

Supplementary Appendix

Supplement to: Anderson AS, Caubel P, Rusnak JM. Nirmatrelvir–ritonavir and viral load rebound in Covid-19. N Engl J Med. DOI: 10.1056/NEJMc2205944

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

Nirmatrelvir-Ritonavir and COVID-19 Viral Load Rebound

Annaliesa S. Anderson, Ph.D., Patrick Caubel, M.D., Ph.D., James M. Rusnak, M.D., Ph.D.

Supplementary Appendix

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1. List of investigators

The analysis was conducted based on the results of the EPIC-HR study reported by Hammond et al. (2022)¹. The list of the EPIC-HR study investigators is reported by Hammond et al. (2022)¹.

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	Torrance, CA, USA
Aguirre Rivero, Rafael	Centro de Investigacion Clinica Del Pacifico	Acapulco, Mexico
Akhan, Sila	Kocaeli University Medical Faculty, Infection Disease	Kocaeli, Turkey
Aksoy, Firdevs	Karadeniz Teknik Universitesi Farabi Hastanesi	Trabzon, Turkey
Al Barwani, Aalia	Trio Clinical Trials	Houston, TX, USA
Amishima, Masaru	National Hokkaido Medical Center	Sapporo, Hokkaido, Japan
Anderson, Duane	Excel Clinical Research	Las Vegas, NV, USA
Antonov, Chavdar	Multiprofile Hospital for Active Treatment - Sveti Nikolay Chudotvoretz	Lom, Bulgaria

Avihingsanon, Anchalee	Bangkok Centre Hotel	Bangrak, Bangkok, Thailand
	Chula Field Hospital	Pathum Wan District, Bangkok, Thailand
	Thai Red Cross Emerging Infectious Diseases Clinic	Pathumwan, Bangkok, Thailand
	HIV Netherlands Australia Thailand Research Collaboration, Thai Red Cross AIDS Research Center	Pathumwan, Bangkok, Thailand
Ayesu, Kwabena	Omega Research Orlando	Orlando, FL, USA
Ayyappath, Paramez	Lisie Hospital	Kochi, Kerala, India
Balik, Ismail	Ankara University Medical Faculty, Ibni-Sina Hospital	Ankara, Turkey
Barrat Hernandez, Alejandro	FAICIC Clinical Research	Veracruz, Veracruz, Mexico
Batista de Moura Xavier de Moraes, Joao	Hospital Agamenon Magalhaes	Recife, Brazil
Benitez, Omar	South Florida Research Center	Miami, FL, USA
Benitez, Wilfrido	Eastern Research	Hialeah, FL, USA
Berenfus, Vadym	Lviv City Clinic Hospital #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	Tsarevo, Bulgaria
Budhreja, Akshay	Aakash Healthcare	New Delhi, India
Buendía Magaña, Ruben	Eme Red Hospitalaria	Mérida, Yucatán, Mexico
Buendia Suárez, Isabel	Instituto de Investigaciones Clínicas para la Salud	Durango, Durango, Mexico
Cannon, Kevin	Accellacare	Wilmington, NC, USA
Capote, Eddy	Herco Medical and Research Center	Coral Gables, FL, USA
Chaudhari, Piyush	Jehangir Clinical Development Centre	Pune, Maharashtra, India
Chua, Hock Hin	Hospital Umum Sarawak	Kuching, Sarawak, Malaysia
Chusri, Sarunyou	Prince of Songkla University, Songklanagarind Hospital	Hat Yai, Songkhla, Thailand
Cortes, Anais	Inpatient Research Clinic	Hialeah, FL, USA
Crawford, Paul	Research by Design	Chicago, IL, USA
Curbelo Calleiro, Maria	Medimpact Clinical & Investigational Center	Miami, FL, USA
Czerech, Ewa	KLIMED Marek Klimkiewicz	Bialystok, Poland
Dange, Amol	Lifepoint Research	Pune, Maharashtra, India
De La Vega, Dagoberto	Unlimited Medical Research Group	Hialeah Gardens, FL, USA
Del Carpio Orantes, Luis	Sociedad de Metabolismo y Corazon	Veracruz, Veracruz, Mexico
Deno, Yohanna	CDC Research Institute	Port Saint Lucie, FL, USA

