Supplemental Material*

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Contents

* This supplemental material was provided by the authors to give readers further details on their article. The material was not copyedited.

A. SUPPLEMENT METHODS

Supplement Table 1. Specification and emulation of a target randomized controlled trial of nirmatrelvir-ritonavir versus no outpatient SARS-CoV-2 treatment* among non-hospitalized veterans who tested positive for SARS-CoV-2 from January 1-July 31, 2022

Target Trial Specification	Target Trial Emulation
Eligibility Criteria	
Aged ≥18 years at the time of positive SARS-CoV-2 test performed January 1, 2022-July 31, 2022.	Same
VA enrollees (excludes VA employees who are not enrollees).	Same
Followed by a primary care provider in the VA healthcare system, defined as having a primary care outpatient encounter in the preceding 18 months.	Same
Documented first positive laboratory-based SARS-CoV-2 NAAT or antigen test in a respiratory specimen performed between January 1-July 31, 2022. Patients with reinfection during this period (i.e., those who also have a documented positive SARS-CoV-2 NAAT or antigen test before January 1, 2022) were not included.	Same We identified all VA enrollees who had a first positive laboratory-based SARS-CoV-2 NAAT or antigen test using the VA COVID-19 National Surveillance Tool (NST) as documented in CSDR. This includes all patients tested within the VA as well as patients with such tests performed outside the VA but documented in VA records. Tests performed outside the VA are identified by methods including NLP and confirmed by manual review of the EHR before being documented in the NST.
Symptomatic infection (≥1 symptoms) at the time of diagnosis (1, 2).	Not included CSDR provides data on 15 pre-specified COVID-19-related symptoms documented in the EHR in the 30 days prior to the first positive SARS-CoV-2 test. These symptoms are extracted using a combination of ICD-10 codes, COVID-19 screening questionnaires, and natural language processing (NLP). Because ascertainment of symptoms is incomplete and since CSDR does not distinguish whether symptoms were present at the time of testing positive, we did not require presence of ≥1 symptoms. Presence or absence of symptoms were included in propensity score matching instead.
No hospitalization or death through the date following the positive SARS-CoV-2 test (test-positive date) and no hospitalization on or before the date of randomized assignment to nirmatrelvir-ritonavir or no treatment.	Same Participants were not hospitalized on or within 7 days before test-positive date. Participants remained alive and not hospitalized through the test-positive date and the subsequent day. Participants receiving nirmatrelvir-ritonavir were not hospitalized on or before the date of treatment initiation.

	Matched untreated participants were not hospitalized on or before their assigned index date (which was the same number of days from the test-positive date as the matched treated patient, see below)
Did not initiate nirmatrelvir-ritonavir before the test-positive date.	Same
Persons treated with nirmatrelvir-ritonavir did not receive more than one outpatient COVID-19 therapy on the same day. Untreated persons did not receive any other outpatient COVID-19 therapy on or prior to the matched antiviral treatment date.	Same Persons receiving nirmatrelvir-ritonavir were not treated with other outpatient COVID-19 treatments (molnupiravir, bebtelovimab, sotrovimab, casirivimab-imdevimab, bamlanivimab-etesevimab, remdesivir) on or prior to the nirmatrelvir-ritonavir treatment date. Untreated persons did not receive any other outpatient COVID-19 therapy on or prior to the matched antiviral treatment date (index date).
Having ≥1 risk factors for progression to severe COVID-19 by the FDA EUA/CDC criteria (**Supplement Table 2**).	Same
Access to nirmatrelvir-ritonavir.	Same Persons were identified by the VHA facility where they tested positive for SARS-CoV-2. We restricted to facilities that prescribed nirmatrelvir-ritonavir during the study period. Facilities were allocated antiviral medications in quantities that exceeded prescribing demand.
Persons with any of the following, which are contraindications to nirmatrelvir-ritonavir, were excluded: - Moderate or severe liver disease - Advanced renal impairment (CKD IV or V, on dialysis, or eGFR<30) - Prescription of medications that are contraindicated with nirmatrelvir-ritonavir per FDA in the 90 days prior to test-positive date (**Supplement Table 4**)	Same
Treatment Strategies	
Randomized to treatment with one of the following within 5 days of symptom onset: - Nirmatrelvir-ritonavir Vs. - No treatment	We determined the date of treatment with nirmatrelvir-ritonavir from pharmacy fill date of the medication. Since symptom onset date could not be ascertained in the EHR, we used treatment within 5 days of the test-positive date rather within 5 days of symptom onset. In clinical practice, adherence to EUA criteria (treatment within 5 days of symptom onset) is closely monitored and enforced by VA PBM.
Treatment Assignment	
Eligible participants were randomly assigned to: - Nirmatrelvir-ritonavir vs no treatment	**Sequential matching:** *Exact-matching* We first exact-matched each eligible participant who received nirmatrelvir-ritonavir to all eligible participants who did not receive any treatment using four factors:

	- NIH tier of prioritization for anti-SARS-CoV-2 therapies (**Supplementary Table 5**) - VISN, the 19 geographical administrative regions of the VA - Facility complexity level (1a highest complexity vs. non-1a) - Calendar time, centered +/- 7 days around the test-positive date of the matched comparator *Propensity-score matching* After exact-matching by these four factors, we performed an additional propensity score matching step ultimately aiming to identify the best-matching comparator. We used matching with replacement in a 1:k variable ratio, where k varied based on the number of propensity score ties. We included all ties to avoid imbalance due to random pruning. The characteristics included in the propensity score logistic regression model are shown in **Supplement Table 6**.
Outcomes	
Primary Outcome: Incidence of 31 predefined post-COVID-19 conditions from day 31-180 after index date. Incidence of a specific condition was defined by absence of documentation of that condition in the 12 months prior to the test-positive date and documentation during the period 31-180 days after the index date	Same
Follow-up	
For each person, follow-up began from day 31 after randomization and continued until day 180 for post-COVID-19 conditions	Same An index date was assigned to untreated patients which was the same interval from the test-positive date. Untreated persons had to fulfill enrollment criteria as of that index date (e.g., a person treated on day 3 after testing positive was matched to a person who was untreated, alive, and not hospitalized 3 days after testing positive). This study design ensured that dates of eligibility determination, treatment, and follow-up initiation were the same (**Figure 1**). Matched groups who were alive through day 30 after the index date and did not have the condition documented during the 12 months prior to infection were followed from day 31 to 180
Causal Contrasts	
Intention-to-treat (ITT) effect	Observational analogue of ITT effect
Statistical Analysis	
31-180-day incidence of each post-COVID-19 condition	Same

*Includes treatments available in the VHA during the study period (nirmatrelvir-ritonavir, molnupiravir, bebtelovimab, sotrovimab, and outpatient remdesivir).

Abbreviations: ATSDR, Agency for Toxic Substances and Disease Registry; CAN, Care Assessment Needs; CDC, Centers for Disease Control and Prevention; CLC, Community Living Center; CDW, Corporate Data Warehouse; CSDR, COVID-19 Shared Data Resource; eGFR, estimated glomerular filtration rate; EHR, electronic health records; EUA, emergency use authorization; FDA, Food and Drug Administration; ICU, Intensive Care Unit; ITT, Intention-to-treat; NAAT, nucleic acid amplification test; NIH, National Institutes of Health; NLP, Natural Language Processing; NST, National Surveillance Tool; PASC, Post-acute Sequelae of COVID-19; PBM, Pharmacy Benefits Management Services; PCP, Primary Care Provider; SVI, Social Vulnerability Index; VA, Veterans Affairs; VHA, Veterans Health Administration; VISN, VA Integrated Services Network

Eligibility criteria and study population

Participants were limited to test-positive VA enrollees. We limited eligibility to Veterans with at least one risk factor for progression to severe COVID-19, including hospitalization or death, according to the Centers for Disease Control and Prevention (CDC) (3) as shown in Supplement Table 2 below.

Supplement Table 2. Risk factors for progression to severe COVID-19 according to the CDC (3)

Age ≥ 65 years*
Underlying Medical Conditions
Cancer
Cardiovascular disease including cardiomyopathy, chronic rheumatic heart disease, congestive heart failure, coronary artery disease, hypertension, myocardial infarction, peripheral artery disease, pulmonary heart disease
Chronic kidney disease including dialysis
Chronic liver disease including chronic hepatitis and cirrhosis
Chronic lung disease including asthma, chronic obstructive pulmonary disease, emphysema, pulmonary fibrosis
Chronic neurologic conditions including epilepsy, multiple sclerosis, and Parkinson's disease
Dementia
PTSD
Diabetes
HIV
Immunosuppressive medications or cancer therapies (see **Supplementary Table 3**)
Mental health conditions including bipolar disorder, major depressive disorder, post-traumatic stress disorder, and schizophrenia
Overweight (body mass index 25 to <30 kg/m^2) or obese (body mass index ≥30 kg/m^2) or
Pregnancy
Sickle cell disease
Stroke or cerebrovascular disease
Thalassemia
Current or former tobacco use
Substance use
Alcohol use disorder
Non-alcohol substance use disorder

*Age at the time of positive SARS-CoV-2 test or underlying conditions, tobacco, or substance use documented in the 2 years prior to positive SARS-CoV-2 test.

Supplement Table 3. Immunosuppressive and cancer medications*

ABATACEPT, ABEMACICLIB, ABRAXANE, ACALABRUTINIB, ADALIMUMAB, AFATINIB, ALDESLEUKIN, ALECTINIB, ALEMTUZUMAB,† ALPELISIB, ANAKINRA, ANTI-THYMOCYTE GLOBULIN, † APREMILAST, APSPARAGINASE, ARSENIC TRIOXIDE, ASCIMINIB, ASPARAGINASE, ATEZOLIZUMAB, AVACOPAN, AVAPRITINIB, AVELUMAB, AXITINIB, AZACITIDINE, AZATHIOPRINE, BARICITINIB, BASILIXIMAB, BELANTAMAB, BELATACEPT, BELIMUMAB, BELINOSTAT, BELUMOSUDIL, BELZUTIFAN, BENDAMUSTINE, BENRALIZUMAB, BEVACIZUMAB, BEXAROTENE, BINIMETINIB, BINMETINIB, BLEOMYCIN, BLINATUMOMAB, BORTEZOMIB, BOSUTINIB, BRENTUXIMAB, BRIGATINIB, BRODALUMAB, BUDESONIDE, ‡ BUSULFAN, CABAZITAXEL, CABOZANTINIB, CANAKINUMAB, CAPECITABINE, CAPMATINIB, CARBOPLATIN, CARFILZOMIB, CARMUSTINE, CEMIPLIMAB, CERITINIB, CERTINIB, CERTOLIZUMAB, CETUXIMAB, CHLORAMBUCIL, CISPLATIN, CISPLATINUM, CLADRIBINE, CLOFARABINE, COBIMETINIB, COPANLISIB, COPAXONE, CRIZOTINIB, CYCLOPHOSPHAMIDE, CYCLOSPORINE, CYTARABINE, DABRAFENIB, DACARBAZINE, DACOMITINIB, DACTINOMYCIN, DARATUMUMAB, DASATINIB, DAUNORUBICIN, DENOSUMAB, DEXAMETHASONE,‡ DIMETHYL FUMARATE, DOCETAXEL, DOXORUBICIN, DUPILUMAB, DURVALUMAB, DUVELISIB, ECULIZUMAB, ELOTUZUMAB, ENASIDENIB, ENCORAFENIB, ENFORTUMAB, ENTRECTINIB, ENZALUTAMIDE, EPIRUBICIN, ERDAFITINIB, ERIBULIN, ERLOTINIB, ESTRAMUSTINE, ETANERCEPT, ETOPOSIDE, EVEROLIMUS, FATUMUMAB, FINGOLIMOD, FLUDARABINE, FLUOROURACIL, FLUTAMIDE, GEFITINIB, GEMCITABINE, GEMTUZUMAB, GENGRAF, GILTERITINIB, GLASDEGIB, GLATIRAMER, GLATIRAMIR ACETATE, GOLIMUMAB, GUSELKUMAB, HERCEPTIN, HYDROCORTISONE,‡ HYDROXYCHLOROQUINE, HYDROXYUREA, IBRUTINIB, IDARUBICIN, IDELALISIB, IFOSFAMIDE, IMATINIB, INFIGRATINIB, INFLECTRA, INFLIXIMAB, INOTUZUMAB, INTERFERON, INVIBRUTINIB, IPILIMUMAB, IRINOTECAN, ISATUXIMAB, IVOSIDENIB, IXAZOMIB, IXEKIZUMAB, LAPATINIB, LAROTRECTINIB, LEFLUNOMIDE, LENALIDOMIDE, LENVATINIB, LETROZOLE, LOMUSTINE, LONCASTUXIMAB, LURBINECTEDIN, MARGETUXIMAB, MECHLORETHAMINE, MELPHALAN, MEPOLIZUMAB, MERCAPTOPURINE, METHOTREXATE, METHYLPREDNISOLONE,‡ MIDOSTAURIN, MITOMYCIN, MITOXANTRONE, MOGAMULIZUMAB, MYCOPHENOLATE, MYCOPHENOLIC ACID, NATALIZUMAB, NELARABINE, NERATINIB, NILOTINIB, NILUTAMIDE, NIRAPARIB, NIVOLUMAB, OBINUTUZUMAB, OCRELIZUMAB,† OFATUMUMAB,† OLAPARIB, OSIMERTINIB, OXALIPLATIN, PACLITAXEL, PALBOCICLIB, PANITUMUMAB, PANOBINOSTAT, PAZOPANIB, PEGASPARGASE, PEGINTERFERON, PEMBROLIZUMAB, PEMETREXED, PEMIGATINIB, PENTOSTATIN, PERTUZUMAB, PEXIDARTINIB, PIMECROLIMUS, POLATUZUMAB, POMALIDOMIDE, PONATINIB, PRALATREXATE, PREDNISOLONE, ‡ PREDNISONE, ‡ PROCARBAZINE, RAMUCIRUMAB, RASBURICASE, RAVULIZUMAB, REGORAFENIB, RENFLEXIS, RESLIZUMAB, RIBOCICLIB, RILONACEPT, RIPRETINIB, RISANKIZUMAB, RISKANIKIZUMAB, RITUXIMAB,† ROMIDEPSIN, ROPEGINTERFERON, RUCAPARIB, RUXOLITINIB, SACITUZUMAB, SARILUMAB, SATRALIZUMAB, SECUKINUMAB, SELINEXOR, SELPERCATINIB, SILTUXIMAB, SIPONIMOD, SIPULEUCEL, SIROLIMUS, SORAFENIB, SULFASALAZINE, SUNITINIB, SUTIMLIMAB, TACROLIMUS, TAFASITAMAB, TAGRAXOFUSP, TALAZOPARIB, TAZEMETOSTAT, TEMOZOLOMIDE, TEMSIROLIMUS, TERIFLUNOMIDE, THALIDOMIDE, THIOGUANINE, THIOPHOSPHORAMIDE, THIOTEPA, TILDRAKIZUMAB, TIPIRACIL, TIVOZANIB, TOCILIZUMAB, TOFACITINIB, TRABECTEDIN, TRAMETINIB, TRASTUZUMAB, TRIFLURIDINE, TUCATINIB, UMBRALISIB, UPADACITINIB, USTEKINUMAB, VALRUBICIN, VANDETANIB, VEDOLIZUMAB, VENETOCLAX, VINBLASTINE, VINCRISTINE, VINORELBINE, VORINOSTAT, ZANUBRUTINIB

*Prescriptions filled within 90 days of test-positive date unless otherwise indicated
†Filled within one year of test-positive date
‡For systemic steroids, two prescriptions filled within one year of test-positive date, one of which must have been filled within 90 days

Exclusions for contraindications to nirmatrelvir-ritonavir

We excluded persons with advanced renal impairment, defined as any of following:

- Estimated glomerular filtration rate (eGFR) less than 30 milliliters per minute based on labs obtained in the six months prior to positive SARS-CoV-2 test (test date) and calculated using Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) 2021.

