Supplementary Appendix

Supplement to: Hammond J, Fountaine RJ, Yunis C, et al. Nirmatrelvir for vaccinated or unvaccinated adult outpatients with Covid-19. N Engl J Med 2024;390:1186-95. DOI: 10.1056/NEJMoa2309003

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

Supplementary Appendix

List of Investigators

Name	Institute	Location
Aazami, Hessam	Hope Clinical Research Hope Clinical Research (COVID Satellite Site)	Canoga Park, CA, USA West Hills, CA, USA
Abinante, Matthew	Ascada Research	Fullerton, CA, USA
Abrishamian, Luis	South Bay Clinical Research Institute	Redondo Beach, CA, USA
Akhan, Sila	Kocaeli University Medical Faculty	Kocaeli, Turkey
Aksoy, Firdevs	Karadeniz Teknik Universitesi Farabi	Trabzon, Turkey
Al Barwani, Aalia	Trio Clinical Trials	Houston, TX, USA
Alexander, Samuel	Southern Clinical Research Associates	Metairie, LA, USA
Álvarez, Tomás	Instituto Médico de la Fundación Estudios Clínicos (Fundación Estudios Clínicos)	Rosario, Argentina
Anderson, Duane	Excel Clinical Research	Las Vegas, NV, USA
Antila, Martti	Clinica de Alergia Martti Antila	Sorocaba, Brazil
Antonov, Chavdar	MHAT Sveti Nikolay Chudotvoretz	Lom, Bulgaria
Avihingsanon, Anchalee	Bangkok Centre Hotel Thai Red Cross Emerging Infectious Diseases (EDI) Clinic The HIV Netherlands Australia Thailand Research Collaboration (HIV-NAT)	Bangrak, Thailand Pathumwan, Thailand Pathumwan, Thailand
Ayesu, Kwabena	Omega Research Orlando Omega Research Orlando	Orlando, FL, USA Debary, FL, USA
Balik, Ismail	Ankara University Medical Faculty, Ibni-Sina Hospital	Ankara, Turkey
Barrat Hernández, Alejandro	FAICIC Clinical Research	Veracruz, Mexico
Batista de Moura Xavier de Moraes, João	Hospital Agamenon Mãgalhaes	Recife, Brazil
Benitez, Omar	South Florida Research Center	Miami, FL, USA
Benitez, Wilfrido	Eastern Research	Hialeah, FL, USA
Berenfus, Vadym	Lviv City Clinic Hospital No.4	Lviv, Ukraine
Boghara, Haresh	Epic Medical Research	Red Oak, TX, USA
Brabham, David	PharmaTex Research	Amarillo, TX, USA
Buchvarov, Mladen	Outpatient Clinic for Primary Outpatient Medical Care "Puls"	Tsarevo, Bulgaria
Buendia Magaña, Ruben	Eme Red Hospitalaria	Mérida, Mexico
Buendia Suárez, Isabel	Instituto de Investigaciones Clínicas para la Salud	Durango, Mexico
Caeiro, Juan	Hospital Privado Centro Médico de Córdoba	Córdoba, Argentina
Calinescu, Cornell	Matrix Mobile Health Clinic #49, #35, and #62	Scottsdale, AZ, USA
Cannon, Kevin	Accellacare	Wilmington, NC, USA
Capote, Eddy	Herco Medical and Research Center	Coral Gables, FL, USA
Caruntu, Florin	Delta Health Care	Bucuresti, Romania
Cavalcante, Adilson	CEMEC – Centro Multidisciplinar de Estudos Clínicos	São Paulo, Brazil
Chang, Li Cheng	Klinik Kesihatan Kuang	Rawang, Malaysia
Chayakulkeeree, Methee	Baiyoke Suite Hotel Riverside Bangkok Hotel Siriraj Hospital, Mahidol University	Ratchathewi, Thailand Bangplud, Thailand BangkokNoi, Thailand
Cheah, Wee Kooi	Hospital Taiping	Taiping, Malaysia
Chusri, Sarunyou	Prince of Songkla University, Songklanagarind Hospital	Hat Yai, Thailand

