	0	0	5 (0.4)
Liver function test increased	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Lymphocyte count decreased	0	0	0	0	0	0	1 (0.1)	1 (0.1)	1 (0.1)	0	0	3 (0.3)
Neutrophil count decreased	0	0	0	0	0	0	2 (0.2)	0	0	0	0	2 (0.2)
Neutrophil count increased	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)	0	0	0	0	0	0
Oxygen saturation decreased	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Platelet count decreased	1 (0.1)	0	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	1 (0.1)
Platelet count increased	2 (0.2)	0	0	0	0	2 (0.2)	0	1 (0.1)	0	0	0	1 (0.1)
Procalcitonin	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Procalcitonin increased	0	0	0	0	0	0	2 (0.2)	0	0	0	0	2 (0.2)
Prothrombin time prolonged	1 (0.1)	0	0	2 (0.2)	0	3 (0.3)	1 (0.1)	2 (0.2)	2 (0.2)	0	0	5 (0.4)
Red blood cell count increased	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Serum ferritin decreased	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Serum ferritin increased	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)	5 (0.4)	0	1 (0.1)	0	0	6 (0.5)
Thyroxine free increased	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Thyroxine increased	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Transaminases increased	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Weight increased	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
White blood cell count decreased	0	2 (0.2)	0	0	0	2 (0.2)	0	2 (0.2)	1 (0.1)	0	0	3 (0.3)
White blood cell count increased	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)	0	0	0	0	0	0
Metabolism and nutrition disorders	5 (0.5)	9 (0.8)	3 (0.3)	0	0	17 (1.5)	4 (0.4)	6 (0.5)	4 (0.4)	0	0	14 (1.3)
Decreased appetite	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0

Dehydration	0	2 (0.2)	0	0	0	2 (0.2)	0	1 (0.1)	0	0	0	1 (0.1)
Diabetes mellitus	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)	0	0	0	0	0	0
Diabetes mellitus inadequate control	0	0	1 (0.1)	0	0	1 (0.1)	0	0	1 (0.1)	0	0	1 (0.1)
Glucose tolerance impaired	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Gout	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Hyperglycemia	0	1 (0.1)	1 (0.1)	0	0	2 (0.2)	1 (0.1)	1 (0.1)	2 (0.2)	0	0	4 (0.4)
Hyperkalemia	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Hypertriglyceridemia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Hypervolemia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Hypokalemia	2 (0.2)	1 (0.1)	0	0	0	3 (0.3)	2 (0.2)	1 (0.1)	0	0	0	3 (0.3)
Hypomagnesemia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Hyponatremia	0	2 (0.2)	0	0	0	2 (0.2)	0	0	0	0	0	0
Hypophosphatemia	0	0	1 (0.1)	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Impaired fasting glucose	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Lack of satiety	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Type 2 diabetes mellitus	0	1 (0.1)	0	0	0	1 (0.1)	1 (0.1)	2 (0.2)	0	0	0	3 (0.3)
Musculoskeletal and connective tissue disorders	10 (0.9)	3 (0.3)	0	0	0	13 (1.2)	9 (0.8)	2 (0.2)	0	0	0	11 (1.0)
Arthralgia	2 (0.2)	1 (0.1)	0	0	0	3 (0.3)	1 (0.1)	0	0	0	0	1 (0.1)
Back pain	2 (0.2)	1 (0.1)	0	0	0	3 (0.3)	2 (0.2)	0	0	0	0	2 (0.2)
Intervertebral disc degeneration	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Intervertebral disc protrusion	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Muscle spasms	0	0	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)
Musculoskeletal stiffness	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Myalgia	6 (0.5)	1 (0.1)	0	0	0	7 (0.6)	2 (0.2)	0	0	0	0	2 (0.2)
Pain in extremity	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)
Spinal osteoarthritis	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Colon adenoma	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Nervous system disorders	70 (6.3)	8 (0.7)	2 (0.2)	0	0	80 (7.2)	20 (1.8)	6 (0.5)	0	0	0	26 (2.3)
Amnesia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Anosmia	3 (0.3)	0	0	0	0	3 (0.3)	0	0	0	0	0	0