Desantis, Kimberly	Meridian Clinical Research	Endwell, NY, USA
Diaz, Jorge	Doral Medical Research	Hialeah, FL, USA
Dobрева, Vanya	DCC Sveti Georgi	Plovdiv, Bulgaria
Dombi, Attila	Trial Pharma Kft	Bekescsaba, Hungary
Drasnar, Tomas	Nemocnice Slany	Slany, Czech Republic
Duardo-Guerra, Yamirka	LCC Medical Research Institute	Miami, FL, USA
Dukes, Carl	Sun Research Institute	San Antonio, TX, USA
Fakih, Faisal	Clinical Site Partners	Winter Park, FL, USA
Fam, Tem Lom	Hospital Miri	Miri, Sarawak, Malaysia
Fatakia, Adil	Tandem Clinical Research GI	Marrero, LA, USA
Fernandez-Miro, Humberto	Global Health Clinical Trials	Miami, FL, USA
Flores Figueroa, Jose	JM Research	Cuernavaca, Morelos, Mexico
Fouche, Leon	Limpopo Clinical Research Initiative	Thabazimbi, South Africa
Galitz, Lawrence	GCP Research, Global Clinical Professionals	St. Petersburg, FL, USA
Galvez, Oscar	Qway Research	Hialeah, FL, USA
Garcia, Lazaro	Entrust Clinical Research	Miami, FL, USA
Gavrylov, Anatoliy	Kharkiv Regional Clinical Infectious Diseases Hospital	Kharkiv, Ukraine
Georgieva, Stela	Multiprofile Hospital for Active Treatment Targovishte	Targovishte, Bulgaria
Georgiev, Emil	Diagnostic-Consultative Center I Lom	Lom, Bulgaria
Giriappa, Balachandra	BGS Global Institute of Medical Sciences and Hospital	Bangalore, Karnataka, India
Gudzheva, Rumyana Gavrailova	Diagnostic-Consultative Center XXII - Sofia	Sofia, Bulgaria
Gunduz, Alper	Basaksehir Cam ve Sakura Sehir Hastanesi	Istanbul, Turkey
Gunluoglu, Gulsah	Istanbul Yedikule Gogus Hastaliklari	Istanbul, Turkey
Haracherova, Kameliya	Specialized Hospital for Active Treatment in Pulmonology and Phthisiology – Stara Zagora	Stara Zagora, Bulgaria
Harcza, Eleonora	Agria-Study Kft	Eger, Hungary
Haytova, Nezabravka	Specialized Hospital for Active Treatment of Pneumo-Phthisiatric Diseases - Vratsa	Vratsa, Bulgaria
Hernández Pichardo, Joselito	Asociacion Mexicana para la Investigacion Clinica A.C. (AMIC)	Pachuca de Soto, Hidalgo, Mexico
Hernandez, Humberto	Sunrise Research Institute	Sunrise, FL, USA
Hernandez, Manuel	Savin Medical Group	Miami Lakes, FL, USA
Hirai, Yuji	Tokyo Medical University Hachioji Medical Center	Hachioji, Tokyo, Japan
Hoosen, Farzana	Synapta Clinical Research Center	Durban, South Africa
Hristova, Iskra	Medical Center Leo Clinic	Varna, Bulgaria

Hristovski, Boyan	MHAT St. Sofia	Sofia, Bulgaria
Hussen, Nazreen	East Rand Research Centre T/A Worthwhile Clinical Trials	Benoni, South Africa
Igbinadolor, Awawu	Monroe Biomedical Research	Monroe, NC, USA
Inan, Dilara	Akdeniz Universitesi Hastanesi	Antalya, Turkey
Issa, Husam	Tranquility Research	Webster, TX, USA
Jain, Manish	Maharaja Agrasen Superspeciality Hospital	Jaipur, Rajasthan, India
Jeady, Wilner	Next Level Urgent Care	Houston, TX, USA
Jimenez, Mario	Kendall South Medical Center	Miami, FL, USA
Jindal, Atul	AIIMS Raipur	Raipur, Chhattisgarh, India
Kalfov, Veselin	Specialized Hospital for Active Treatment of Pneumo-Phthisiatric Diseases - Haskovo	Haskovo, Bulgaria
Kandemir, Fatma	Mersin University	Mersin, Turkey
Kang, Seung Ji	Chonnam National University Bitgoeul Hospital	Nam-gu, 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 #1 of Kyiv City Council	Kyiv, Ukraine
Khandelwal, Vipul	Apex Hospitals	Jaipur, Rajasthan, India
Kim, Jin Yong	Incheon Medical Center	Incheon, Republic of Korea
Kim, Kenneth	Ark Clinical Research	Long Beach, CA, USA
Kireieva, Tetiana	City Clinical Hospital #16 of Dnipro City Council	Dnipro, Ukraine
Kireyev, Igor	City Student Hospital of Kharkiv City Council	Kharkiv, Ukraine
Kirov, Mihail	Medical Centre Leo Clinic	Lovech, Bulgaria
Kobrynska, Olena	Central City Clinical Hospital of Ivano-Frankivsk City	Ivano-Frankivsk, Ukraine
Kochar, Sanjay	Sardar Patel Medical College	Pavan Puri Bikaner, Rajasthan, India
Kohli, Anita	Institute for Liver Health	Tucson, AZ, USA
Koksal, Iftihar	Acibadem University Atakent Hospital Infection Disease	Istanbul, Turkey
Kolar, Jan	Zdraví-Fit, s.r.o.	Protivín, Czech Republic
Komitov, Iliyan	Multiprofile Hospital for Active Treatment – Sliven to Military Medical Academy	Sliven, Bulgaria
Kosinski, Joseph	Premier Medical Group	Clarksville, TN, USA
Koval, Tetiana	Poltava Regional Clinical Infectious Diseases Hospital	Poltava, Ukraine
Kowalczyk, John	American Institute of Research	Los Angeles, CA, USA
Kozlov, Roman	Smolensk State Medical University	Smolensk, Russian Federation
Krainson, James and Rosenthal, Mark	Clinical Site Partners	Miami, FL, USA
Kutner, Mark	Suncoast Research Group	Miami, FL, USA