Cibik, Viliam	MUDr. Viliam Cibik, PhD.	Pruske, Slovakia
Cortes, Anais	Inpatient Research Clinic	Hialeah, FL, USA
Curbelo Calleiro, Maria	I.V.A.M. Clinical & Investigational Center	Miami, FL, USA
Czerech, Ewa	KLIMED Marek Klimkiewicz	Bialystok, Poland
De La Vega, Dagoberto	Unlimited Medical Research Group	Hialeah Gardens, FL, USA
Del Carpio Orantes, Luis	Sociedad de Metabolismo y Corazon	Veracruz, Mexico
Deno, Yohanna	CDC Research Institute	Port Saint Lucie, FL, USA
Diaz, Jorge	Doral Medical Research	Hialeah, FL, USA
Dobreva, Vanya	DCC Sveti Georgi	Plovdiv, Bulgaria
Dombi, Attila	Trial Pharma	Bekescsaba, Hungary
Drasnar, Tomáš	Nemocnice Slaný	Slaný, Czech Republic
Duardo-Guerra, Yamirka	LCC Medical Research Institute	Miami, FL, USA
Fakih, Faisal	Clinical Site Partners	Winter Park, FL, USA
Fam, Tem Lom	Hospital Miri	Miri, Malaysia
Fatakia, Adil	New Orleans Sinus Center (COVID-19 Testing) Tandem Clinical Research GI	Marrero, LA, USA Marrero, LA, USA
Fernandez-Miro, Humberto	Global Health Clinical Trials	Miami, FL, USA
Flores Figueroa, Jose	JM Research	Cuernavaca, Mexico
Fonseca, Allex	CECOR – Centro Oncológico de Roraima	Boa Vista, Brazil
Fulat, Muhammed Ameen	Clinical Trial Systems	Pretoria, South Africa
Galitz, Lawrence	GCP, Global Clinical Professionals	St. Petersburg, FL, USA
Garcia, Lazaro	Entrust Clinical Research	Miami, FL, USA
Gavrylov, Anatoliy	Regional Clinical Infectious Diseases Hospital	Kharkiv, Ukraine
Geldenhuys, Johan	FCRN Clinical Trial Centre	Vereeniging, South Africa
Georgiev, Emil	Diagnostic-Consultative Center I – Lom	Lom, Bulgaria
Georgieva, Stela	MHAT Targovishte	Targovishte, Bulgaria
Gorgos, Linda	AXCES Research Group	Sante Fe, NM, USA
Gudzheva, Rumyana Gavrailova	Diagnostic-Consultative Center XXII – Sofia	Sofia, Bulgaria
Gunduz, Alper	Basaksehir Cam ve Sakura Sehir Hastanesi	Istanbul, Turkey
Haracherova, Kameliya	Specialized Hospital for Active Treatment in Pulmonology and Phthisiology – Stara Zagora	Stara Zagora, Bulgaria
Harcsa, Eleonora	Agria-Study	Eger, Hungary
Hassler, Shawn	Optimus Medical Group	San Francisco, CA, USA
Haytova, Nezabravka	Specialized Hospital for Active Treatment of Pneumo-Phthisiatric Diseases – Vratsa	Vratsa, Bulgaria
Hellstrom, Elizabeth	Be Part Research	Paarl, South Africa
Hernández Pichardo, Joselito	Asociación Mexicana para la Investigación Clínica	Pachuca de Soto, Mexico
Hernandez, Manuel	Savin Medical Group	Miami Lakes, FL, USA
Hoosen, Farzana	Synapta Clinical Research Center	Durban, South Africa
Hrebenar, Slavomir	Plucna ambulancia Hrebenar	Spisska Nova Ves, Slovakia
Hristova, Iskra	Medical Center Leo Clinic	Varna, Bulgaria

Hristovski, Boyan	MHAT St. Sofia	Sofia, Bulgaria
Hussen, Nazreen	Worthwhile Clinical Trials	Benoni, South Africa
Igbinadolor, Awawu	Monroe Biomedical Research	Monroe, NC, USA
Ilashchuk, Tetiana	City Clinical Hospital No.3 of Chernivtsi City Council	Chernivtsi, Ukraine
Imura, Haruki	Rakuwakai Otowa Hospital	Kyoto-shi, Japan
Inan, Dilara	Akdeniz Universitesi Hastanesi	Antalya, Turkey
Issa, Husam	Tranquility Research	Webster, TX, USA
Jandali, Imad	Asclepes Research Centers	Spring Hill, FL, USA Lutz, FL, USA
Jeudy, Wilner	Next Level Urgent Care	Houston, TX, USA
Jimenez, Mario	Kendall South Medical Center	Miami, FL, USA
Kalfov, Veselin	Specialized Hospital for Active Treatment of Pneumo-Phthisiatric Diseases – Haskovo	Haskovo, Bulgaria
Kandemir, Fatma	Mersin University Medical Faculty	Mersin, Turkey
Kang, Seung ji	Chonnam National University Bitgoeul Hospital	Gwangju, Republic of Korea
Karabay, Oguz	Sakarya University Training and Research Hospital	Sakarya, Turkey
Karaoglan, Ilkay	Gaziantep Universitesi Tip Fakultesi Sahinbey Uygulama ve Arastirma Hastanesi	Gaziantep, Turkey
Karpenko, Olena	Kyiv City Clinical Hospital No.1	Kyiv, Ukraine
Killion, Jennifer	Accellacare	Ames, IA, USA
Kim, Kenneth	Ark Clinical Research	Long Beach, CA, USA
Kirov, Mihail	Medical Centre Leo Clinic	Lovech, Bulgaria
Kobrynska, Olena	Central City Clinical Hospital of Ivano-Frankivsk City Council	Ivano-Frankivsk, Ukraine
Kohli, Anita	Arizona Clinical Trials	Tuscon, AZ, USA
Koksal, Iftihar	Acibadem University Atakent Hospital	Istanbul, Turkey
Kolář, Jan	Zdraví-Fit	Protivín, Czech Republic
Komitov, Iliyan	MHAT – Sliven to Military Medical Academy	Sliven, Bulgaria
Koval, Tetiana	Poltava Regional Clinical Infectious Diseases Hospital	Poltava, Ukraine
Kovalenko, Svitlana	Chernivtsi Regional Clinical Hospital	Chernivtsi, Ukraine
Laningham, Robert	Conroe Willis Medical Research	Conroe, TX, USA
Lima, Maria Patelli	Hospital e Maternidade Celso Pierro – PUC Campinas	Campinas, Brazil
Lima, Marina	Hospital Dia do Pulmao	Blumenau, Brazil
Lodyga, Michal (previously Kierkus, Jaroslaw)	WIP Warsaw IBD Point Profesor Kierkus	Warszawa, Poland
Logoida, Pavlo	Polyclinic of Center for Medical Services and Rehabilitation	Kyiv, Ukraine
Lopes, Suzara	Chronos Pesquisa Clinica	Brasilia, Brazil
López Romo, Alicia	Christus – Latam Hub Center of Excellence and Innovation Center	Monterrey, Mexico
Luz, Kleber	Centro de Estudos e Pesquisas em Moléstias Infecciosas	Natal, Brazil
Mabale, Primrose	Reimed Vosloorus	Boksburg, South Africa
Macias, Francisco	USPA Advance Concept Medical Research Group	South Miami, FL, USA
Macias, Pablo	Clinical Research Institute Saltillo	Saltillo, Mexico
Mannheimer, Sharon	NYC Health + Hospitals/Harlem	New York, NY, USA
Martin Quiros, Alejandro	Hospital Universitario de la Paz	Madrid, Spain