- Diagnosis of stage VI or V chronic kidney disease or end stage renal disease based on specific ICD10 codes (N18.4, N18.5, N18.6) recorded as least once in the two years prior to test date.
- Dialysis at test date.

We also excluded persons with moderate or severe liver disease documented in the two years prior to the test date as captured by VA's COVID-19 Shared Data Resource (CSDR).
Finally, we excluded persons with a prescription for contraindicated medications filled within 90 days prior to the test date as shown in the table below (4):

Supplement Table 4. List of medications contraindicated with use of nirmatrelvir-ritonavir[*]

Alfuzosin	Flecainide	Propafenone
Amiodarone	Ivabradine	Quinidine
Apalutamide	Ivacaftor/lumacaftor	Ranolazine
Carbamazepine	Lomitapide	Rifampicin
Colchicine	Lurasidone	Rifampin
Dihydroergotamine	Methylergonovine	Sildenafil
Dronedarone	Midazolam	Silodosin
Eletriptan	Naloxegol	St. John's Wort
Eplerenone	Phenobarbital	Tolvaptan
Ergotamine	Phenytoin	Triazolam
Flibanserin	Pimozide	Ubrogepant
Finerenone	Primidone	Voclosporin

[*]List modified from the Food and Drug Administration patient eligibility screening checklist tool for prescribers. Lovastatin and simvastatin have been excluded from this list as they can be held during and for up to 5 days after treatment with nirmatrelvir-ritonavir.

Supplement Table 5. National Institutes of Health (NIH) tiers[*] of prioritization for anti-SARS-CoV-2 therapies (used as an exact-matching criterion)

NIH Tier	Risk Group Definition[†]
1	- Receipt of immunosuppressive or cancer medications[‡] *or* - HIV with most recent absolute CD4 count ≤2 years is ≤200 cells/mm^3 *or* - Unvaccinated[§] and age ≥75 years *or* - Unvaccinated, age 65-74 years, and ≥1 risk factor for severe COVID-19[‖]
2	- Unvaccinated, age 65-74 years, and no risk factors for severe COVID-19 *or* - Unvaccinated, age <65 years, and ≥1 risk factor for severe COVID-19
3	- Vaccinated[§] and age ≥75 years *or* - Vaccinated, age 65-74 years and ≥1 risk factor for severe COVID-19
4	- Vaccinated, age 65-74 years, and no risk factors for severe COVID-19 *or* - Vaccinated, age <65 years, and ≥1 risk factor for severe COVID-19
Other	- Vaccination status not determined (individuals not included in Tier 1)

[*]Per NIH definitions: https://www.covid19treatmentguidelines.nih.gov/overview/prioritization-of-therapeutics/?msclkid=9db67596cf2311ec8b6f159cc2c59087
[†]All factors determined with reference to positive SARS-CoV-2 test
[‡]As defined in Supplement Table 3
[§]As defined in under COVID-19-Vaccination Status. To categorize vaccination as a binary variable for the National Institutes of Health (NIH) tiers of prioritization for anti-SARS-CoV-2 therapies, we considered unvaccinated and partially vaccinated Veterans as 'unvaccinated' for tiers 1 and 2 and fully vaccinated and boosted as 'vaccinated'
[‖]As defined in Supplement Table 2

COVID-19 vaccination status

We aggregated all administered vaccine doses documented in VA-CDW, CMS-Medicare and VA Community Care data. Vaccine records with service dates prior to December 11, 2020, the earliest date of EUA for COVID-19 vaccination in the United States, were excluded. To ensure that vaccine doses documented in more than one source were not counted more than once, after combining records from all sources, we treated 2 vaccine doses as duplicates if they were documented within 7 days of each other.

We included Moderna, Pfizer-BioNTech, and Janssen vaccine types, which were approved in the United States during the period of study and comprised most of all vaccine types. To allow for complete categorization of vaccination, we also included Novavax (authorized after the end of this study period). Vaccine doses of unknown or other type (e.g., Oxford-AstraZeneca) were categorized as other.

Non-immunocompromised (5)

1. Veterans were considered unvaccinated if they did not receive any COVID-19 vaccine or received a vaccine dose other than Janssen less than 14 days prior to the first positive SARS-CoV-2 test (test date).
2. Partial vaccination was indicated by receipt of a single mRNA dose (Pfizer-BioNTech or Moderna) or a single Novavax dose alone or in combination with another vaccine other than Janssen <14 days prior to the index date or a Janssen (Johnson & Johnson) dose <14 days before the test date.
3. Primary vaccination was indicated by receipt of 2 doses of any mRNA or Novavax vaccine or a single dose of Janssen ≥14 days before the test date.
4. Booster vaccination was indicated by any primary regimen above, followed by an additional dose(s) of mRNA, Janssen, or Novavax vaccine ≥7 days before the test date.
5. Other was indicated by any vaccination not captured above.

Immunocompromised (6)

Veterans were considered immunocompromised if they had recently received immunosuppressive or cancer medications as described in Supplementary Table 3, were persons with HIV with most recent absolute CD4 count ≤2 years ≤200 cells/mm,^{3} or had been documented to have a hematologic malignancy within 2 years preceding test-positive date.

1. Veterans were considered unvaccinated if they did not receive any COVID-19 vaccine or received a vaccine dose other than Janssen less than 14 days prior to the test date.
2. Partial vaccination was indicated by receipt of 2 doses of an mRNA vaccine, a single dose of Janssen, or a single dose of Novavax. It was also indicated by receipt of 3 doses of an mRNA vaccine, a single dose of Janssen followed by a single dose of an mRNA vaccine, or 2 doses of Novavax <7 days before the test date.
3. Primary vaccination was indicated by receipt of 3 doses of an mRNA vaccine, a single dose of Janssen followed by a single dose of an mRNA vaccine, or 2 doses of Novavax ≥7 days before the test date.
4. Booster vaccination was indicated by any primary regimen above, followed by an additional dose(s) of mRNA, Janssen, or Novavax vaccine ≥7 days before the test date.
5. Other was indicated by any vaccination not captured above.

The Table below describes factors included in a propensity logistic regression model.

Supplement Table 6. Characteristics included in propensity score matching models for COVID-19 treatment*

1. Calendar month of test
2. Age
3. Sex

4. Race/ethnicity
5. Urban/rural residence based in RUCA codes (rurality) (7)
6. Area Deprivation Index (ADI) (8)
7. Tobacco
8. Alcohol
9. Other substances
11. Presence of any COVID-19 symptoms documented in the 30 days prior to the test-positive date†
12. COVID-19 vaccination: None, partial, primary, booster and other
13. Time since completion of last vaccine dose (for primary or booster vaccination): 0-4, >4 months
14. BMI: <18.5, 18.5-24.9, 25-29.9, 30-34.9, 35-39.9, ≥40 kg/m^2
15. Number of high-risk conditions for progression to severe COVID-19 (**Supplement Table 7**)
16. Chronic kidney disease
17. Diabetes
18. Immunocompromised (see COVID-19 Vaccination Status section above)
19. Cardiovascular disease
20. Chronic lung disease
21. Hematologic malignancies
22. Dementia
23. Care Assessment Needs (CAN) score
24. Healthcare utilization: number of clinical encounters

*Unless otherwise specified, factors were ascertained as of the index date. Urban/rural residence and ADI were determined using ZIP codes for Veteran's most recent place of residence in the one year prior to index date. Substance use and underlying conditions were ascertained based on documentation in the two years prior to index date. Number of outpatient visits of any type were counted in the one year prior to index date.
†Any of 15 pre-specified COVID-19-related symptoms present on the day of positive SARS-CoV-2 test or within the preceding 30 days.

Supplement Table 7. List of underlying conditions totaled for inclusion in propensity score matching models for COVID-19 treatment*

Any immunosuppressive or cancer medications (Supplement Table 3)
Acute myocardial infarction or coronary atherosclerosis
Asthma
Cancer
Cardiomyopathy or heart failure
Cerebrovascular disease including stroke
Chronic kidney disease or dialysis
Chronic liver disease including cirrhosis
Chronic neuromuscular disease
Chronic obstructive pulmonary disease or emphysema
Dementia
Diabetes
Epilepsy
HIV
Hypertension
Mental health disorders including depression, bipolar, post-traumatic stress disorder, schizophrenia, PTSD
Multiple sclerosis
Overweight (body mass index ≥25 kg/m^2)
Parkinson's disease

Peripheral artery disease
Pregnancy
Pulmonary fibrosis
Pulmonary heart disease
Sickle cell disease
Thalassemia

*Conditions presented in Supplementary Table 2 are organized into more discrete groupings. Age, tobacco, and substance use are included separately in propensity score models.

Additional exclusions applied during matching

We applied additional exclusions during matching. Due to lack of overlap, persons aged >115 years, missing ADI or who were categorized in the other vaccination category were excluded. Untreated persons who died or were hospitalized on or before their assigned index date were also excluded as were untreated persons who received other outpatient COVID-19 treatments (molnupiravir, sotrovimab, remdesivir) on or prior to the antiviral treatment date.

Inverse probability censoring weights to account for deaths on days 1-30 from index date

We used inverse probability of censoring weights (IPCW) (9) to account for exclusion from the analytical cohort due to censoring from deaths on days 1-30. Weights were calculated as the probability of being censored based on a Cox proportional hazards regression model that included treatment and 24 demographic, geographic, healthcare utilization, and clinical factors. We examined weights for extreme values (range: 1.000 to 1.993, mean: 1.005, standard deviation: 0.018, median: 1.001, and interquartile range: 1.000 to 1.004). We chose unstabilized weights for simplicity since stabilized weights changed by < 0.65% for all measures.

Supplement Table 8. List of conditions evaluated as potential post-COVID incident conditions from day 31 to 180 after the index date*

	Conditions and symptoms attributed to post-COVID illness	Description
	Cardiac	
1	Acute coronary syndrome	Includes unstable angina, non-ST-elevation myocardial infarction, ST-elevation myocardial infarction, myocardial infarction.
2	Cardiac dysrhythmias	Includes atrial flutter, atrial fibrillation, tachycardia, atrioventricular block, cardiac arrhythmia.
3	Cardiovascular disease	Includes coronary artery disease, peripheral arterial/vascular disease, thoracic/abdominal aneurysm.
4	Chest pain	
5	Heart failure and cardiomyopathy	Includes any valvular disease (mitral, aortic, tricuspid, pulmonary), any heart failure, any cardiomyopathy, pulmonary hypertension.
6	Hypertension	
7	Myocarditis and pericarditis	
	Pulmonary	
8	Respiratory symptoms	Includes shortness of breath/dyspnea, cough, and abnormal sputum.
9	Asthma	
10	COPD and emphysema	
	Renal	
11	Acute and chronic kidney injury and dialysis	Includes acute kidney injury, chronic kidney disease, dialysis.

	Thromboembolic	
12	Venous thromboembolism	Includes involvement of any deep veins.
13	Pulmonary embolism	
	Gastrointestinal	
14	Gastrointestinal symptoms	Includes nausea, vomiting, diarrhea, constipation, abdominal pain, abdominal distension, gas pain, eructation, flatulence.
15	Gastrointestinal disorders	Irritable bowel syndrome, gastroesophageal reflux disease, peptic ulcer disease, functional dyspepsia, acute gastritis, cholangitis, acute pancreatitis.
	Neurologic	
16	Cerebrovascular disease	Includes stroke; transient ischemic attack; occlusion of vertebral, basilar, cerebral, cerebellar, or carotid arteries; cerebral aneurysm. Does not include vascular dementia.
17	Dysautonomia	Includes disorders of the autonomic nervous system and postural orthostatic tachycardia syndrome, only available since October 1, 2022.
18	Dementia	
19	Smell and taste disturbance	
20	Headache	Includes migraine.
21	Sleeping disorders	Includes any central or complex sleep apnea, insomnia. Does not include obstructive sleep apnea.
	Mental Health	
22	Depression	
23	Other mood disorders	Includes bipolar disorder, schizophrenia, psychosis.
24	Anxiety	
25	PTSD	
26	Substance-related disorders	Includes alcohol, cannabis, opioids, stimulants, cocaine.
	Musculoskeletal	
27	Myalgia and myositis	Includes any myositis, muscle wasting and atrophy, contracture of muscle, myalgias.
	Endocrine	
28	Diabetes	Any diabetes excluding gestational diabetes.
	General	
29	Malaise and fatigue	
30	Postviral fatigue	Includes the following conditions with ICD-10 codes available since October 1, 2022: postviral fatigue syndrome, myalgic encephalomyelitis/chronic fatigue syndrome, other post infection and related fatigue syndromes.
31	Erectile dysfunction	
	Negative Outcome Control	
	Cancer	Any malignancy except squamous cell carcinoma and basal cell carcinoma of the skin.

*ICD-10 codes used to define each condition were modified from Veterans Affairs Centralized Interactive Phenomics Resource (CIPHER) Program through two-clinician review: https://github.com/nrajeevan/ICD_codes_post_covid_conditions

Statistical programs and code used for analysis

All statistical analyses were performed using Stata/MP 17.0 for Windows (64-bit) (StataCorp LLC, College Station, TX). Stata packages used were *kmatch*, *coefplot*, and *vcemway*.