Brain stem stroke	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Dizziness	2 (0.2)	1 (0.1)	0	0	0	3 (0.3)	5 (0.4)	1 (0.1)	0	0	0	6 (0.5)
Dysgeusia	58 (5.2)	3 (0.3)	1 (0.1)	0	0	62 (5.6)	3 (0.3)	0	0	0	0	3 (0.3)
Facial paralysis	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Headache	14 (1.3)	1 (0.1)	0	0	0	15 (1.4)	11 (1.0)	3 (0.3)	0	0	0	14 (1.3)
Hypersomnia	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Memory impairment	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Parosmia	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Restless legs syndrome	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Syncope	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Tremor	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Vascular dementia	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Product issues	2 (0.2)	1 (0.1)	0	0	0	3 (0.3)	0	0	0	0	0	0
Product after taste	2 (0.2)	1 (0.1)	0	0	0	3 (0.3)	0	0	0	0	0	0
Psychiatric disorders	4 (0.4)	3 (0.3)	0	0	0	7 (0.6)	2 (0.2)	2 (0.2)	0	0	0	4 (0.4)
Anxiety	3 (0.3)	0	0	0	0	3 (0.3)	0	1 (0.1)	0	0	0	1 (0.1)
Confusional state	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Depression	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Insomnia	0	2 (0.2)	0	0	0	2 (0.2)	2 (0.2)	0	0	0	0	2 (0.2)
Stress	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Renal and urinary disorders	0	0	0	1 (0.1)	0	1 (0.1)	0	1 (0.1)	1 (0.1)	1 (0.1)	0	3 (0.3)
Chronic kidney disease	0	0	0	1 (0.1)	0	1 (0.1)	0	0	1 (0.1)	0	0	1 (0.1)
Renal impairment	0	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)	0	2 (0.2)
Reproductive system and breast disorders	1 (0.1)	0	0	0	0	1 (0.1)	2 (0.2)	1 (0.1)	0	0	0	3 (0.3)
Heavy menstrual bleeding	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Intermenstrual bleeding	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Vaginal hemorrhage	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Respiratory, thoracic and mediastinal disorders	17 (1.5)	5 (0.5)	1 (0.1)	0	0	23 (2.1)	9 (0.8)	5 (0.4)	13 (1.2)	5 (0.4)	2 (0.2)	34 (3.0)
Acute respiratory failure	0	0	1 (0.1)	0	0	1 (0.1)	0	0	3 (0.3)	1 (0.1)	1 (0.1)	5 (0.4)
Allergic cough	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Asthma	1 (0.1)	0	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	1 (0.1)
Cough	5 (0.5)	1 (0.1)	0	0	0	6 (0.5)	4 (0.4)	1 (0.1)	2 (0.2)	0	0	7 (0.6)
Dyspnea	4 (0.4)	3 (0.3)	0	0	0	7 (0.6)	3 (0.3)	2 (0.2)	4 (0.4)	0	0	9 (0.8)
Epistaxis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Hemoptysis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0