Martinez, Cindy	Premium Medical Research	Miami, FL, USA
Martinez, Orvil	Advance Medical Research Center	San Juan, Puerto Rico
Mas, Luis	Advance Clinical Research Group	Cutler Bay, FL, USA
McHarry, Kirsten	TASK Eden	George, South Africa
McKinnell, James	Lightship	El Segundo, CA, USA
Merchante, Nicolas	Hospital Universitario Virgen de Valme	Sevilla, Spain
Merkely, Béla	Semmelweis University Varosmajori Sziv es Ergyogyaszati Klinika	Budapest, Hungary
Mert, Ali	Medipol Mega University Hospital	Istanbul, Turkey
Metev, Hristo	Specialized Hospital for Active Treatment of Pneumo-Physiatric Diseases Dr. Dimitar Gramatikov – Ruse	Ruse, Bulgaria
Minova, Lyudmyla	Oleksandrivska Kyiv City Clinical Hospital	Kyiv, Ukraine
Mir Remedios, Ariel	C'A Research	Miami, FL, USA
Mitha, Essack	Sandton Medical Clinic	Sandton, South Africa
Mitreva, Roza	MHAT – Samokov	Samokov, Bulgaria
Mogashoa, Salphy	Botho Ke Bontle Health Services	Pretoria, South Africa
Monlux, George	MOORE Clinical Research	Brandon, FL, USA
Moosa, Naeem	Lenasia Clinical Trial Centre	Johannesburg, South Africa
Mootsikapun, Piroon	Khon Kaen University Field Hospital Srinagarind Hospital	Khon Kaen, Thailand Khon Kaen, Thailand
Moroz, Larysa	Vinnytsia City Clinical Hospital No.1	Vinnytsia, Ukraine
Mustafa, Mahiran	Hospital Raja Perempuan Zainab II	Kota Bharu, Malaysia
Nagasaki, Yoji	Kyushu Medical Center	Fukuoka-shi, Japan
Napora, Piotr	Centrum Badań Klinicznych Piotr Napora	Wrocław, Poland
Narejos Perez, Silvia	EBA Centelles	Centelles, Spain
Nazir, Jawad	Avera McKennan Hospital & University Health Center Avera Research Institute	Sioux Falls, SD, USA Sioux Falls, SD, USA
Nemechkin, Oleg	MHAT Sveti Ivan Rilski – Razgrad	Razgrad, Bulgaria
Newman Lobato Souza, Tâmara	Instituto de Infectologia Emílio Ribas	São Paulo, Brazil
Ngcakani, Nomangesi	Global Clinical Trials	Gqeberha, South Africa
Nieradko-Iwanic Ka, Barbara (previously Blicharski, Tomasz)	Tomasz Blicharski Lubelskie Centrum Diagnostyczne	Swidnik, Poland
Nuñez, Juan	Clinica Mayo Urgencias Medicas Cruz Blanca	San Miguel de Tucuman, Argentina
Oshita, Masaru	Benchmark Research	Sacramento, CA, USA
Ostrovskyy, Mykola	Ivano-Frankivsk Regional Phthisiopulmonology Center of Ivano-Frankivsk Regional Council	Ivano-Frankivsk, Ukraine
Paluga, Igor	ALERGIA	Topolcany, Slovakia
Panayotov, Plamen	Individual Practice for Primary Medical Care – Dr. P. Panayotov	Burgas, Bulgaria
Paoli-Bruno, Jorge	Coral Research Clinic	Miami, FL, USA
Papp, Albert	Trial Pharma	Gyula, Hungary
Paredes Deiros, Roger	Hospital Universitari Germans Trias i Pujol	Badalona, Spain
Parev, Atanas	MHAT St. Panteleimon – Plovdiv	Plovdiv, Bulgaria
Park, Sang-Won	Boramae Medical Center	Seoul, Republic of Korea
Patel, Bhaktasharan	Future Innovative Treatments	Colorado Springs, CO, USA