Propensity score for being treated

```
logistic trt i.(gender race_eth rurality smoke_2yrs alc_2yrs  ///
                        drug_2yrs diabetes immuno hemo_malig ckd cvd    ///
                        lung dementia cat_bmi cat_can cat_vax_with_time  ///
                        any_symptoms cat_num_op_visits) age sum_con adi        ///
                        month_test
predict ps, pr
```

Matching

```
kmatch ps trt, ematch((asis) `exact_vars')                    ///
                nn(`k') keepall pscore(ps) caliper(`cal')      ///
                idgenerate(control_id) idvar(id)               ///
                generate(km_*)

For Trials #1 and #2
local exact_vars = "tier TestDate visn complexity"
local k=4

For Trial #3
local exact_vars = "tier TestDate visn complexity days_to_trt"
local k=1

For Trials #1-#3
sum ps, detail
local cal = 0.2*r(sd)
```

Weights

```
bysort match_id trt : generate double iw_variable_ratio = 1/_N
```

Reweight for 31-180 day outcomes and subgroup analysis

```
** identify if only one in match group or last one isn't treated
bysort match_id (trt) : generate byte n_grp = _N
bysort match_id (trt) : generate byte last_trt = (trt[_N]==1)

** drop those match groups
keep if n_grp > 1 & last_trt==1

** re-weight no treatment
replace iw_variable_ratio = 1/(n_grp-1) if !trt
tab trt [iw=iw_variable_ratio], missing
```

30-day Outcomes

```
forvalues i = 1(-1)0 {
        ** number of events
        tab trt if trt==`i' & event==1 [iw=iw_variable_ratio]
```

```
        ** 30-day risk
        proportion event if trt==`i' [iw=iw_variable_ratio],      ///
                vce(cluster id)
        ** risk difference
        vcemway glm event trt [iw=iw_variable_ratio],                ///
                family(binomial) link(identity)                      ///
                cluster(id match_id) vmcfactor(default)
        ** risk ratio
        vcemway glm event trt [iw=iw_variable_ratio],                ///
                family(binomial) link(log) cluster(id match_id)      ///
                vmcfactor(default)
}
```

31-180 Day Outcomes Time-to-Event

```
stset days if !missing(event) [iw=iw_variable_ratio], failure(event=1)

**********************************************************************
** take into account matched with replacement and variable ratio
** matching, so need three versions: 1) clustered by match id ("_m"),
** 2) clustered by patient id ("_p"), and 3) no cluster ("_u")
**********************************************************************
**
** no clusters
**
** stset with weights and no cluster
stset days if !missing(event) [iw=iw_variable_ratio],  ///
                failure(event=1)

** run Cox PH model and get matrix
stcox i.trt, noshow
matrix tmp = V_u

** get scores (residuals)
capture drop score*
predict double score* if e(sample), score

** get dimensions of matrix and save original row and column names
scalar n_row = rowsof(V_u)
local orig_rownames : rownames V_u

** build new labels for matrix based on scores
local n_row = n_row
local new_rownames = ""
forvalues i=1/`n_row' {
        local new_rownames = "`new_rownames' score`i':"
}

matrix rownames V_u = `new_rownames'
matrix rownames V_u = _cons
matrix colnames V_u = `new_rownames'
matrix colnames V_u = _cons

** get robust sandwich variance estimator
```

```
_robust score* if e(sample) [iw=iw_variable_ratio], v(V_u)

** reset labels of matrix
matrix rownames V_u = `orig_rownames'
matrix colnames V_u = `orig_rownames'

matrix rownames V_u = _:
matrix colnames V_u = _:

** number of rows
scalar n_u = _N

** cleanup
drop score*

**
** clusters within matches
**
** stset with weights
** NOTE: weights not constant across cluster (case=1 and control=1/k) so need to
** expand cases to count of matched controls and set the case weight to 1/k; will
** finish by resetting case weight and dropping extra cases
**
** get frequency weight for case
capture drop fw
bysort match_id (trt): generate fw = cond(trt==1, round(1/iw_variable_ratio[1]), 1)

** expand with flag for extras
capture drop fw_drop
expand fw if trt==1, generate(fw_drop)
replace iw_variable_ratio = 1/fw if trt==1

** add some wiggle for duplicates
capture drop orig_days
generate long orig_days = days
bysort match_id days : replace days =                                   ///
                                        days + (0.001*(_n-1)) if _n > 1

** stset with weights and match_id clusters
stset days if !missing(event) [iw=iw_variable_ratio], ///
                failure(event=1) id(match_id) exit(time .)

** run Cox PH model and get matrix
stcox i.trt, noshow
matrix tmp = V_m

** get scores (residuals)
capture drop score*
predict double score* if e(sample), score

** get dimensions of matrix and save original row and column names
scalar n_row = rowsof(V_m)
local orig_rownames : rownames V_m
```

```
** build new labels for matrix based on scores
local n_row = n_row
local new_rownames = ""
forvalues i=1/`n_row' {
        local new_rownames = "`new_rownames' score`i':"
}

matrix rownames V_m = `new_rownames'
matrix rownames V_m = _cons
matrix colnames V_m = `new_rownames'
matrix colnames V_m = _cons

** get robust sandwich variance estimator
_robust score* if e(sample) [iw=iw_variable_ratio], v(V_m) cluster(match_id)

** reset labels of matrix
matrix rownames V_m = `orig_rownames'
matrix colnames V_m = `orig_rownames'

matrix rownames V_m = _:
matrix colnames V_m = _:

** cleanup
replace iw_variable_ratio = 1 if trt==1
drop if fw_drop==1
drop fw fw_drop
drop score*

replace days = orig_days
drop orig_days

** number of unique matches
duplicates report match_id
scalar n_m = r(unique_value)

**
** clusters within patients
** NOTE: "no treatment" that were matched to more than one treated
** with different 1:k matches will not have constant weights within id
** these will need to be expanded and a new influence weight set
** to allow the influence weights to be equivalent. This will be done
** by calculating the lowest-ish common denominator (LCM) of number of
** ties. "no treatment" matched with replacement and same 1:k will be
** left as is.
**
** for checking
capture drop orig_sum
bysort id : egen orig_sum = total(iw_variable_ratio)

** k for 1:k in that match
capture drop k
generate byte k = round(1/iw_variable_ratio)

** largest k
```

```
capture drop max_k
bysort id : egen byte max_k = max(k)

** LCM
capture drop tmp_lcm
generate float tmp_lcm = 1
gsort id -k
by id : replace tmp_lcm =       ///
                    cond(_n==1, tmp_lcm*k, cond(mod(tmp_lcm[_n-1], k),        ///
                                    tmp_lcm[_n-1]*k, tmp_lcm[_n-1]))

capture drop lcm
bysort id : egen float lcm = max(tmp_lcm)

** get frequency weight for "no treatment" since "treatment" always 1
capture drop fw
bysort match_id (trt): generate fw = cond(trt==0, lcm/k, 1)

** expand with flag for extras
capture drop fw_drop
expand fw if trt==0, generate(fw_drop)

** set new weight
replace iw_variable_ratio = 1/lcm if trt==0

** check new weight
capture drop chk_sum
bysort id : egen chk_sum = total(iw_variable_ratio)
assert(orig_sum==chk_sum)
drop chk_sum

** add some wiggle for duplicates
sum days, detail
capture drop orig_days
generate long orig_days = days
bysort id days : replace days = days + (0.001*(_n-1)) if _n > 1

** stset with weights and id clusters
stset days if !missing(event) [iw=iw_variable_ratio],  ///
                    failure(event=1) id(id) exit(time .)

** run Cox PH model and get matrix
capture noisily stcox i.trt, noshow
model_check _rc b_p V_p
matrix tmp = V_p

** get scores (residuals)
capture drop score*
predict double score* if e(sample), score

** get dimensions of matrix and save original row and column names
scalar n_row = rowsof(V_p)
local orig_rownames : rownames V_p
```

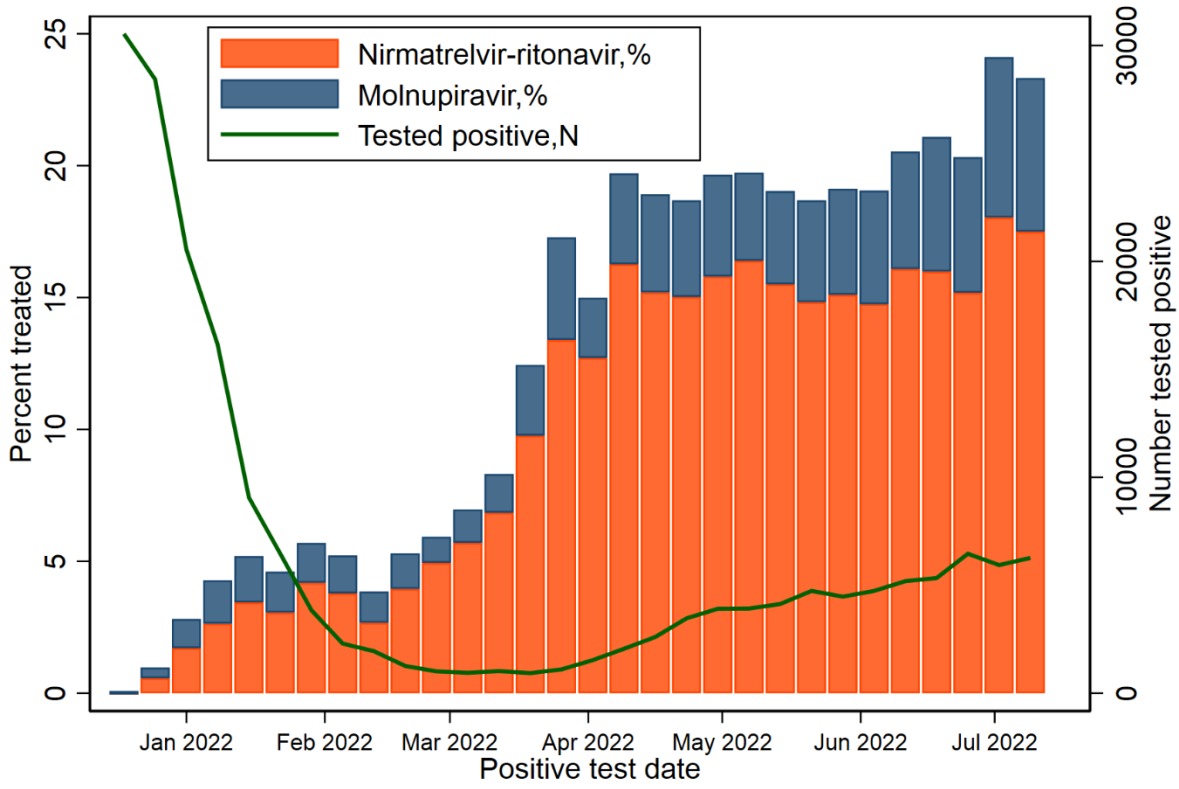
```
** build new labels for matrix based on scores
local n_row = n_row
local new_rownames = ""
forvalues i=1/`n_row' {
        local new_rownames = "`new_rownames' score`i':"
}

matrix rownames V_p = `new_rownames'
matrix rownames V_p = _cons
matrix colnames V_p = `new_rownames'
matrix colnames V_p = _cons

** get robust sandwich variance estimator
_robust score* if e(sample) [iw=iw_variable_ratio], v(V_p) cluste(id)

** reset labels of matrix
matrix rownames V_p = `orig_rownames'
matrix colnames V_p = `orig_rownames'

matrix rownames V_p = _:
matrix colnames V_p = _:

** number of unique patients
duplicates report id
scalar n_p = r(unique_value)

** cleanup
replace iw_variable_ratio = 1/k if trt==0
drop if fw_drop==1
drop k max_k *lcm fw fw_drop
drop score*

replace days = orig_days
drop orig_days

** check
capture drop chk_sum
bysort id : egen chk_sum = total(iw_variable_ratio)
assert(orig_sum==chk_sum)
drop orig_sum chk_sum

**
** Build final variance matrix
**
matrix V = (n_m/(n_m-1))*V_m + (n_p/(n_p-1))*V_p - (n_u/(n_u-1))*V_u
```

31-180 Day Outcomes Competing risks

```
stset days if !missing(event) [iw=iw_variable_ratio], failure(event=1)
vcemway stcrreg i.trt, compete(event==2) cluster(id match_id)       ///
                                        vmcfactor(default)
```

B. SUPPLEMENT RESULTS

Supplement Figure 1. Positive SARS-CoV-2 tests and oral antiviral treatments among study participants, January 1, 2022 to July 31, 2022*



*Among N=191,057 eligible Veterans per Figure 1

Supplement Table 9. Persons excluded from the trial emulation due to hospitalization on test-positive date (day 0) or the following date (day 1), according to whether antiviral treatment was received

Dropped due to hospitalization on day 0 or 1 after positive test date, n (%)	Nirmatrelvir-ritonavir N=10,738	No treatment N=153,382
No hospitalization days 0/1*	10,552 (99.3)	143,441 (93.5)
Day 1 hospitalization	45 (0.4)	1609 (1.1)
Day 0 hospitalization	141 (1.3)	8332 (5.4)
Chi^2 test (p-value)	<0.001	

* Match-eligible cohort

Supplement Table 10. Baseline characteristics of Veterans who tested positive for SARS-CoV-2 in the Veterans Health Administration from January 1, 2022 to July 31, 2022, who fulfilled eligibility criteria for an emulated target trial of nirmatrelvir-ritonavir versus no treatment

Characteristic	Nirmatrelvir-ritonavir	No treatment*
Total	10,552	143,441
Age, years, median [IQR]	66.0 [54.0,74.0]	59.0 [44.0,71.0]
Age group, N (%)		
18-49	1,929(18.3)	46,843(32.7)
50-64	2,960(28.1)	42,266(29.5)
65-74	3,168(30.0)	31,727(22.1)
≥75	2,495(23.6)	22,605(15.8)
Male sex, N (%)	9,056(85.8)	120,085(83.7)
Race/Ethnicity, N (%)		
Hispanic	958(9.1)	14,760(10.3)
White	6,687(63.4)	87,132(60.7)
Black	1,993(18.9)	27,414(19.1)
Other	337(3.2)	4,704 (3.3)
Unknown	577(5.5)	9,431 (6.6)
Rurality, N (%)†		
Rural	2,501(23.7)	38,060(26.5)
Urban	7,970(75.5)	104,315(72.7)
Missing	81(0.8)	1,066(0.7)
Region, N (%)‡		
West	2,589(24.5)	36,873(25.7)
Midwest	2,144(20.3)	25,183(17.6)
Northeast	2,211(21.0)	20,907(14.6)
South	3,608(34.2)	60,478(42.2)
Facility complexity		
Lower complexity	5,783(54.8)	74,759(52.1)
Highest complexity	4,769(45.2)	68,682 (47.9)
Area Deprivation Index, median [IQR]	51.7 [33.3,71.0]	55.5 [36.6,72.2]
Month of positive test, N (%)		
January	917(8.7)	80,483 (56.1)
February	558(5.3)	15,102 (10.5)
March	222(2.1)	4,112(2.9)
April	689(6.5)	4,068(2.8)
May	2,029(19.2)	10,195(7.1)
June	2,648(25.1)	13,601(9.5)
July	3,489(33.1)	15,880(11.1)
≥1 symptom, N (%)§		
No	2,809(26.6)	73,122(51.0)
Yes	7,743(73.4)	70,319(49.0)