Kwon, Ki Tae	Kyungpook National University Chilgok Hospital	Daegu, Republic of Korea
Laningham, Robert	Conroe Willis Medical Research	Conroe, TX, USA
Logoida, Pavlo	Polyclinic of Center for Medical Services and Rehabilitation	Kyiv, Ukraine
Lopes, Suzara	Chronos Pesquisa Clinica	Brasilia, Brazil
Lopez Romo, Alicia	Christus - Latam Hub Center of Excellence and Innovation	Monterrey, Nuevo Leon,
Macias Torres, Pablo	Clinical Research Institute Saltillo	Saltillo, Coahuila, Mexico
Macias, Francisco	USPA Advance Concept Medical Research Group	South Miami, FL, USA
Maheshwari, Sanjiv	Jawahar Lal Nehru Medical College	Ajmer, Rajasthan, India
Marinova, Dora	UMHAT Medica Ruse	Ruse, Bulgaria
Marquez Diaz, Francisco	Hospital Cardiologica Aguascalientes	Aguascalientes, Aguascalientes, Mexico
Martin, Anna	Xera Med Research	Boca Raton, FL, USA
Martinez Rivera, Orvil	Advance Medical Research Center	San Juan, Puerto Rico, Puerto Rico
Martinez, Carlos and Casas, Julio	Beautiful Minds Clinical Research Center	Cutler Bay, FL, USA
Martinez, Cindy	Premium Medical Research	Miami, FL, USA
Martynenko, Tatiana	Barnaul City Hospital Number 5	Barnaul, Russian Federation
Mas, Luis	Advance Clinical Research Group	Cutler Bay, FL, USA
Mert, Ali	Medipol Mega University Hospital	Istanbul, Turkey
Metev, Hristo	Specialized Hospital for Active Treatment of Pneumo-Phthisiatric Diseases Dr. Dimitar Gramatikov - Ruse	Ruse, Bulgaria
Minova, Lyudmyla	Alexander Clinical Hospital	Kyiv, Ukraine
Mir Remedios, Ariel	C'A Research	Miami, FL, USA
Mitрева, Roza	Multiprofile Hospital for Active Treatment - Samokov	Samokov, Bulgaria
Mladenova-Todorova, Albena	Multiprofile Hospital For Active Treatment	Shumen, Bulgaria
Modia, Jigar	Jupiter Hospital	Vadodara, Gujarat, India
Mogashoa, Salphy	Botho ke Bontle Health Services	Pretoria, South Africa
Monlux, George	MOORE Clinical Research	Brandon, FL, USA
Mootsikapun, Piroon	Srinagarind Hospital, Khon Kaen University	Khon Kaen, Khon Kaen, Thailand
Moroz, Larysa	Vinnysia City Clinical Hospital No. 1	Vinnysia, Ukraine
Mussaji, Murtaza	LinQ Research	Pearland, TX, USA
Napora, Piotr	Centrum Badań Klinicznych Piotr Napora Lekarze Spółka Partnerska	Wroclaw, Poland
Narejos Perez, Silvia	EBA Centelles	Centelles, Barcelona, Spain
Navarro-Alvarez, Samuel	InfectoLab Consultorios de Especialidad en Infectologia	Baja California, Tijuana, Mexico