Patel, Lisa	Santos Research Center	Tampa, FL, USA
Penchev, Mladen	Medical Center-1-Sevlievo	Sevlievo, Bulgaria
Perez Gonzalez, Alexandre	Hospital Alvaro Cunqueiro	Vigo, Spain
Piñeiro Puebla, Yanely	Angels Clinical Research Institute	Miami, FL, USA
Pinheiro, Renata Alexandra	IBPClin – Instituto Brasil de Pesquisa Clínica	Rio de Janeiro, Brazil
Polat, Gulru	Izmir Suat Seren Chest Disease and Surgery Training and Research Hospital	Izmir, Turkey
Popova, Maya	MOBAL Dr. Stefan Cherkezov	Veliko Tarnovo, Bulgaria
Pryshlyak, Oleksandra	Ivano-Frankivsk Regional Clinical Infectious Diseases Hospital	Ivano-Frankivsk, Ukraine
Pullman, John	Mercury Street Medical Group	Butte, MT, USA
Ramirez Hernandez, Amado	Arké SMO	Veracruz, Mexico
Ramirez Navarro, Ariel	Reed Medical Research	Miami, FL, USA
Ratvaj, Vlastimil	HODOSI – MED	Moldava nad Bodvou, Slovakia
Reyes, Ramon	BFHC Research	San Antonio, TX, USA
Ribeiro, Maria Pia	Instituto Nacional de Infectologia Evandro Chagas	Rio de Janeiro, Brazil
Rivera Martínez, Norma	Oaxaca Site Management Organization	Oaxaca de Juárez, Mexico
Rosenthal, Mark (previously Krainson, James)	CSP Miami	Miami, FL, USA
Sachdeva, Yessica	Arizona Clinical Trials	Mesa, AZ, USA
Salazar, Hernan	Endeavor Clinical Trials	San Antonio, TX, USA
Samoilova, Svitlana	Kyiv Railway Clinical Hospital No.2	Kyiv, Ukraine
Sánchez Salazar, Sergio	Eukarya Pharmasite	Monterrey, Mexico
Sanchez Vallejo, Gregorio	Fundacion Cardiomet CEQUIN	Armenia, Colombia
Sato, Victor	Hospital Alemão Oswaldo Cruz	São Paulo, Brazil
Schneider, Linda	TMPG Clinical Research	Newport News, VA, USA
Sebastian, Peter	Dr PJ Sebastian Clinical Research Centre	Durban, South Africa
Sekino, Hisakuni	Sekino Hospital	Toshima-ku, Japan
Shinkai, Masaharu	Tokyo Shinagawa Hospital	Shinagawa-ku, Japan
Siddiqui, Mohammad (previously Mussaji, Murtaza)	LinQ Research	Pearland, TX, USA
Siegel, Amy	ARC Clinical Research at William Cannon	Austin, TX, USA
Simon Campos, Jesus	Köhler & Milstein Research	Mérida, Mexico
Simova, Iana	MHAT Heart and Brain	Pleven, Bulgaria
Sims, James	St Hope Foundation	Bellaire, TX, USA
Simsek-Yavuz, Serap	Istanbul University Istanbul Medical Faculty	Istanbul, Turkey
Skolnick, Alan	SignatureCare Emergency Center	Houston, TX, USA
Sosa Faria, Javier	Clinical Research Management Group	Ponce, Puerto Rico
Sousa Regueiro, María Dolores	Complexo Hospitalario Universitario da Coruna	A Coruña, Spain
Sprinz, Eduardo	Hospital De Clinicas De Porto Alegre	Porto Alegre, Brazil
Suarez, Rosa	ProLive Medical Research	Miami, FL, USA

Suleman, Moosa	Ahmed Al-Kadi Private Hospital	Durban, South Africa
Tabak, Omer	Istanbul University Cerrahpasa – Cerrahpasa Medical Faculty	Istanbul, Turkey
Tasova, Yesim	Cukurova University Medical Faculty	Balcali, Turkey
Tiholov, Rumen	MHAT Sveti Ivan Rilski – Kozloduy	Kozloduy, Bulgaria
Tokunaga, Paula	Centro de Estudos Clinicos do Interior Paulista (CECIP)	São Paulo, Brazil
Tomas, Juan	Hospital de Clinicas Presidente Nicolas Avellaneda	San Miguel de Tucuman, Argentina
Tsushima, Kenji	International University of Health and Welfare Narita Hospital	Narita-shi, Japan
Ünal, Serhat	Hacettepe University Medical Faculty Hospital	Ankara, Turkey
Valia Vera, Juan Carlos	IMED Valencia	Burjassot, Spain
Vanegas Arias, Ana	Fundacion Centro de Investigacion Clinica	Medellin, Colombia
Varkonyi, Istvan	Debreceni Egyetem Klinikai Központ	Debrecen, Hungary
Vasquez, Eduardo	Pro-Care Research Center	Miami Gardens, FL, USA
Velez, Patricia	Centro de Investigacion en Reumatologia y Especialidades Medicas	Bogota, Colombia
Vico, Marisa	Instituto de Investigaciones Clinicas Zarate	Zárate, Argentina
Victoria, Rafaelito	Atella Clinical Research	La Palma, CA, USA
Vyshnyvetskyy, Ivan	Hospital No.1 of Zhytomyr City Council Department of Infectious Diseases	Zhytomyr, Ukraine
Webster, Brian	Innovo Research−Wilmington Health	Wilmington, NC, USA
Weston, Patrick	Synergy Healthcare	Bradenton, FL, USA
Wever, David	Cahaba Research	Pelham, AL, USA
Winnie, Michael	South Texas Clinical Research	Corpus Christi, TX, USA
Zilahi, Zsolt	Medifarma-98	Nyíregyháza, Hungary