Vaccination status and time since last dose, N (%)[‖]		
No doses	1,807(17.1)	40,744(28.4)
Partial	402(3.8)	6,189(4.3)
Primary/>4 months	2,788(26.4)	47,547(33.1)
Primary/0-4 months	125(1.2)	4,899(3.4)
Booster/>4 months	3,756(35.6)	18,401(12.8)
Booster/0-4 months	1,663(15.8)	25,554(17.8)
NIH Tier, N (%)		
1	1,645(15.6)	19,218(13.4)
2	1,211(11.5)	31,931(22.3)
3	4,486(42.5)	39,436(27.5)
4	3,210(30.4)	52,856(36.8)
Smoking, N (%)		
Never	4,507(42.7)	59,489(41.5)
Former	4,354(41.3)	53,678(37.4)
Current	1,352(12.8)	23,785(16.6)
Unknown	339(3.2)	6,489(4.5)
Alcohol use disorder, N (%)	1,924(18.2)	31,153(21.7)
Substance use disorder, N (%)	360(3.4)	6,467(4.5)
Number of underlying conditions, median [IQR]	4.0 [3.0,5.0]	4.0[2.0,5.0]
Number of underlying conditions, N (%)		
0-1	622(5.9)	13,422(9.4)
2-3	3,662(34.7)	56,196(39.2)
4-5	3,870(36.7)	46,854(32.7)
≥6	2,398(22.7)	26,969(18.8)
CAN Score for mortality w/in 1yr at test date N (%)[¶]		
0-30	3,419(32.4)	65,608(45.7)
31-55	2,944(27.9)	34,030(23.7)
56-75	2,144(20.3)	21,105(14.7)
76-90	1,481(14.0)	14,523(10.1)
95-96	181(1.7)	2,176(1.5)
97-98	181(1.7)	2,350(1.6)
99	91(0.9)	1,423(1.0)
Missing	111(1.1)	2,226(1.6)
Underlying condition, N (%)		
Obesity (body mass index ≥30 kg/m^2)	8,760(83.0)	118,397(82.5)
Chronic kidney disease	1,061(10.1)	12,709(8.9)
Diabetes	3,501(33.2)	37,801(26.4)

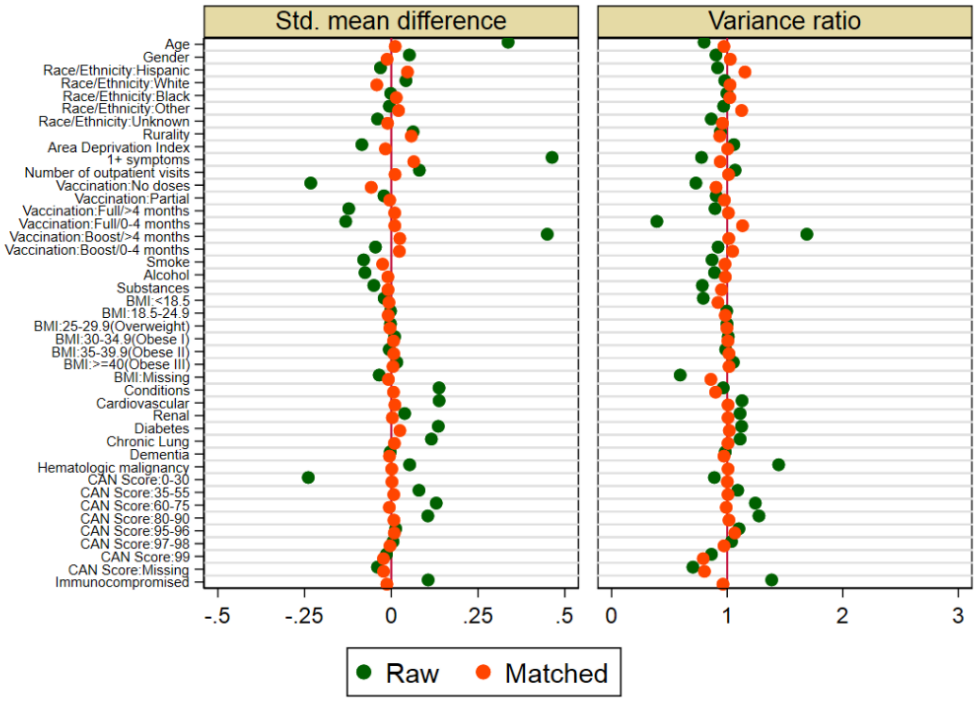
Immunosuppressive medications or cancer therapies‖	1,034(9.8)	9,517(6.6)
Hematologic malignancy	248(2.4)	2,241(1.6)
Cancer	1,789(17.0)	17,362(12.1)
Cardiovascular disease	3,496(33.1)	37,246(26.0)
Chronic lung disease	3,349(31.7)	37,184(25.9)
Chronic liver disease	914(8.7)	10,956(7.6)
Dementia	324(3.1)	4,518(3.1)
Mental Health conditions¶	4,540(43.0)	68,965(48.1)
Number of healthcare encounters in prior 12 months, median [IQR]	33.0 [19.0,53.0]	30.0 [17.0,49.0]
Number of healthcare encounters in prior 12 months, N (%)		
0-8	618(5.9)	11,219(7.8)
9-15	1,298(12.3)	20,060(14.0)
16-30	2,910(27.6)	42,541(29.7)
31+	5,726(54.3)	69,621(48.5)
Days from test to treatment		
0-1	9,476(89.8)	-
2+	1,076(10.2)	-

CAN = Care Assessment Need; NIH = National Institutes of Health
*Baseline characteristics represent unweighted persons
†Based on rural-urban commuting area (RUCA) codes
‡Regions are based on Veterans Integrated Service Networks (VISNs). West includes VISNs 19-22; Midwest 10,12,15,23; Northeast 1,2,4,5; South 6-9, 16-17
§Any of 15 pre-specified COVID-19-related symptoms present on the day of positive SARS-CoV-2 test or within the preceding 30 days
‖There were 239 persons with other vaccination status.
¶Includes major depressive disorder, bipolar disorder, post-traumatic stress disorder, schizophrenia

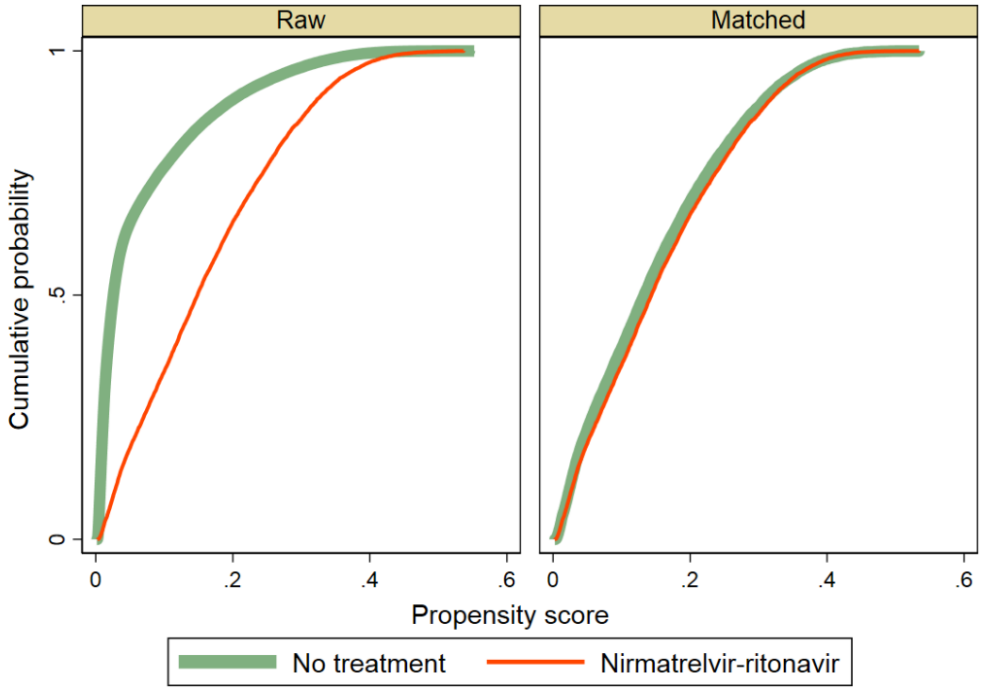
Supplement Figure 2. Distribution of baseline characteristics and propensity scores in persons treated with nirmatrelvir-ritonavir and their comparators receiving no COVID-19 treatment, before and after matching

A. Absolute standardized mean differences and variance ratios of baseline characteristics between nirmatrelvir-ritonavir treatment versus no treatment shown for the raw and matched data

Prior to matching, the absolute standardized difference in baseline characteristics between the nirmatrelvir-ritonavir treatment versus no treatment groups ranged from 0.002-0.463 with a median of 0.052 (IQR: 0.016-0.122). After matching, the absolute standardized differences ranged from 0.001-0.065 with a median of 0.010 (IQR: 0.006-0.023).



B. Cumulative distribution of propensity score between nirmatrelvir-ritonavir treatment versus no treatment shown for the raw and matched data demonstrate balance after matching



Supplement Table 11. Comparison of matched groups in an emulated target trial of nirmatrelvir-ritonavir versus no treatment among Veterans who tested positive for SARS-CoV-2 from January 1, 2022 to July 31, 2022 with respect to 31-180 day incidence of conditions that have been proposed as potential post-COVID conditions

31-180 day outcome	Nirmatrelvir-ritonavir N=9593 Cumulative Incidence* per 100 persons	No treatment N=9593 Cumulative Incidence* per 100 persons	Cumulative Incidence Difference (95% CI) per 100 persons	Sub-Hazard Ratio (95% CI)	Adjusted† Sub-Hazard Ratio (95% CI)
Cardiac‡	13.39	14.31	-0.92 (-1.90- 0.06)	0.93 (0.85-1.02)	0.95 (0.86-1.04)
Acute coronary syndrome	2.16	2.54	-0.38 (-0.84- 0.09)	0.85 (0.67-1.08)	0.90 (0.71-1.15)
Cardiac dysrhythmias	4.22	4.32	-0.09 (-0.73- 0.54)	0.98 (0.82-1.17)	1.00 (0.84-1.20)
Cardiovascular disease	2.60	3.12	-0.52 (-1.06- 0.01)	0.83 (0.67-1.03)	0.87 (0.70-1.08)
Chest pain	3.76	3.55	0.22 (-0.36- 0.79)	1.06 (0.88-1.28)	1.08 (0.89-1.31)
Heart failure and cardiomyopathy	2.09	2.56	-0.47 (-0.92-0.02)	0.81 (0.65-1.02)	0.88 (0.70-1.12)
Hypertension	7.54	8.29	-0.75 (-2.07- 0.57)	0.91 (0.75-1.09)	0.92 (0.76-1.12)
Myocarditis and pericarditis	0.05	0.08	-0.03 (-0.10- 0.04)	0.63 (0.19-2.07)	0.70 (0.21-2.34)
Pulmonary‡	7.68	7.46	0.22 (-0.71-1.15)	1.03 (0.91-1.17)	1.03 (0.90-1.17)
Respiratory symptoms#	6.56	5.93	0.62 (-0.17-1.42)	1.11 (0.95-1.29)	1.11 (0.95-1.30)
Asthma	1.47	1.11	0.36 (0.02- 0.69)	1.32 (0.96-1.82)	1.33 (0.97-1.82)
COPD and emphysema	1.62	1.97	-0.35 (-0.75- 0.05)	0.82 (0.62-1.08)	0.82 (0.63-1.08)
Renal‡					
Acute and chronic kidney injury and dialysis	3.98	4.48	-0.50 (-1.13- 0.13)	0.89 (0.74-1.06)	
Thromboembolic‡	0.54	0.83	-0.29 (-0.52-.005)	0.65 (0.44-0.97)	0.70 (0.46-1.04)
Venous thromboembolism	0.36	0.49	-0.13 (-0.32- 0.05)	0.73 (0.43-1.23)	0.76 (0.45-1.29)
Pulmonary embolism	0.25	0.40	-0.15 (-0.32- 0.01)	0.62 (0.35-1.12)	0.67 (0.37-1.21)
Gastrointestinal‡	10.76	11.45	-0.69 (-1.64- 0.27)	0.94 (0.84-1.04)	
Gastrointestinal symptoms¶	7.05	7.72	-0.68 (-1.54- 0.18)	0.91 (0.79-1.05)	
Gastrointestinal disorders	6.63	6.48	0.14 (-0.71-1.00)	1.02 (0.88-1.19)	
Neurologic‡	5.02	4.94	0.08 (-0.53- 0.70)	1.02 (0.87-1.19)	1.04 (0.89-1.21)
Cerebrovascular disease	1.61	1.60	0.01 (-0.36- 0.38)	1.01 (0.76-1.33)	1.04 (0.79-1.38)
Dysautonomia	0.05	0.02	0.03 (-0.03- 0.08)	2.14 (0.41-11.31)	

Dementia	0.66	0.74	-0.08 (-0.32- 0.16)	0.89 (0.58-1.36)	
Smell and taste disturbance	0.09	0.08	0.02 (-0.07- 0.10)	1.23 (0.44-3.40)	
Headache	2.93	2.89	0.03 (-0.48- 0.55)	1.01 (0.82-1.25)	
Sleeping disorders	0.22	0.19	0.03 (-0.10- 0.16)	1.14 (0.56-2.32)	
Mental health‡	8.01	7.79	0.22 (-0.55- 0.98)	1.03 (0.91-1.16)	
Depression	3.20	3.08	0.12 (-0.46- 0.70)	1.04 (0.84-1.28)	
Other mood disorders	0.46	0.46	-0.00 (-0.20- 0.20)	1.00 (0.60-1.65)	
Anxiety	4.01	3.57	0.44 (-0.16-1.04)	1.13 (0.93-1.36)	
PTSD	2.69	2.75	-0.06 (-0.58- 0.47)	0.98 (0.78-1.23)	
Substance-related disorders	1.04	1.20	-0.16 (-0.47- 0.15)	0.87 (0.63-1.20)	
Musculoskeletal					
Myalgia and myositis	11.74	11.20	0.54 (-0.65-1.73)	1.05 (0.93-1.19)	
Endocrine					
Diabetes	2.23	2.46	-0.23 (-0.76- 0.30)	0.91 (0.70-1.17)	0.94 (0.72-1.21)
General					
Malaise and fatigue	3.73	3.57	0.16 (-0.40- 0.72)	1.04 (0.87-1.26)	
Post-viral Fatigue	0.08	0.05	0.03 (-0.04- 0.11)	1.60 (0.46-5.57)	
Erectile Dysfunction	1.91	1.71	0.20 (-0.20- 0.59)	1.12 (0.86-1.46)	1.12 (0.86-1.47)
Negative Outcome Control					
Cancer	2.99	3.08	-0.09 (-0.63- 0.46)	0.97 (0.78-1.20)	

*For each post-COVID condition, 31-180-day incidence after the test-positive date is calculated only in matched groups within which all persons do not have prevalence of the condition of interest at baseline (i.e., not documentation within 12 months prior to infection). Incidence rates account for the competing risk of death. Methods for estimating incidence are non-parametric and methods for the sub-hazard ratio are semi-parametric, so they will not be entirely "consistent" in terms of reflecting differences between the comparison groups.