Hiccups	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Hypoxia	0	0	0	0	0	0	1 (0.1)	2 (0.2)	1 (0.1)	0	0	4 (0.4)
Interstitial lung disease	1 (0.1)	0	0	0	0	1 (0.1)	0	0	2 (0.2)	0	0	2 (0.2)
Nasal congestion	2 (0.2)	2 (0.2)	0	0	0	4 (0.4)	0	0	0	0	0	0
Oropharyngeal pain	4 (0.4)	0	0	0	0	4 (0.4)	0	0	0	0	0	0
Pneumonitis	0	0	0	0	0	0	0	0	2 (0.2)	2 (0.2)	1 (0.1)	5 (0.4)
Pulmonary embolism	0	0	0	0	0	0	0	0	0	2 (0.2)	0	2 (0.2)
Respiratory failure	0	0	0	0	0	0	0	0	1 (0.1)	0	0	1 (0.1)
Rhinorrhea	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Skin and subcutaneous tissue disorders	7 (0.6)	0	2 (0.2)	0	0	9 (0.8)	7 (0.6)	1 (0.1)	1 (0.1)	0	0	9 (0.8)
Acne	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Alopecia	1 (0.1)	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	0	1 (0.1)
Erythema	0	0	0	0	0	0	4 (0.4)	0	0	0	0	4 (0.4)
Hyperhidrosis	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Hyperkeratosis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Pruritis	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Rash	2 (0.2)	0	0	0	0	2 (0.2)	2 (0.2)	0	1 (0.1)	0	0	3 (0.3)
Rash maculopapular	0	0	1 (0.1)	0	0	1 (0.1)	0	0	0	0	0	0
Skin exfoliation	2 (0.2)	0	0	0	0	2 (0.2)	0	0	0	0	0	0
Skin edema	1 (0.1)	0	0	0	0	1 (0.1)	0	0	0	0	0	0
Urticaria	0	0	0	0	0	0	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)
Social circumstances	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Disease risk factor	0	1 (0.1)	0	0	0	1 (0.1)	0	0	0	0	0	0
Vascular disorders	3 (0.3)	3 (0.3)	1 (0.1)	1 (0.1)	0	8 (0.7)	6 (0.5)	5 (0.4)	1 (0.1)	0	0	12 (1.1)
Deep vein thrombosis	0	0	0	0	0	0	0	1 (0.1)	0	0	0	1 (0.1)
Embolism	0	0	0	0	0	0	1 (0.1)	0	1 (0.1)	0	0	2 (0.2)
Hyperemia	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Hypertension	4 (0.4)	2 (0.2)	1 (0.1)	0	0	7 (0.6)	1 (0.1)	1 (0.1)	0	0	0	2 (0.2)
Hypertensive crisis	0	0	0	1 (0.1)	0	1 (0.1)	0	0	0	0	0	0
Hypotension	0	1 (0.1)	0	0	0	1 (0.1)	1 (0.1)	3 (0.3)	0	0	0	4 (0.4)
Orthostatic hypotension	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Thrombophlebitis	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)
Vein collapse	0	0	0	0	0	0	1 (0.1)	0	0	0	0	1 (0.1)

COVID-19=coronavirus disease 2019; NMV/r=nirmatrelvir 300 mg + ritonavir 100 mg; SAS=safety analysis set.

* All patients randomly assigned to study intervention who received ≥1 dose of study intervention.

† Participants are only counted once per treatment per event. Includes adverse events that started on or prior to Day 34 visit.

‡ MedDRA v24.1 coding dictionary applied.

Table S6. Treatment-emergent serious adverse events by decreasing frequency (all causalities; SAS population*)†

Preferred Term‡	NMV/r (N=1109) n (%)	Placebo (N=1115) n (%)
COVID-19 pneumonia	6 (0.5)	37 (3.3)
COVID-19	2 (0.2)	8 (0.7)
Creatinine renal clearance decreased	2 (0.2)	3 (0.3)
Abscess	1 (0.1)	0
Brain stem stroke	1 (0.1)	0
Chest discomfort	1 (0.1)	0
Dyspnoea	1 (0.1)	3 (0.3)
Facial paralysis	1 (0.1)	0
Haemoglobin decreased	1 (0.1)	0
Hypertensive crisis	1 (0.1)	0
Oxygen saturation decreased	1 (0.1)	0
Palpitations	1 (0.1)	0
Pneumonia	1 (0.1)	11 (1.0)
Sepsis	1 (0.1)	0
Acute respiratory failure	0	5 (0.4)
Alanine aminotransferase increased	0	1 (0.1)
Anaemia	0	1 (0.1)
Atypical pneumonia	0	1 (0.1)
Colon adenoma	0	1 (0.1)
Craniocerebral injury	0	1 (0.1)
Eye injury	0	1 (0.1)
Fibrin D dimer increased	0	1 (0.1)
Hand fracture	0	1 (0.1)
Hypoxia	0	2 (0.2)
Interstitial lung disease	0	2 (0.2)
Pneumonitis	0	5 (0.4)
Pulmonary embolism	0	2 (0.2)
Rectal haemorrhage	0	1 (0.1)
Respiratory failure	0	1 (0.1)
Road traffic accident	0	1 (0.1)
Wrist fracture	0	1 (0.1)

COVID-19=coronavirus disease 2019; NMV/r=nirmatrelvir 300 mg + ritonavir 100 mg; SAS=safety analysis set.

* All patients randomly assigned to study intervention who received ≥1 dose of study intervention.
† Participants are only counted once per treatment per event. Includes adverse events that started on or prior to Day 34 visit.
‡ MedDRA v24.1 coding dictionary applied.

Supplementary References

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