Additional Eligibility Criteria

Fertile participants were also required to use a highly effective method of contraception. Participants were excluded if they had ≥1 predefined, underlying condition associated with increased risk of developing severe Covid-19,[2-5] including age ≥65 years; body mass index (BMI) ≥30 kg/m^2; active smoking; chronic lung, cardiovascular, kidney, or sickle cell disease; hypertension; diabetes; cancer; neurodevelopmental disorders or other medically complex condition; or medical-related technological dependence. Before implementation of protocol amendment 5, a participant had a complete vaccination schedule, the exclusion criterion for comorbidity was invalidated. Other key exclusion criteria included pregnancy or breastfeeding; history of hospitalization for Covid-19; current or anticipated need for hospitalization ≤48 hours after randomization; confirmed previous infection with SARS-CoV-2; active liver, renal, or HIV disease or concurrent systemic infection; concurrent comorbidity requiring hospitalization/surgery within the previous 7 days or considered life-threating within the previous 30 days; and known history of certain abnormalities in clinical laboratory testing within 6 months before study screening.

Prohibited prior or concomitant therapies included medications that are highly dependent on CYP3A4 for clearance and may be unsafe at elevated plasma concentrations (during and through 4 days after treatment); strong inducers of CYP3A4 (≤28 days before and during treatment); monoclonal antibodies, antivirals, or convalescent Covid-19 plasma for Covid-19 treatment; and Covid-19 vaccines within 12 months of screening (before the Day 34 visit) in all participants except those fully vaccinated at baseline with underlying risk factors for severe Covid-19, as specified above.

Study Product and Blinding

Nirmatrelvir was provided as 150-mg tablets, while ritonavir was provided as 100-mg capsules; each had a matching placebo. Participants were instructed to take 2 tablets and 1 capsule (ie, 300 mg nirmatrelvir and 100 mg ritonavir or matching placebo) every 12 hours for 5 days (ie, 10 doses total). At the end of treatment, participants were followed up until Week 24.

Ethical Conduct

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

Study Drug Responsibilities

Nirmatrelvir 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.

Table S1. Signs and Symptoms Attributable to Covid-19

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

Results from local reverse transcriptase polymerase chain reaction or other molecular tests detecting viral RNA or protein performed within 5 days of randomization or rapid antigen tests performed at screening were used to confirm SARS-CoV-2 infection.
Severity ratings for each symptom over the previous 24 hours used a 4-point scale where: 0=absent, 1=mild, 2=moderate, and 3=severe; vomiting/diarrhea and loss of smell/taste used a 4-point frequency scale and 3-point Likert scale, respectively.

Table S2. Demographic and Clinical Characteristics of Participants Included in the Full Analysis Set*

Characteristic	Nirmatrelvir/Ritonavir (n=658)	Placebo (n=638)	Total (N=1296)
Sex, n (%)			
Male	312 (47.4)	284 (44.5)	596 (46.0)
Female	346 (52.6)	354 (55.5)	700 (54.0)
Age, median (range), y	41 (18–87)	42 (18–82)	42 (18–87)
Race, n (%)			
White	515 (78.3)	502 (78.7)	1017 (78.5)
Black or African American	28 (4.3)	23 (3.6)	51 (3.9)
Asian	70 (10.6)	72 (11.3)	142 (11.0)
American Indian or Alaska Native	39 (5.9)	32 (5.0)	71 (5.5)
Not reported	5 (0.8)	7 (1.1)	12 (0.9)
Unknown	1 (0.2)	2 (0.3)	3 (0.2)
Ethnicity, n (%)			
Hispanic or Latino	274 (41.6)	262 (41.1)	536 (41.4)
Not reported	4 (0.6)	6 (0.9)	10 (0.8)
Geographic region, n (%)			
United States	216 (32.8)	206 (32.3)	422 (32.6)
Europe	222 (33.7)	215 (33.7)	437 (33.7)
Rest of world	220 (33.4)	217 (34.0)	437 (33.7)
BMI, kg/m^2, median (range)	24.91 (17.45–58.82)	24.92 (14.20–53.14)	24.91 (14.20–58.82)
Baseline comorbidities, n (%)†			
Cardiovascular disorders	7 (1.1)	8 (1.3)	15 (1.2)
Chronic lung disease	9 (1.4)	13 (2.0)	22 (1.7)
Cigarette smoker	86 (13.1)	86 (13.5)	172 (13.3)
Diabetes mellitus	34 (5.2)	32 (5.0)	66 (5.1)
Hypertension	83 (12.6)	77 (12.1)	160 (12.3)
Vaccinated, n (%)	374 (56.8)	364 (57.1)	738 (56.9)
Serology status, n (%)			
Positive‡	482 (73.3)	475 (74.5)	957 (73.8)
Negative	161 (24.5)	149 (23.4)	310 (23.9)
Unknown	15 (2.3)	14 (2.2)	29 (2.2)
Viral load, log_{10} copies/mL, n (%)§			
0	99 (15.0)	106 (16.6)	205 (15.8)
< 4	171 (26.0)	188 (29.5)	359 (27.7)
≥ 4	474 (72.0)	438 (68.7)	912 (70.4)
≥ 5	424 (64.4)	381 (59.7)	805 (62.1)
≥ 6	340 (51.7)	302 (47.3)	642 (49.5)
< 7	433 (65.8)	426 (66.8)	859 (66.3)