†Adjusted sub-hazard ratios were calculated for selected conditions after adjustment for baseline medications which constitute drug-drug interactions or contraindications to nirmatrelvir-ritonavir that could potentially affect the documented incidence of that condition. Cardiac, renal, diabetes and cerebrovascular disease outcomes were adjusted for statins, DOAC, and antiplatelet agents. Erectile dysfunction was adjusted for PDE5 inhibitors. Thromboembolic events were adjusted for DOAC and antiplatelet agents. Pulmonary outcomes were adjusted for salmeterol.

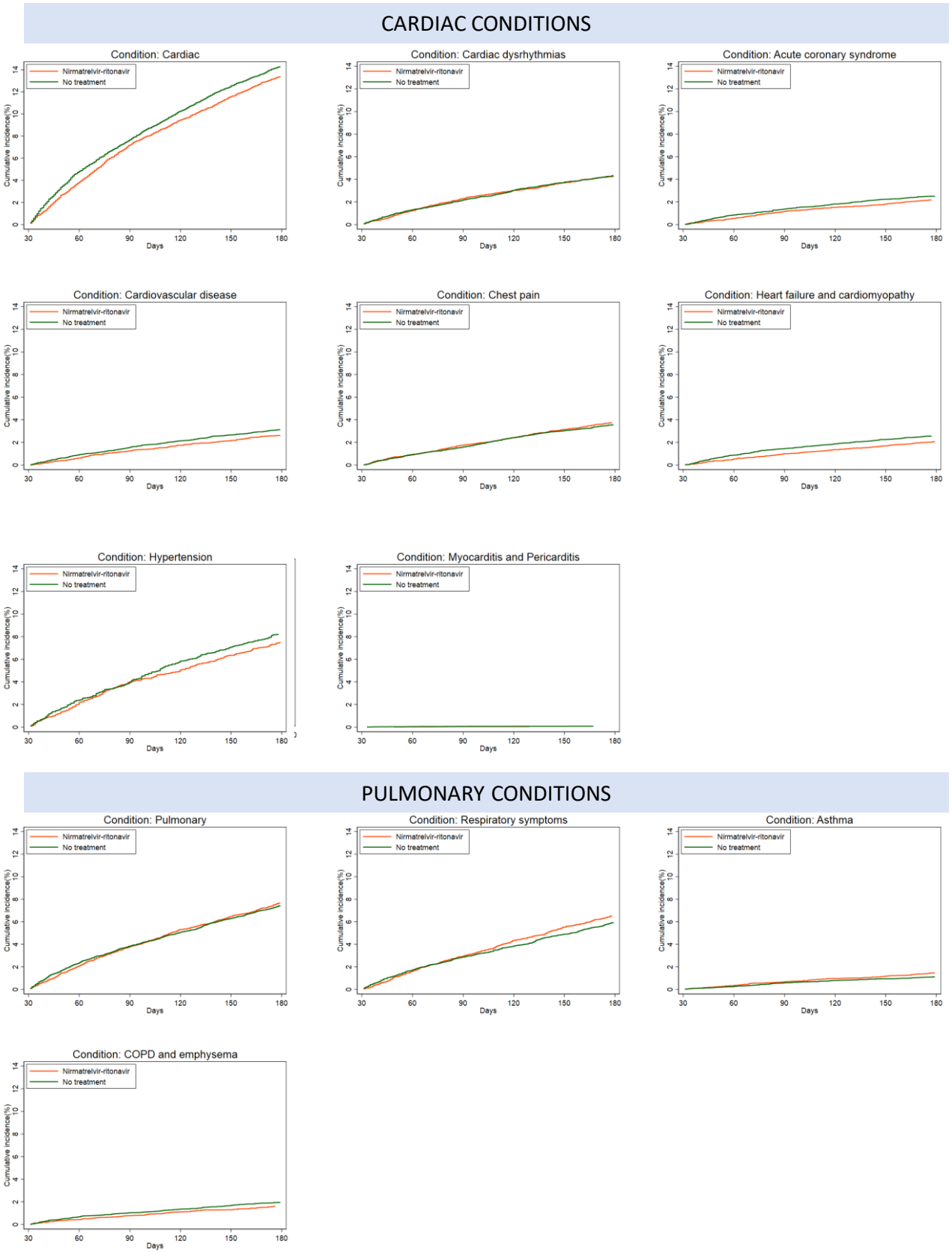
Phosphodiesterase 5 [PDE5] inhibitors included sildenafil, tadalafil, vardenafil); Statins included simvastatin, lovastatin, atorvastatin, rosuvastatin; Direct oral anticoagulants [DOAC] included apixaban, rivaroxaban; Antiplatelet agents included clopidogrel, ticagrelor.

‡For the organ systems the incidence of at least one of the conditions listed under each system was calculated

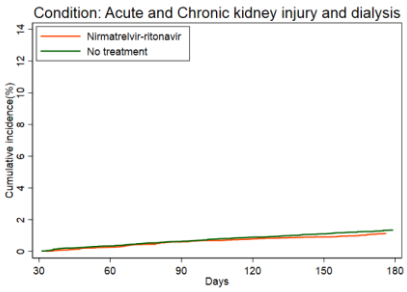
¶Gastrointestinal symptoms included: nausea, vomiting, diarrhea, constipation, abdominal pain, abdominal distension, gas pain, eructation, flatulence

#Respiratory symptoms included: shortness of breath/dyspnea, cough and abnormal sputum

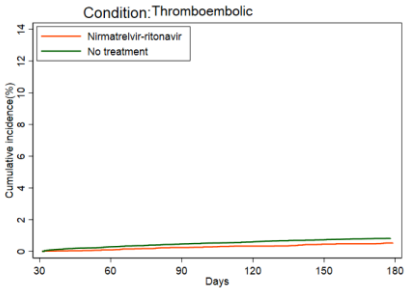
Supplement Figure 3. Cumulative incidence curves for each PCC shown in Supplement Table 11 comparing the nirmatrelvir-ritonavir versus no treatment groups.