≥ 7	212 (32.2)	200 (31.3)	412 (31.8)
≥ 8	81 (12.3)	71 (11.1)	152 (11.7)
≥ 9	5 (0.8)	4 (0.6)	9 (0.7)
≥ 10	0	0	0
Mean (SD)	5.3 (2.8)	5.0 (2.8)	5.1 (2.8)
Median (range)	6.2 (0.0, 9.5)	6.0 (0.0, 9.4)	6.0 (0.0, 9.5)
Baseline severity, n (%)|			
None	8 (1.2)	11 (1.7)	19 (1.5)
Mild	205 (31.2)	178 (27.9)	383 (29.6)
Moderate	308 (46.8)	307 (48.1)	615 (47.5)
Severe	114 (17.3)	129 (20.2)	243 (18.8)
Duration since first symptom, n (%)			
≤3 days	476 (72.3)	464 (72.7)	940 (72.5)
>3 days	182 (27.7)	174 (27.3)	356 (27.5)
Median (range)	3 (0–5)	3 (0–6)	3 (0–6)
Number of risk factors of interest, n (%)			
0	335 (50.9)	314 (49.2)	649 (50.1)
1	177 (26.9)	186 (29.2)	363 (28.0)
2	95 (14.4)	84 (13.2)	179 (13.8)
3	32 (4.9)	40 (6.3)	72 (5.6)
4	18 (2.7)	10 (1.6)	28 (2.2)
>4	1 (0.2)	4 (0.6)	5 (0.4)
Risk status, n (%)			
High risk	319 (48.5)	317 (49.7)	636 (49.1)
Standard risk (no risk factors)	335 (50.9)	314 (49.2)	649 (50.1)
Other	4 (0.6)	7 (1.1)	11 (0.8)
Most common risk factors¶, n (%)			
BMI ≥30 kg/m^2	109 (16.6)	122 (19.1)	231 (17.8)
Smoker	86 (13.1)	86 (13.5)	172 (13.3)
Hypertension	83 (12.6)	77 (12.1)	160 (12.3)
Diabetes mellitus	34 (5.2)	32 (5.0)	66 (5.1)
≥65 years of age	36 (5.5)	29 (4.5)	65 (5.0)

BMI=body mass index; SD=standard deviation.
*All participants who were randomly assigned to study intervention regardless of whether study intervention was administered. Does not include participants excluded from the analysis (shown in **Figure 1**).
†Presented for comorbidities present in ≥1% of participants overall.
‡Positive serostatus was defined as SARS-CoV-2 anti-N (nucleocapsid) or anti-S (spike) positive.
§Swabs for viral load were tested as previously described.[9]
|Severity for the worst targeted sign/symptom.
¶Occurring in ≥5% of participants in any group.

Table S3. Representativeness of Study Population

Disease Under Investigation	**Covid-19**
Special considerations related to	
Sex and gender	Covid-19 affects both sexes with similar frequency, although males appear to be at increased risk of progressing to severe disease, with somewhat higher rates of hospitalization and death compared with females. Currently, there is no known data regarding Covid-19 case rates or poor outcomes associated with gender identity.
Age	Covid-19 affects people of all age groups. Compared with younger populations, older adults are more likely to progress to severe illness from COVID-19, including hospitalization and death. As of August 20, 2022, more than half of US Covid-19–associated hospitalizations were in adults ≥65 years.
Race or ethnicity	Covi -19 affects people of all races and ethnicities. In the United States, Black/African American, Hispanic/Latino, and American Indian/Alaska Native individuals have experienced a disproportionate Covid-19 burden, including increased case rates and associated hospitalizations and deaths.
Geography	COVID-19 case, hospitalization, and mortality rates vary globally. The spread of SARS-CoV-2 and outcomes for Covid-19 are affected by the prevalence of risk factors in the population, healthcare infrastructure, treatment availability, vaccination rates, circulating SARS-CoV-2 variants, control strategies, and intervention measures, which vary globally.
Other considerations	The secondary attack rate among household contacts of individuals infected with the Omicron variant is estimated to be up to 81%. Infection control guidance for household contacts includes isolation, social distancing, hand washing, and mask wearing, with the effectiveness of these measures dependent on several factors. Currently, postexposure prophylactic treatment for house contacts of SARS-CoV-2–infected individuals is not available, although such an approach is recommended in other infectious disease settings.
Overall representativeness of this trial	The participants in this trial demonstrated the expected ratio of men to women, with slightly more women than men enrolled. Adult participants ≥18 years of age were enrolled. The median (range) age for study participants was 42 (18–87) years. The majority of participants were White (78.5%); 3.9% of participants were Black/African American. Hispanic/Latino individuals comprised 41.4% of randomized participants in the study. Participants were enrolled at centers globally, with 32.6% enrolled from the United States and 33.7% from Europe.

Table S4. Analysis of Covid-19–Related Hospitalization or Death by Subgroup of Vaccination Status*

	Overall		High Risk†		Standard Risk‡	
Time to Sustained Alleviation	**Nirmatrelvir/ Ritonavir**	**Placebo**	**Nirmatrelvir/ Ritonavir**	**Placebo**	**Nirmatrelvir/ Ritonavir**	**Placebo**
Number of participants evaluated	654	634	317	314	333	313
Participants with event, n (%)						
Participants with Covid-19 hospitalization	5 (0.8)	10 (1.6)	3 (0.9)	7 (2.2)	2 (0.6)	3 (1.0)
Participants with death	0	1 (0.2)	0	1 (0.3)	0	0
Estimated proportion (95% CI)	0.77 (0.32, 1.85)	1.59 (0.86, 2.93)	0.95 (0.31, 2.92)	2.25 (1.08, 4.65)	0.61 (0.15, 2.41)	0.96 (0.31, 2.96)
Difference from placebo (95% CI)	–0.81 (–2.00, 0.374)		–1.29 (–3.26, 0.67)		–0.36 (–1.73, 1.02)	
Relative reduction vs placebo, %	51.2		57.6		36.9	
Participants with Covid-19–related medical visits§, n (%)	15 (2.3)	25 (3.9)	6 (1.9)	17 (5.4)	9 (2.7)	7 (2.2)
Total number of medical visits across all participants	24	36	6	26	18	9
Number of medical visits per day						
Mean (SD)	0.001 (0.011)	0.002 (0.016)	0.001 (0.004)	0.003 (0.022)	0.0019 (0.015)	0.0008 (0.006)
LS mean (95% CI)	0.001 (0.001, 0.002)	0.002 (0.001, 0.004)	0.001 (0.000, 0.003)	0.003 (0.001, 0.013)	0	0
Versus placebo						
LS mean ratio (95% CI)	0.50 (0.22, 1.13)		0.18 (0.06, 0.56)		1.49 (0.43, 5.12)	
Duration of hospitalization visits, d						
Mean (SD)	0.05 (0.59)	0.18 (1.79)	0.06 (0.65)	0.29 (2.40)	0.04 (0.54)	0.08 (0.83)
Median (range)	0 (0, 9)	0 (0, 32)	0 (0, 9)	0 (0, 32)	0 (0, 9)	0 (0, 10)
Difference from placebo‖	–0.13		–0.23		–0.04	

95% CI of difference**	–0.22, –0.03		–0.39, –0.04		–0.11, 0.03	
Duration of ICU visits, days	0	0.07 (1.00)	0	0.10 (1.31)	0	0.032 (0.57)
Mean (SD)	0	0 (0–21)	0	0 (0-21)	0	0 (0, 10)
Median (range)	0 (0, 9)	0 (0, 32)				
Duration of non-ICU visits, d						
Mean (SD)	0.05 (0.59)	0.12 (1.48)	0.06 (0.65)	0.19 (2.20)	0.04 (0.54)	0.05 (0.61)
Median (range)	0 (0, 9)	0 (0, 32)	0 (0, 9)	0 (0, 32)	0 (0, 9)	0 (0, 9)

ICU, intensive care unit; LS, least squares.
*All participants who were randomly assigned to study intervention who took ≥1 dose of study intervention.
†High-risk participants were vaccinated with ≥1 risk factor for severe Covid-19.
‡Standard risk participants were vaccinated or unvaccinated with no risk factors for severe Covid-19.
§Medical visits included emergency room, practitioner's office, home healthcare services, urgent care, telephone consultation, outpatient infusion center, other.
|Based on bootstrap method with 100,000 replicates, each replicate is randomly selected (with replacement) from each subgroup of the analysis set.
**The probability that average days spent in hospital is greater in the nirmatrelvir/ritonavir 100 mg group. The two-sided p-value is 2 x the proportion.

Table S5. Treatment-Emergent Grade 3, 4, and 5 Adverse Events by System Organ Class and Preferred Term (All Causalities; Safety Analysis Population*)†

System Organ Class Preferred Term‡	Nirmatrelvir/ritonavir (N=654) n (%)			Placebo (N=634) n (%)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Participants with event(s)	18 (2.8)	6 (0.9)	0	19 (3.0)	6 (0.9)	1 (0.2)
Blood and lymphatic system disorders	1 (0.2)	1 (0.2)	0	0	0	0
Neutropenia	1 (0.2)	0	0	0	0	0
Thrombocytopenia	0	1 (0.2)	0	0	0	0
Gastrointestinal disorders	0	0	0	2 (0.3)	0	0
Nausea	0	0	0	1 (0.2)	0	0
Vomiting	0	0	0	1 (0.2)	0	0
Infections and infestations	5 (0.8)	0	0	7 (1.1)	3 (0.5)	1 (0.2)
Bronchitis	1 (0.2)	0	0	0	0	0
Covid-19	0	0	0	1 (0.2)	0	0
Covid-19 pneumonia	3 (0.5)	0	0	5 (0.8)	1 (0.2)	1 (0.2)
Pharyngitis	0	0	0	1 (0.2)	0	0
Pneumonia	1 (0.2)	0	0	0	2 (0.3)	0
Sepsis	0	0	0	0	1 (0.2)	0
Investigations	8 (1.2)	4 (0.6)	0	6 (0.9)	2 (0.3)	0
Alanine aminotransferase increased	2 (0.3)	1 (0.2)	0	0	0	0
Aspartate aminotransferase increased	2 (0.3)	0	0	0	0	0
Blood creatine phosphokinase increased	0	1 (0.2)	0	1 (0.2)	0	0
Blood creatinine increased	0	0	0	1 (0.2)	0	0
Blood fibrinogen decreased	1 (0.2)	0	0	0	0	0
Blood glucose increased	2 (0.3)	0	0	0	0	0
Blood potassium increased	1 (0.2)	0	0	0	0	0