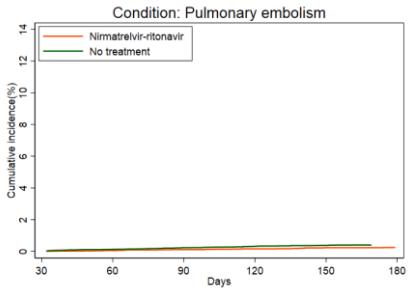


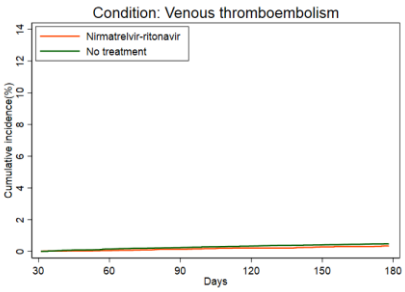
RENAL CONDITIONS



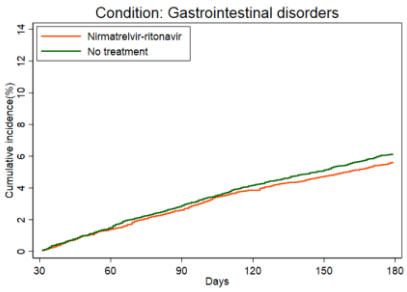
THROMBOEMBOLIC CONDITIONS

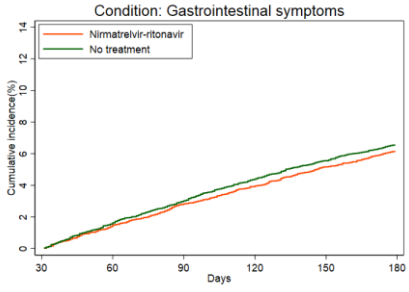


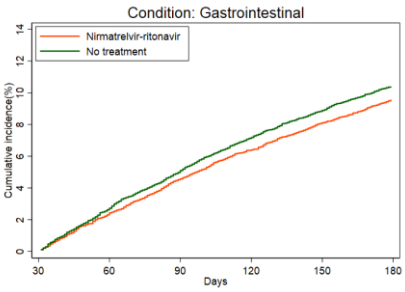




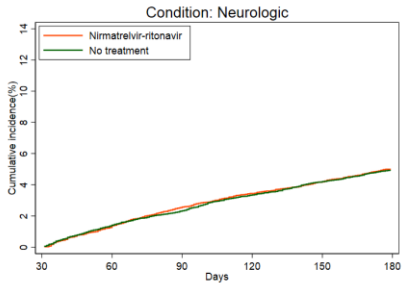
GASTROINTESTINAL CONDITIONS

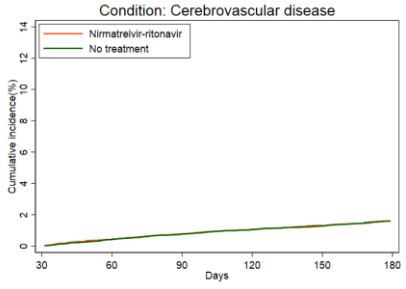


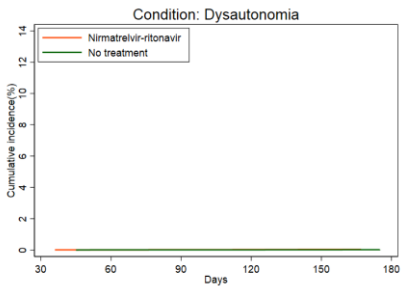


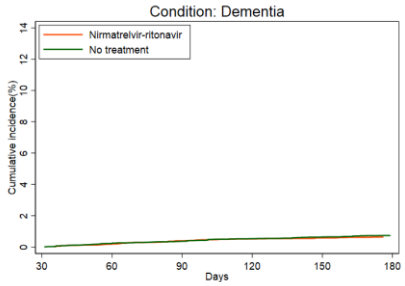


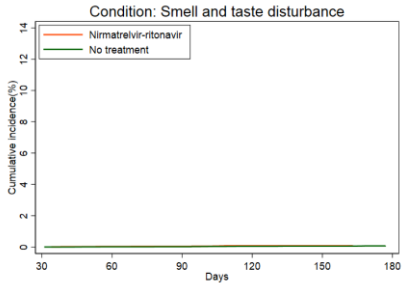
NEUROLOGIC CONDITIONS

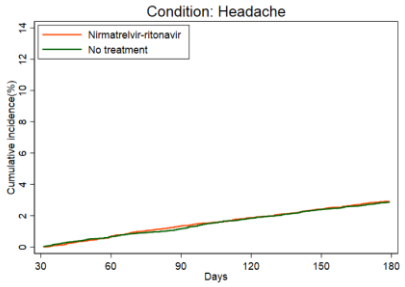


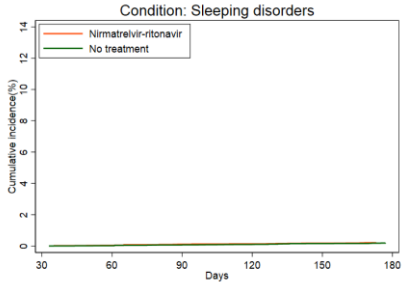




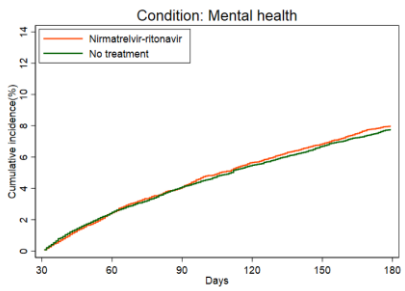


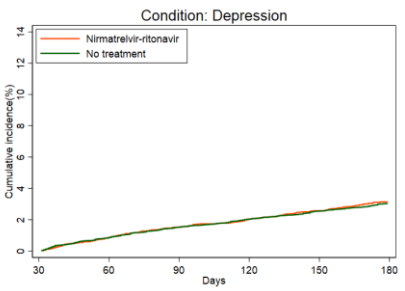


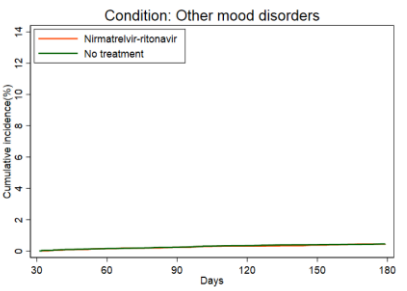


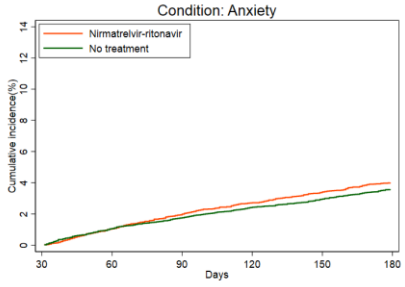


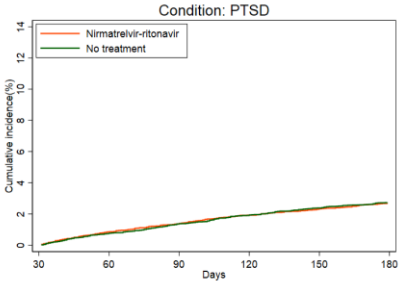
MENTAL HEALTH CONDITIONS

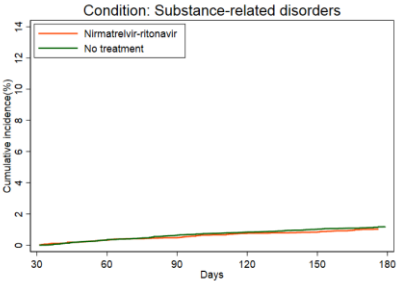




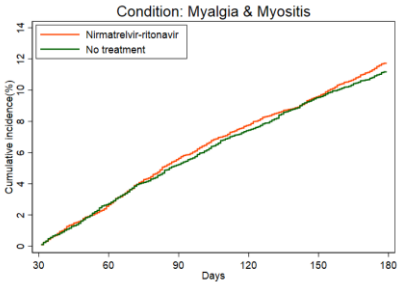




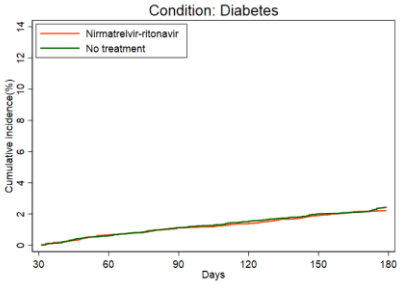




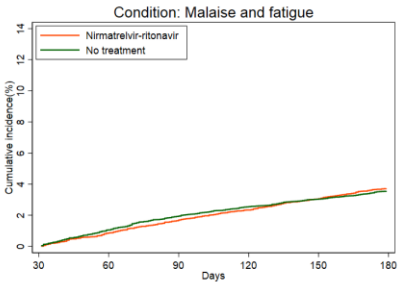
MUSCULOSKELETAL CONDITIONS

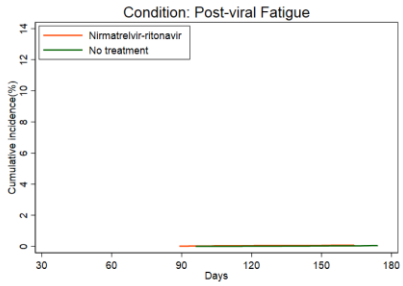


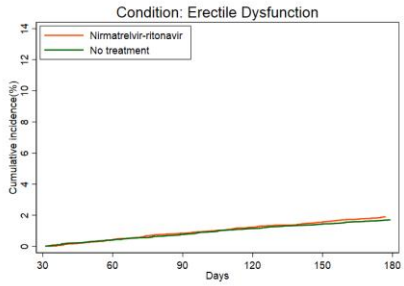
ENDOCRINE CONDITIONS



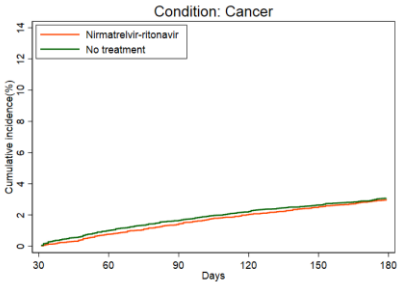
GENERAL CONDITIONS







NEGATIVE OUTCOME CONTROL: CANCER



Supplement Table 12. Comparison of matched groups in an emulated target trial of nirmatrelvir-ritonavir versus no treatment among Veterans who tested positive for SARS-CoV-2 from January 1, 2022 to July 31, 2022 with respect to cumulative 31-180 day incidence of post-COVID conditions: results limited to participants who tested positive in VA laboratory tests.

31-180-day outcome	Nirmatrelvir-ritonavir N=7779 Cumulative Incidence* per 100 persons	No treatment N=7779 Cumulative Incidence* per 100 persons	Cumulative Incidence Difference (95% CI) per 100 persons	Sub-Hazard Ratio (95% CI)
Cardiac‡	13.15	13.89	-0.74 (-1.81- 0.34)	0.94 (0.85-1.04)
Acute coronary syndrome	2.07	2.27	-0.20 (-0.78- 0.30)	0.91 (0.69-1.19)
Cardiac dysrhythmias	4.06	4.23	-0.17 (-0.88- 0.53)	0.96 (0.78-1.17)
Cardiovascular disease	2.45	2.88	-0.43 (-1.01- 0.15)	0.85 (0.66-1.09)
Chest pain	3.90	3.83	0.07 (-0.60- 0.73)	1.02 (0.83-1.25)
Heart failure and cardiomyopathy	2.05	2.37	0.32 (-0.81- 0.17)	0.86 (0.67-1.12)
Hypertension	7.37	7.43	-0.05 (-1.54-1.43)	0.99 (0.79-1.24)
Myocarditis and pericarditis	0.04	0.08	-0.04 (-0.12- 0.03)	0.47 (0.10-2.16)
Pulmonary‡	7.68	7.81	-0.13 (-1.19-0.93)	0.98 (0.86-1.13)
Respiratory symptoms#	6.73	6.35	0.38 (-0.54-1.30)	1.06 (0.90-1.26)
Asthma	1.50	1.13	0.37 (-0.00- 0.75)	1.33 (0.95-1.88)
COPD and emphysema	1.63	2.14	-0.51 (-0.97-0.05)	0.76 (0.56-1.03)
Renal‡				
Acute and chronic kidney injury and dialysis	4.07	4.40	-0.34 (-1.04- 0.37)	0.92 (0.76-1.12)
Thromboembolic‡	0.53	0.77	-0.24 (-0.49- 0.01)	0.69 (0.43-1.09)
Venous thromboembolism	0.31	0.49	-0.18 (-0.38- 0.02)	0.63 (0.34-1.16)
Pulmonary embolism	0.26	0.37	-0.11 (-0.29- 0.07)	0.70 (0.35-1.39)
Gastrointestinal‡	10.85	11.68	-0.84 (-1.91- 0.24)	0.92 (0.82-1.04)
Gastrointestinal symptoms¶	7.14	7.86	-0.73 (-1.71- 0.26)	0.90 (0.77-1.06)
Gastrointestinal disorders	6.66	6.56	0.09 (-0.88-1.07)	1.01 (0.85-1.21)
Neurologic‡	5.04	4.78	0.26 (-0.42- 0.94)	1.06 (0.89-1.25)
Cerebrovascular disease	1.53	1.49	0.05 (-0.35- 0.45)	1.03 (0.76-1.41)
Dysautonomia	0.05	0.01	0.04 (-0.01- 0.10)	5.33 (0.45-62.86)
Dementia	0.64	0.67	-0.04 (-0.29- 0.22)	0.95 (0.58-1.55)

Smell and taste disturbance	0.10	0.08	0.02 (-0.08- 0.12)	1.25 (0.43-3.65)
Headache	3.05	3.14	-0.09 (-0.69- 0.50)	0.97 (0.78-1.21)
Sleeping disorders	0.23	0.15	0.08 (-0.06- 0.22)	1.55 (0.67-3.62)
Mental health‡	8.23	7.77	0.46 (-0.40-1.31)	1.06 (0.93-1.21)
Depression	3.21	3.08	0.13 (-0.53- 0.79)	1.04 (0.82-1.32)
Other mood disorders	0.47	0.55	--0.08 (-0.31- 0.15)	0.86 (0.51-1.45)
Anxiety	4.09	3.63	0.46 (-0.22-1.15)	1.13 (0.92-1.39)
PTSD	2.82	2.83	-0.01 (-0.61- 0.60)	1.00 (0.77-1.29)
Substance-related disorders	1.09	1.10	-0.01 (-0.35- 0.33)	0.99 (0.69-1.42)
Musculoskeletal				
Myalgia and myositis	11.48	11.85	-0.37 (-1.74- 0.99)	0.97 (0.84-1.11)
Endocrine				
Diabetes	2.20	2.40	-0.20 (-0.79- 0.40)	0.92 (0.68-1.24)
General				
Malaise and fatigue	3.77	3.50	0.28 (-0.35- 0.90)	1.08 (0.88-1.33)
Postviral fatigue	0.08	0.04	0.04 (-0.04- 0.11)	1.85 (0.38-8.99)
Erectile dysfunction	1.83	1.87	-0.04 (-0.48- 0.41)	0.98 (0.74-1.30)
Negative Outcome Control				
Cancer	2.79	2.91	-0.12 (-0.71- 0.47)	0.96 (0.75-1.22)

*For each post-COVID condition, 31-180-day incidence after the test-positive date is calculated only in matched groups within which all persons do not have prevalence of the condition of interest at baseline (i.e. not documentation within 12 months prior to infection). Incidence rates account for the competing risk of death. Methods for estimating incidence are non-parametric and methods for the sub-hazard ratio are semi-parametric, so they will not be entirely "consistent" in terms of reflecting differences between the comparison groups.

‡For the organ systems the incidence of at least one of the conditions listed under each system was calculated

¶Gastrointestinal symptoms included: nausea, diarrhea, constipation, abdominal pain, abdominal distension, gas pain, eructation, flatulence

#Respiratory symptoms included: shortness of breath/dyspnea, cough and abnormal sputum

Supplement Table 13. Comparison of matched groups in an emulated target trial of nirmatrelvir-ritonavir versus no treatment among Veterans who tested positive for SARS-CoV-2 from January 1, 2022 to July 31, 2022 with respect to cumulative 31-90 day incidence of post-COVID conditions.

31-90 day outcome	Nirmatrelvir-ritonavir N=9593 **Cumulative Incidence*** per 100 persons	No treatment N=9593 **Cumulative Incidence*** per 100 persons	**Cumulative Incidence Difference (95% CI)** per 100 persons	**Sub-Hazard Ratio (95% CI)**
Cardiac‡	7.09	7.56	-0.47 (-1.39 -0.45)	0.93 (0.82-1.05)
Acute coronary syndrome	1.11	1.35	-0.24 (-0.68- 0.19)	0.82 (0.59-1.14)
Cardiac dysrhythmias	2.27	2.13	0.15 (-0.43-0.72)	1.07 (0.84-1.37)
Cardiovascular disease	1.21	1.52	-0.31 (-0.78-0.16)	0.79 (0.58-1.09)
Chest pain	1.74	1.56	0.18 (-0.31-0.66)	1.11 (0.84-1.48)
Heart failure and cardiomyopathy	0.98	1.43	-0.45 (-0.88-0.03)	0.68 (0.49-0.94)
Hypertension	3.97	3.92	0.05 (-1.02-1.12)	1.01 (0.78-1.31)
Myocarditis and pericarditis	0.04	0.06	-0.02 (-0.10 0.07)	0.72 (0.18-2.86)
Pulmonary‡	3.72	3.79	-0.07 (-0.75-0.61)	0.98 (0.82-1.17)
Respiratory symptoms#	2.91	2.82	0.09 (-0.59-0.76)	1.03 (0.82-1.29)
Asthma	0.65	0.57	0.08 (-0.21-0.37)	1.15 (0.72-1.83)
COPD and emphysema	0.77	1.02	-0.25 (-0.62-0.12)	0.75 (0.52-1.10)
Renal‡				
Acute and Chronic kidney injury and dialysis	2.04	2.20	-0.16 (-0.73-0.41)	0.93 (0.72-1.19)
Thromboembolic‡	0.24	0.47	-0.23 (-0.45-0.00)	0.51 (0.29-0.90)
Venous thromboembolism	0.14	0.24	--0.10 (-0.26- 0.07)	0.58 (0.26-1.27)
Pulmonary embolism	0.12	0.23	-0.12 (-0.28-0.04)	0.50 (0.22-1.12)
Gastrointestinal‡	5.14	5.46	--0.33 (-1.18-0.53)	0.94 (0.80-1.10)
Gastrointestinal symptoms¶	3.29	3.43	--0.14 (-0.88-0.60)	0.96 (0.78-1.18)
Gastrointestinal disorders	2.94	3.05	--0.11 (-0.82-0.61)	0.96 (0.77-1.21)
Neurologic‡	2.52	2.30	0.22 (-0.32-0.76)	1.10 (0.88-1.37)
Cerebrovascular disease	0.77	0.76	0.01 (-0.32-0.33)	1.01 (0.67-1.51)

Dysautonomia	0.02	0.01	0.01 (-0.04-0.05)	1.50 (0.13-16.96)
Dementia	0.40	0.36	0.04 (-0.19- 0.26)	1.10 (0.64-1.88)
Smell and taste disturbance	0.04	0.02	0.02 (-0.04- 0.08)	1.78 (0.35-9.11)
Headache	1.32	1.15	0.17 (-0.25- 0.59)	1.15 (0.82-1.60)
Sleeping disorders	0.12	0.07	0.05 (-0.06- 0.15)	1.65 (0.56-4.90)
Mental health‡	4.00	4.04	-0.03 (-0.73- 0.67)	0.99 (0.84-1.17)
Depression	1.52	1.52	-0.00 (-0.51- 0.51)	1.00 (0.74-1.34)
Other mood disorders	0.24	0.24	-0.00 (-0.18- 0.18)	0.99 (0.50-1.98)
Anxiety	1.94	1.74	0.20 (-0.33- 0.73)	1.12 (0.86-1.45)
PTSD	1.36	1.36	0.00 (-0.47- 0.47)	1.00 (0.72-1.39)
Substance-related disorders	0.47	0.62	-0.15 (-0.44- 0.14)	0.76 (0.48-1.21)
Musculoskeletal				
Myalgia & Myositis	5.54	5.18	0.36 (-0.63- 1.35)	1.07 (0.89-1.29)
Endocrine				
Diabetes	1.10	1.11	-0.01 (-0.45- 0.44)	0.99 (0.69-1.42)
General	0.00	0.00		
Malaise and fatigue	1.65	1.93	-0.28 (-0.79- 0.23)	0.85 (0.66-1.11)
Postviral Fatigue			--	--
Erectile Dysfunction	0.83	0.76	0.07 (-0.26- 0.40)	1.09 (0.72-1.65)
Negative Outcome Control				
Cancer	1.39	1.63	-0.25 (-0.73- 0.24)	0.85 (0.63-1.15)

*For each post-COVID condition, 31-90 day incidence is calculated only in matched groups within which all persons do not have prevalence of the condition of interest at baseline (i.e. not documentation within 12 months prior to infection). Incidence rates account for the competing risk of death. Methods for estimating incidence are non-parametric and methods for the sub-hazard ratio are semi-parametric, so they will not be entirely "consistent" in terms of reflecting differences between the comparison groups.

‡ For the organ systems the incidence of at least one the conditions listed under each system was calculated

¶ Gastrointestinal symptoms included: nausea, diarrhea, constipation, abdominal pain, abdominal distension, gas pain, eructation, flatulence

#Respiratory symptoms included: shortness of breath/dyspnea, cough and abnormal sputum

Supplement Table 14. Comparison of matched groups in an emulated target trial of nirmatrelvir-ritonavir versus no treatment among Veterans who tested positive for SARS-CoV-2 from January 1, 2022 to July 31, 2022 with respect to cumulative 31-180 day incidence of post-COVID conditions: applying inverse probability censoring weights (IPCW) to account for persons who died from day 1-30 after index date

31-180 day outcome	Nirmatrelvir-ritonavir N=9607** **Cumulative Incidence*** per 100 persons	No treatment N=9649** **Cumulative Incidence*** per 100 persons	**Cumulative Incidence Difference (95% CI)** per 100 persons	**Sub-Hazard Ratio (95% CI)**
Cardiac‡	13.43	14.36	-0.93 (-2.12- 0.25)	0.93 (0.85-1.02)
Acute coronary syndrome	2.19	2.56	-0.37 (-0.96- 0.23)	0.85 (0.68-1.08)
Cardiac dysrhythmias	4.25	4.35	-0.09 (-0.89- 0.70)	0.98 (0.82-1.17)
Cardiovascular disease	2.62	3.14	-0.52 (-1.19- 0.15)	0.83 (0.67-1.03)
Chest pain	3.77	3.56	0.21 (-0.50- 0.92)	1.06 (0.88-1.28)
Heart failure and cardiomyopathy	2.09	2.58	-0.48 (-1.06- 0.10)	0.81 (0.64-1.02)
Hypertension	7.54	8.25	-0.71 (-2.19- 0.77)	0.91 (0.75-1.10)
Myocarditis and Pericarditis	0.05	0.08	-0.03 (-0.13- 0.07)	0.63 (0.19-2.06)
Pulmonary‡	7.68	7.48	0.20 (-0.73-1.12)	1.03 (0.90-1.16)
Respiratory symptoms#	6.56	5.96	0.60 (-0.36- 1.56)	1.10 (0.95-1.29)
Asthma	1.47	1.11	0.36 (-0.05-0.77)	1.32 (0.97-1.82)
COPD and emphysema	1.62	1.98	-0.36 (-0.87- 0.16)	0.82 (0.62-1.07)
Renal‡	0.00	0.00		
Acute and Chronic kidney injury and dialysis	3.17	3.82	-0.65 (-1.31- 0.02)	**0.83 (0.69-0.99)**
Thromboembolic‡	0.54	0.84	-0.29 (-0.60- 0.02)	**0.65 (0.44-0.97)**
Venous thromboembolism	0.36	0.49	-0.13 (-0.37- 0.11)	0.73 (0.43-1.23)
Pulmonary embolism	0.25	0.41	-0.16 (-0.37- 0.06)	0.62 (0.34-1.11)
Gastrointestinal‡	9.57	10.42	-0.85 (-1.95- 0.26)	0.91 (0.82-1.02)
Gastrointestinal symptoms¶	6.18	6.59	-0.41 (-1.38- 0.57)	0.94 (0.81-1.09)
Gastrointestinal disorders	5.65	6.14	-0.49 (-1.46- 0.47)	0.92 (0.78-1.08)

Neurologic‡	5.04	4.97	0.07 (-0.70- 0.84)	1.01 (0.87-1.18)
Cerebrovascular disease	1.62	1.61	0.01 (-0.46- 0.48)	1.01 (0.76-1.33)
Dysautonomia	0.05	0.02	0.03 (-0.04- 0.09)	2.14 (0.41-11.25)
Dementia	0.66	0.75	-0.09 (-0.40- 0.22)	0.88 (0.58-1.35)
Smell and taste disturbance	0.09	0.08	0.02 (-0.09- 0.12)	1.23 (0.44-3.39)
Headache	2.94	2.89	0.04 (-0.60- 0.69)	1.02 (0.82-1.25)
Sleeping disorders	0.22	0.19	0.03 (-0.14- 0.19)	1.13 (0.56-2.31)
Mental health‡	8.01	7.80	0.21 (-0.73- 1.15)	1.03 (0.91-1.16)
Depression	3.18	3.08	0.10 (-0.61- 0.82)	1.03 (0.84-1.27)
Other mood disorders	0.46	0.46	0.00 (-0.25- 0.25)	1.00 (0.60-1.65)
Anxiety	4.01	3.58	0.43 (-0.32- 1.18)	1.12 (0.93-1.35)
PTSD	2.69	2.75	-0.06 (-0.72- 0.59)	0.98 (0.78-1.23)
Substance-related disorders	1.04	1.20	-0.16 (-0.56- 0.24)	0.87 (0.63-1.19)
Musculoskeletal				
Myalgia & Myositis	11.75	11.19	0.56 (-0.81- 1.94)	1.05 (0.93-1.19)
Endocrine				
Diabetes	2.23	2.46	-0.23 (-0.87- 0.41)	0.91 (0.70-1.17)
General				
Malaise and fatigue				
Postviral Fatigue				
Erectile Dysfunction	1.91	1.71	0.20 (-0.29- 0.69)	1.12 (0.86-1.46)
Negative Outcome Control				
Cancer	3.00	3.09	-0.09 (-0.76- 0.58)	0.97 (0.78-1.20)

** These sample sizes reflect the up-weighting from IPCW.

*For each post-COVID condition, 31-180 day incidence after the test-positive date is calculated only in matched groups within which all persons do not have prevalence of the condition of interest at baseline (i.e. not documentation within 12 months prior to infection). Incidence rates account for the competing risk of death. Methods for estimating incidence are non-parametric and methods for the sub-hazard ratio are semi-parametric, so they will not be entirely “consistent” in terms of reflecting differences between the comparison groups.

‡ For the organ systems the incidence of at least one of the conditions listed under each system was calculated

¶ Gastrointestinal symptoms included: nausea, diarrhea, constipation, abdominal pain, abdominal distension, gas pain, eructation, flatulence
[#]Respiratory symptoms included: shortness of breath/dyspnea, cough and abnormal sputum

Supplement Table 15. Comparison of matched groups in an emulated target trial of nirmatrelvir-ritonavir versus no treatment among Veterans who tested positive for SARS-CoV-2 from January 1, 2022 to July 31, 2022 with respect to cumulative 31-180 day incidence of post-COVID conditions: SUBGROUP LIMITED TO PERSONS AGE 18-64

31-180 day outcome	Nirmatrelvir-ritonavir N=1513 **Cumulative Incidence**[*] per 100 persons	No treatment N=1513 **Cumulative Incidence**[*] per 100 persons	**Cumulative Incidence Difference (95% CI)** per 100 persons	**Sub-Hazard Ratio (95% CI)**
Cardiac[‡]	7.07	6.79	0.28 (-1.71- 2.27)	1.04 (0.78-1.39)
Acute coronary syndrome	0.07	0.13	-0.07 (-0.33- 0.19)	0.50 (0.04-6.08)
Cardiac dysrhythmias	2.01	2.63	-0.62 (-1.89 0.65)	0.76 (0.44-1.31)
Cardiovascular disease	0.61	0.48	0.13 (-0.45- 0.71)	1.27 (0.45-3.56)
Chest pain	2.98	1.98	1.00 (-0.28- 2.28)	1.51 (0.92-2.49)
Heart failure and cardiomyopathy	0.41	0.47	-0.07 (-0.60- 0.47)	0.86 (0.27-2.68)
Hypertension	3.13	2.89	0.24 (-1.35- 1.82)	1.08 (0.63-1.86)
Myocarditis and Pericarditis	0.07	0.06	0.01 (-0.18- 0.21)	1.20 (0.07-21.97)
Pulmonary[‡]	5.83	4.78	1.05 (-0.70- 2.80)	1.23 (0.88-1.71)
Respiratory symptoms[#]	3.99	3.88	0.11 (-1.62- 1.84)	1.03 (0.66-1.60)
Asthma	2.81	1.13	**1.68 (0.56-2.81)**	**2.51 (1.34-4.70)**
COPD and emphysema	0.40	0.51	-0.11 (-0.65- 0.44)	0.79 (0.24-2.61)
Renal[‡]				
Acute and Chronic kidney injury and dialysis	1.42	1.30	0.12 (-0.83- 1.06)	1.09 (0.57-2.09)
Thromboembolic[‡]	0.33	0.24	0.09 (-0.33- 0.51)	1.36 (0.29-6.35)
Venous thromboembolism	0.20	0.09	0.11 (-0.18- 0.40)	2.25 (0.29-17.33)
Pulmonary embolism	0.13	0.19	-0.06 (-0.38- 0.27)	0.71 (0.09-5.47)
Gastrointestinal[‡]	9.05	8.76	0.29 (-2.08- 2.66)	1.03 (0.79-1.35)
Gastrointestinal symptoms[¶]	4.95	6.39	-1.44 (-3.59- 0.71)	0.77 (0.52-1.12)
Gastrointestinal disorders	5.95	5.08	0.87 (-1.21- 2.95)	1.18 (0.81-1.71)
Neurologic[‡]	4.89	3.50	1.39 (-0.17- 2.95)	1.41 (0.95-2.08)

Cerebrovascular disease	0.20	0.10	0.11 (-0.19- 0.40)	2.12 (0.22-20.27)
Dysautonomia	0.07	0.04	0.03 (-0.15- 0.20)	1.71 (0.07-43.32)
Dementia			--	--
Smell and taste disturbance			--	--
Headache	6.43	4.02	2.41 (0.37- 4.45)	1.62 (1.06-2.47)
Sleeping disorders	0.13	0.09	0.04 (-0.22- 0.30)	1.50 (0.12-18.26)
Mental health‡	11.78	9.96	1.83 (-0.60- 4.25)	1.19 (0.95-1.50)
Depression	5.60	4.86	0.75 (-1.57- 3.06)	1.15 (0.74-1.80)
Other mood disorders	0.50	0.74	-0.23 (-0.89- 0.42)	0.68 (0.24-1.92)
Anxiety	6.82	5.15	1.67 (-0.68- 4.01)	1.34 (0.89-2.01)
PTSD	5.73	4.91	0.82 (-1.51- 3.15)	1.17 (0.74-1.85)
Substance-related disorders	1.75	1.81	-0.06 (-1.17- 1.05)	0.96 (0.51-1.81)
Musculoskeletal				
Myalgia & Myositis	13.26	10.35	2.92 (-0.50- 6.34)	1.31 (0.96-1.79)
Endocrine				
Diabetes	0.85	0.53	0.32 (-0.37- 1.00)	1.59 (0.51-4.97)
General	0.00	0.00		
Malaise and fatigue	1.81	2.17	-0.36 (-1.52- 0.80)	0.83 (0.47-1.47)
Postviral Fatigue			--	--
Erectile Dysfunction	1.52	1.16	0.36 (-0.56- 1.28)	1.31 (0.66-2.62)
Negative Outcome Control				
Cancer	0.48	0.38	0.10 (-0.42- 0.62)	1.25 (0.36-4.36)

*For each post-COVID condition, 31-180 day incidence after the test-positive date is calculated only in matched groups within which all persons do not have prevalence of the condition of interest at baseline (i.e. not documentation within 12 months prior to infection). Incidence rates account for the competing risk of death. Methods for estimating incidence are non-parametric and methods for the sub-hazard ratio are semi-parametric, so they will not be entirely "consistent" in terms of reflecting differences between the comparison groups.

‡ For the organ systems the incidence of at least one of the conditions listed under each system was calculated

¶ Gastrointestinal symptoms included: nausea, diarrhea, constipation, abdominal pain, abdominal distension, gas pain, eructation, flatulence

#Respiratory symptoms included: shortness of breath/dyspnea, cough and abnormal sputum

Supplement Table 16. Comparison of matched groups in an emulated target trial of nirmatrelvir-ritonavir versus no treatment among Veterans who tested positive for SARS-CoV-2 from January 1, 2022 to July 31, 2022 with respect to cumulative 31-180 day incidence of post-COVID conditions: SUBGROUP LIMITED TO PERSONS AGE 65+

31-180 day outcome	Nirmatrelvir-ritonavir N=7634 **Cumulative Incidence*** per 100 persons	No treatment N=7634 **Cumulative Incidence*** per 100 persons	**Cumulative Incidence Difference (95% CI)** per 100 persons	**Sub-Hazard Ratio (95% CI)**
Cardiac‡	14.79	15.69	-0.90 (-2.28- 0.49)	0.94 (0.85-1.03)
Acute coronary syndrome	2.79	3.18	-0.40 (-1.16- 0.36)	0.87 (0.69-1.11)
Cardiac dysrhythmias	4.73	4.69	0.04 (-0.91- 0.98)	1.01 (0.83-1.22)
Cardiovascular disease	3.32	3.88	-0.56 (-1.42- 0.30)	0.85 (0.68-1.07)
Chest pain	3.80	3.89	-0.09 (-0.93- 0.74)	0.97 (0.79-1.20)
Heart failure and cardiomyopathy	2.58	3.06	-0.48 (-1.21- 0.24)	0.84 (0.66-1.06)
Hypertension	10.74	11.30	-0.56 (-2.83- 1.71)	0.95 (0.76-1.18)
Myocarditis and Pericarditis	0.04	0.07	-0.03 (-0.13- 0.07)	0.55 (0.12-2.50)
Pulmonary‡	8.12	8.16	-0.04 (-1.13- 1.05)	0.99 (0.87-1.14)
Respiratory symptoms#	7.11	6.52	0.59 (-0.54- 1.73)	1.09 (0.92-1.29)
Asthma	1.23	1.07	0.16 (-0.28- 0.60)	1.15 (0.80-1.66)
COPD and emphysema	1.94	2.40	-0.46 (-1.11- 0.19)	0.81 (0.61-1.07)
Renal‡	0.00	0.00		
Acute and Chronic kidney injury and dialysis	4.79	5.32	-0.53 (-1.51- 0.45)	0.90 (0.75-1.08)
Thromboembolic‡	0.59	0.95	**-0.36 (-0.73 0.01)**	**0.62 (0.41-0.95)**
Venous thromboembolism	0.38	0.54	-0.16 (-0.45- 0.13)	0.71 (0.40-1.24)
Pulmonary embolism	0.28	0.48	-0.20 (-0.46- 0.07)	0.58 (0.32-1.07)
Gastrointestinal‡	11.08	12.11	-1.03 (-2.38- 0.32)	0.91 (0.81-1.03)
Gastrointestinal symptoms¶	7.45	8.24	-0.79 (-2.03- 0.44)	0.90 (0.77-1.05)
Gastrointestinal disorders	6.62	6.78	-0.16 (-1.35- 1.03)	0.98 (0.82-1.16)
Neurologic‡	5.11	5.17	-0.06 (-0.94- 0.82)	0.99 (0.83-1.17)

Cerebrovascular disease	1.97	1.95	0.03 (-0.56- 0.61)	1.01 (0.76-1.35)
Dysautonomia	0.05	0.03	0.03 (-0.05- 0.10)	1.92 (0.32-11.64)
Dementia	0.83	0.89	-0.06 (-0.45- 0.33)	0.93 (0.61-1.43)
Smell and taste disturbance	0.12	0.05	0.07 (-0.04- 0.18)	2.30 (0.63-8.33)
Headache	2.30	2.53	-0.23 (-0.89- 0.44)	0.91 (0.70-1.18)
Sleeping disorders	0.24	0.19	0.04 (-0.14- 0.23)	1.23 (0.56-2.70)
Mental health‡	7.28	7.06	0.22 (-0.81- 1.24)	1.03 (0.89-1.19)
Depression	2.82	2.60	0.22 (-0.52- 0.97)	1.09 (0.85-1.40)
Other mood disorders	0.42	0.41	0.01 (-0.25- 0.28)	1.03 (0.58-1.84)
Anxiety	3.47	3.08	0.39 (-0.38- 1.16)	1.13 (0.90-1.41)
PTSD	2.26	2.37	-0.11 (-0.78- 0.57)	0.96 (0.72-1.27)
Substance-related disorders	0.85	1.14	-0.29 (-0.73- 0.14)	0.74 (0.51-1.09)
Musculoskeletal				
Myalgia & Myositis	11.37	10.95	0.41 (-1.14- 1.97)	1.04 (0.90-1.20)
Endocrine				
Diabetes	2.61	2.98	-0.36 (-1.18- 0.45)	0.88 (0.67-1.16)
General				
Malaise and fatigue	4.24	3.88	0.36 (-0.48- 1.19)	1.09 (0.90-1.33)
Post-viral Fatigue	0.11	0.04	0.06 (-0.04- 0.16)	2.46 (0.59-10.22)
Erectile Dysfunction	2.06	1.85	0.21 (-0.37- 0.79)	1.12 (0.83-1.49)
Negative Outcome Control				
Cancer	3.72	3.71	0.01 (-0.84- 0.86)	1.00 (0.80-1.25)

*For each post-COVID condition, 31-180 day incidence after the test-positive date is calculated only in matched groups within which all persons do not have prevalence of the condition of interest at baseline (i.e. not documentation within 12 months prior to infection). Incidence rates account for the competing risk of death. Methods for estimating incidence are non-parametric and methods for the sub-hazard ratio are semi-parametric, so they will not be entirely "consistent" in terms of reflecting differences between the comparison groups.