Blood pressure increased	1 (0.2)	0	0	0	0	0
Creatinine renal clearance decreased	0	2 (0.3)	0	3 (0.5)	2 (0.3)	0
Glomerular filtration rate decreased	1 (0.2)	0	0	0	0	0
Hemoglobin decreased	0	0	0	2 (0.3)	0	0
Hepatic enzyme increased	1 (0.2)	0	0	0	0	0
Metabolism and nutrition disorders	3 (0.5)	1 (0.2)	0	3 (0.5)	1 (0.2)	0
Electrolyte imbalance	0	1 (0.2)	0	0	0	0
Hyperglycemia	1 (0.2)	0	0	1 (0.2)	0	0
Hyperkalemia	2 (0.3)	0	0	1 (0.2)	0	0
Hypocalcemia	0	0	0	0	1 (0.2)	0
Hyponatremia	0	1 (0.2)	0	0	0	0
Type 2 diabetes mellitus	1 (0.2)	0	0	1 (0.2)	0	0
Nervous system disorders	3 (0.5)	0	0	0	0	0
Dysgeusia	1 (0.2)	0	0	0	0	0
Osmotic demyelination syndrome	1 (0.2)	0	0	0	0	0
Presyncope	1 (0.2)	0	0	0	0	0
Respiratory, thoracic, and mediastinal disorders	1 (0.2)	0	0	0	0	0
Respiratory distress	1 (0.2)	0	0	0	0	0
Vascular disorders	0	0	0	2 (0.3)	0	0
Hemodynamic instability	0	0	0	1 (0.2)	0	0
Hypertension	0	0	0	1 (0.2)	0	0

Covid-19=coronavirus disease 2019; Nirmatrelvir/ritonavir=nirmatrelvir 300 mg + ritonavir 100 mg.
*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 v25.0 coding dictionary applied.

Table S6. Treatment-Related Treatment-Emergent Grade 3, 4, and 5 Adverse Events by System Organ Class and Preferred Term (Safety Analysis Population*)†

System Organ Class Preferred Term‡	Nirmatrelvir/ritonavir (N=654) n (%)			Placebo (N=634) n (%)		
	Grade 3	Grade 4	Grade 5	Grade 3	Grade 4	Grade 5
Participants with event(s)	2 (0.3)	1 (0.2)	0	2 (0.3)	0	0
Gastrointestinal disorders	0	0	0	1 (0.2)	0	0
Vomiting	0	0	0	1 (0.2)	0	0
Investigations	0	1 (0.2)	0	1 (0.2)	0	0
Alanine aminotransferase increased	0	1 (0.2)	0	0	0	0
Blood creatine phosphokinase increased	0	0	0	1 (0.2)	0	0
Nervous system disorders	2 (0.3)	0	0	0	0	0
Dysgeusia	1 (0.2)	0	0	0	0	0
Presyncope	1 (0.2)	0	0	0	0	0

Nirmatrelvir/ritonavir=nirmatrelvir 300 mg + ritonavir 100 mg.
*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 v25.0 coding dictionary applied.

Table S7. Treatment-Emergent Serious Adverse Events by System Organ Class and Preferred Term (All Causalities; Safety Analysis Population*)†

System Organ Class Preferred Term‡	Nirmatrelvir/ritonavir (N=654) n (%)	Placebo (N=634) n (%)
Participants with any serious adverse event	8 (1.2)	12 (1.9)
Infections and infestations	5 (0.8)	11 (1.7)
Covid-19	0	1 (0.2)
Covid-19 pneumonia	3 (0.5)	8 (1.3)
Pneumonia	1 (0.2)	2 (0.3)
Pneumonia aspiration	1 (0.2)	0
Sepsis	0	1 (0.2)
Investigations	1 (0.2)	1 (0.2)
Creatinine renal clearance decreased	0	1 (0.2)
Hepatic enzyme increased	1 (0.2)	0
Metabolism and nutrition disorders	1 (0.2)	0
Electrolyte imbalance	1 (0.2)	0
Neoplasms benign, malignant, and unspecified (including cysts and polyps)	1 (0.2)	0
Colon cancer metastatic	1 (0.2)	0
Nervous system disorders	1 (0.2)	0
Osmotic demyelination syndrome	1 (0.2)	0
Respiratory, thoracic, and mediastinal disorders	1 (0.2)	0
Respiratory distress	1 (0.2)	0

Covid-19=coronavirus disease 2019; Nirmatrelvir/ritonavir=nirmatrelvir 300 mg + ritonavir 100 mg.
*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 v25.0 coding dictionary applied.