‡ For the organ systems the incidence of at least one of the conditions listed under each system was calculated

¶ Gastrointestinal symptoms included: nausea, diarrhea, constipation, abdominal pain, abdominal distension, gas pain, eructation, flatulence

#Respiratory symptoms included: shortness of breath/dyspnea, cough and abnormal sputum

Supplement Table 17. Comparison of matched groups in an emulated target trial of nirmatrelvir-ritonavir versus no treatment among Veterans who tested positive for SARS-CoV-2 from January 1, 2022 to July 31, 2022 with respect to cumulative 31-180 day incidence of post-COVID conditions: SUBGROUP LIMITED TO UNVACCINATED PERSONS

31-180 day outcome	Nirmatrelvir-ritonavir N=1561 **Cumulative Incidence*** per 100 persons	No treatment N=1561 **Cumulative Incidence*** per 100 persons	**Cumulative Incidence Difference (95% CI)** per 100 persons	**Sub-Hazard Ratio (95% CI)**
Cardiac‡	10.63	11.50	-0.87 (-3.32- 1.58)	0.92 (0.73-1.16)
Acute coronary syndrome	0.79	1.91	-1.12 (-2.12- 0.13)	0.41 (0.20-0.86)
Cardiac dysrhythmias	2.61	3.10	-0.49 (-1.90- 0.93)	0.84 (0.52-1.37)
Cardiovascular disease	1.43	2.59	-1.17 (-2.39- 0.05)	0.55 (0.30-0.99)
Chest pain	3.78	2.76	1.01 (-0.45- 2.47)	1.37 (0.87-2.16)
Heart failure and cardiomyopathy	1.31	2.06	-0.75 (-1.82- 0.32)	0.63 (0.34-1.19)
Hypertension	5.39	6.28	-0.89 (-3.51- 1.73)	0.85 (0.53-1.36)
Myocarditis and Pericarditis			--	--
Pulmonary‡	6.85	5.54	1.31 (-0.57- 3.19)	1.24 (0.91-1.69)
Respiratory symptoms#	5.21	3.68	1.52 (-0.28- 3.32)	1.42 (0.94-2.17)
Asthma	1.34	1.24	0.11 (-0.82- 1.03)	1.08 (0.53-2.21)
COPD and emphysema	1.67	1.64	0.03 (-1.03- 1.09)	1.02 (0.54-1.91)
Renal‡				
Acute and Chronic kidney injury and dialysis	3.00	3.07	-0.07 (-1.51- 1.38)	0.98 (0.60-1.60)
Thromboembolic‡	0.51	0.72	-0.20 (-0.83- 0.43)	0.72 (0.27-1.88)
Venous thromboembolism	0.32	0.36	-0.03 (-0.50- 0.43)	0.91 (0.24-3.38)
Pulmonary embolism	0.19	0.46	-0.27 (-0.74- 0.20)	0.42 (0.10-1.67)
Gastrointestinal‡	10.45	9.34	1.11 (-1.34- 3.56)	1.12 (0.87-1.45)
Gastrointestinal symptoms¶	6.21	6.21	-0.01 (-4.28- 2.13)	1.00 (0.71-1.40)
Gastrointestinal disorders	6.09	5.50	0.59 (-4.27- 2.73)	1.11 (0.76-1.61)
Neurologic‡	4.55	4.10	0.45 (-1.15- 2.04)	1.11 (0.77-1.60)

Cerebrovascular disease	0.82	1.00	-0.18 (-0.96- 0.60)	0.82 (0.37-1.85)
Dysautonomia	0.06	0.02	0.05 (-0.10- 0.20)	4.00 (0.05-320.31)
Dementia	0.59	0.62	-0.04 (-0.66- 0.58)	0.94 (0.35-2.55)
Smell and taste disturbance	0.06	0.09	-0.02 (-0.24- 0.20)	0.75 (0.06-10.05)
Headache	3.32	2.66	0.67 (-0.78- 2.12)	1.26 (0.77-2.05)
Sleeping disorders	0.13	0.33	-0.20 (-0.60- 0.20)	0.39 (0.07-2.21)
Mental health‡	8.76	8.26	0.49 (-1.69- 2.68)	1.07 (0.83-1.37)
Depression	3.72	3.52	0.21 (-1.51- 1.93)	1.06 (0.67-1.68)
Other mood disorders	0.47	0.67	-0.20 (-0.82- 0.42)	0.71 (0.25-2.02)
Anxiety	4.50	3.93	0.57 (-1.20- 2.34)	1.15 (0.78-1.71)
PTSD	3.34	3.28	0.06 (-1.56- 1.67)	1.02 (0.64-1.63)
Substance-related disorders	1.79	1.51	0.28 (-0.76- 1.32)	1.19 (0.63-2.26)
Musculoskeletal				
Myalgia & Myositis	11.69	8.72	2.98 (0.04- 5.91)	1.36 (1.01-1.84)
Endocrine				
Diabetes	1.22	1.56	-0.34 (-1.41- 0.74)	0.78 (0.38-1.62)
General				
Malaise and fatigue	3.33	3.01	0.33 (-1.11 1.76)	1.11 (0.70-1.74)
Post-viral Fatigue			--	--
Erectile Dysfunction	1.97	1.34	0.64 (-0.38- 1.65)	1.48 (0.81-2.71)
Negative Outcome Control				
Cancer	2.62	2.11	0.52 (-0.75- 1.78)	1.25 (0.73-2.15)

*For each post-COVID condition, 31-180 day incidence after the test-positive date is calculated only in matched groups within which all persons do not have prevalence of the condition of interest at baseline (i.e. not documentation within 12 months prior to infection). Incidence rates account for the competing risk of death. Methods for estimating incidence are non-parametric and methods for the sub-hazard ratio are semi-parametric, so they will not be entirely "consistent" in terms of reflecting differences between the comparison groups.

‡ For the organ systems the incidence of at least one of the conditions listed under each system was calculated

¶ Gastrointestinal symptoms included: nausea, diarrhea, constipation, abdominal pain, abdominal distension, gas pain, eructation, flatulence

#Respiratory symptoms included: shortness of breath/dyspnea, cough and abnormal sputum

Supplement Table 18. Comparison of matched groups in an emulated target trial of nirmatrelvir-ritonavir versus no treatment among Veterans who tested positive for SARS-CoV-2 from January 1, 2022 to July 31, 2022 with respect to cumulative 31-180 day incidence of post-COVID conditions: SUBGROUP LIMITED TO PERSONS WITH PRIMARY OR BOOSTER VACCINATION

31-180 day outcome	Nirmatrelvir-ritonavir N=7429 **Cumulative Incidence*** per 100 persons	No treatment N=7429 **Cumulative Incidence*** per 100 persons	**Cumulative Incidence Difference (95% CI)** per 100 persons	**Sub-Hazard Ratio (95% CI)**
Cardiac‡	13.77	14.59	-0.82 (-2.20- 0.56)	0.94 (0.85-1.04)
Acute coronary syndrome	2.41	2.61	-0.20 (-0.91- 0.51)	0.92 (0.70-1.21)
Cardiac dysrhythmias	4.49	4.46	0.03 (-0.91- 0.97)	1.01 (0.82-1.23)
Cardiovascular disease	2.83	3.23	-0.39 (-1.20- 0.41)	0.88 (0.69-1.12)
Chest pain	3.79	3.59	0.20 (-0.63- 1.04)	1.06 (0.85-1.32)
Heart failure and cardiomyopathy	2.19	2.63	-0.44 (-1.13- 0.26)	0.83 (0.64-1.07)
Hypertension	8.12	8.77	-0.65 (-2.50- 1.20)	0.92 (0.74-1.15)
Myocarditis and Pericarditis	0.07	0.08	-0.01 (-0.12- 0.11)	0.90 (0.24-3.28)
Pulmonary‡	7.67	7.70	-0.03 (-1.12- 1.05)	0.99 (0.86-1.15)
Respiratory symptoms#	6.73	6.23	0.50 (-0.65- 1.64)	1.08 (0.91-1.29)
Asthma	1.40	1.13	0.26 (-0.21- 0.74)	1.24 (0.86-1.77)
COPD and emphysema	1.57	2.00	-0.43 (-1.04- 0.18)	0.78 (0.57-1.08)
Renal‡				
Acute and Chronic kidney injury and dialysis	4.17	4.68	-0.52 (-1.46- 0.43)	0.89 (0.73-1.08)
Thromboembolic‡	0.50	0.84	**-0.34 (-0.70- 0.02)**	**0.59 (0.37-0.95)**
Venous thromboembolism	0.34	0.51	-0.17 (-0.46- 0.11)	0.66 (0.36-1.21)
Pulmonary embolism	0.24	0.39	-0.15 (-0.40- 0.10)	0.62 (0.31-1.25)
Gastrointestinal‡	10.70	11.73	-1.04 (-2.41- 0.33)	0.91 (0.80-1.02)
Gastrointestinal symptoms¶	7.21	7.92	-0.72 (-1.96- 0.53)	0.91 (0.77-1.07)
Gastrointestinal disorders	6.53	6.69	-0.16 (-1.37- 1.04)	0.97 (0.82-1.16)
Neurologic‡	5.05	5.04	0.00 (-0.89- 0.90)	1.00 (0.84-1.19)
Cerebrovascular disease	1.77	1.74	0.03 (-0.53- 0.60)	1.02 (0.75-1.39)

Dysautonomia	0.05	0.02	0.04 (-0.04- 0.11)	3.00 (0.42-21.31)
Dementia	0.71	0.75	-0.04 (0.40- 0.32)	0.95 (0.58-1.54)
Smell and taste disturbance	0.10	0.08	0.02 (-0.10- 0.14)	1.22 (0.38-3.90)
Headache	2.68	2.87	-0.19 (-0.93- 0.55)	0.93 (0.73-1.20)
Sleeping disorders	0.26	0.18	0.08 (-0.11- 0.27)	1.46 (0.64-3.33)
Mental health‡	7.64	7.43	0.21 (-0.86- 1.28)	1.03 (0.89-1.18)
Depression	3.14	2.81	0.33 (-0.47- 1.14)	1.12 (0.87-1.44)
Other mood disorders	0.45	0.38	0.07 (-0.20- 0.35)	1.20 (0.65-2.21)
Anxiety	3.85	3.43	0.42 (-0.43- 1.27)	1.12 (0.90-1.40)
PTSD	2.45	2.50	-0.05 (-0.78- 0.68)	0.98 (0.74-1.30)
Substance-related disorders	0.85	1.15	-0.30 (-0.75- 0.15)	0.74 (0.50-1.09)
Musculoskeletal				
Myalgia & Myositis	11.72	11.54	0.18 (-1.43- 1.79)	1.02 (0.88-1.17)
Endocrine				
Diabetes	2.45	2.46	-0.01 (-0.77- 0.76)	1.00 (0.74-1.34)
General				
Malaise and fatigue	3.79	3.51	0.29 (-0.53- 1.10)	1.08 (0.87-1.34)
Post-viral Fatigue	0.11	0.05	0.06 (-0.05- 0.17)	2.13 (0.51-8.94)
Erectile Dysfunction	1.87	1.83	0.04 (-0.55- 0.62)	1.02 (0.75-1.38)
Negative Outcome Control				
Cancer	3.09	3.18	-0.10 (-0.90- 0.71)	0.97 (0.76-1.24)

*For each post-COVID condition, 31-180 day incidence after the test-positive date is calculated only in matched groups within which all persons do not have prevalence of the condition of interest at baseline (i.e. not documentation within 12 months prior to infection). Incidence rates account for the competing risk of death. Methods for estimating incidence are non-parametric and methods for the sub-hazard ratio are semi-parametric, so they will not be entirely "consistent" in terms of reflecting differences between the comparison groups.

‡ For the organ systems the incidence of at least one of the conditions listed under each system was calculated

¶ Gastrointestinal symptoms included: nausea, diarrhea, constipation, abdominal pain, abdominal distension, gas pain, eructation, flatulence

#Respiratory symptoms included: shortness of breath/dyspnea, cough and abnormal sputum

C. REFERENCES

1. Hammond J, Leister-Tebbe H, Gardner A, Abreu P, Bao W, Wisemandle W, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med. 2022.
2. Jayk Bernal A, Gomes da Silva MM, Musungaie DB, Kovalchuk E, Gonzalez A, Delos Reyes V, et al. Molnupiravir for Oral Treatment of Covid-19 in Nonhospitalized Patients. N Engl J Med. 2022;386(6):509-20.
3. Centers for Disease Control and Prevention 2022; Available at:https://www.cdc.gov/coronavirus/2019-ncov/hcp/clinical-care/underlyingconditions.html?msclkid=1e40c3e2d09711ec8b9ea081710e6bc2 Last accessed on May 10 2022.
4. U.S. Food and Drug Administration 2022; Available at:https://www.fda.gov/media/158165/download Last accessed on 27 September 2022.
5. Centers for Disease Control and Prevention 2022; Available at:https://www.cdc.gov/vaccines/covid-19/images/COVID19-vaccination-schedule-most-people.png Last accessed on 9 October 2022.
6. Centers for Disease Control and Prevention 2022; Available at:https://www.cdc.gov/vaccines/covid-19/images/COVID19-vaccination-schedule-immunocompromised.png Last accessed on 9 October 2022.
7. U.S. Department of Agriculture 2022;Pageshttps://www.ers.usda.gov/data-products/rural-urban-commuting-area-codes/ Last accessed on May 10 2022.
8. Center for Health Disparities Research 2022; Available at:https://www.neighborhoodatlas.medicine.wisc.edu/ Last accessed on 4 October 2022.
9. Robins JM, Hernan MA, Brumback B**.** Marginal structural models and causal inference in epidemiology. Epidemiology. 2000;11(5):550-60.