Nemechkin, Oleg	Multiprofile Hospital for Active Treatment Sveti Ivan Rilski	Razgrad, Bulgaria
Ohmagari, Norio	National Center for Global Health and Medicine	Shinjuku City, Tokyo, Japan
Oleynichenko, Ekaterina	LLC Trekhgorka Medicine	Odintsovo, Moscow, Russian Federation
Ortiz, Francisco	C & R Research Services USA	Houston, TX, USA
Panayotov, Plamen	Individual Practice for Primary Medical Care	Burgas, Bulgaria
Paoli-Bruno, Jorge	Coral Research Clinic	Miami, FL, USA
Papp, Albert	Trial Pharma	Gyula, Hungary
Parev, Atanas	St. Panteleimon Hospital	Plovdiv, Bulgaria
Parikh, Naval	NAPA Research	Pompano Beach, FL, USA
Park, Sang-Won	SMG-SNU 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
Peralta Lepe, Rogelio	Instituto Jalisciense de Metabolismo	Guadalajara, Jalisco, Mexico
Petkov, Petyo	MHAT Dr. Ivan Seliminski - Sliven	Sliven, Bulgaria
Petrick, Friedrich	MERC Middelburg	Middelburg, South Africa
Pineiro, Yanelly	Angels Clinical Research Institute	Miami, FL, USA
Polat, Gulru	Izmir Suat Seren Chest Disease and Surgery Training and Research Hospital	izmir, Turkey
Pryshlyak, Oleksandra	Ivano-Frankivsk Regional Clinical Infectious Diseases Hospital	Ivano-Frankivsk, Ukraine
Pullman, John	Mercury Street Medical Group	Butte, MT, USA
Ramirez Hernandez, Amado	Arke SMO	Veracruz, Veracruz, Mexico
Ramirez, Ariel	Reed Medical Research	Miami, FL, USA
Reyes, Ramon	BFHC Research	San Antonio, TX, USA
Rivera Martínez, Norma	Oaxaca Site Management Organization	Oaxaca De Juarez, Oaxaca, Mexico
Sachdeva, Yessica	Institute for Liver Health	Mesa, AZ, USA
Sahu, Badal	Nil Ratan Sircar Medical College and Hospital	Kolkata, West Bengal, India
Saiger, Salma	SMS Clinical Research	Mesquite, TX, USA
Samoilova, Svitlana	Kyiv Railway Clinical Hospital No.2	Kyiv, Ukraine
Sanchez Salazar, Sergio	Eukarya Pharmasite	Monterrey, Nuevo Leon, Mexico
Sanchez Vallejo, Gregorio	Fundacion Cardiomet CEQUIN	Armenia, Colombia

Schneider, Linda	TPMG (Tidewater Physicians Multispecialty Group) Clinical Research	Newport News, VA, USA
Siegel, Amy	ARC Clinical Research at William Cannon	Austin, TX, USA
Simon Campos, Jesus	Kohler & Milstein Research	Merida, Yucatan, Mexico
Simova, Iana	MHAT Heart and Brain	Pleven, Bulgaria
Sims, James	St Hope Foundation	Bellaire, TX, USA
Simsek-Yavuz, Serap	Istanbul University	Istanbul, Turkey
Skolnick, Alan	SignatureCare Emergency Center	Houston, TX, USA
Sosa-Faria, Javier	Clinical Research Management Group	Ponce, Puerto Rico, Puerto Rico
Sousa Regueiro, Maria Dolores	Complejo Hospitalario Universitario da Coruna	A Coruña, Spain
Suarez, Rosa	ProLive Medical Research	Miami, FL, USA
Tabak, Omer	Istanbul University Cerrahpasa	Istanbul, Turkey
Tiholov, Rumen	MHAT Sv.Ivan Rilski - Kozloduy	Kozloduy, Bulgaria
Tokunaga, Paula	Centro de Estudos Clinicos do Interior Paulista (CECIP)	Jau, São Paulo, Brazil
Tomaev, Uruzmag	KDC (Evromedservis), OJSC	Moscow, Russian Federation
Tomas, Juan	Hospital De Clínicas Presidente Dr.Nicolas Avellaneda	San Miguel de Tucuman, Tucuman, Argentina
Trevino, Miguel	Innovative Research of West Florida	Clearwater, FL, USA
Tsushima, Kenji	International University of Health and Welfare Narita Hospital	Narita, Chiba, Japan
Ünal, Serhat	Hacettepe University Medical Faculty Hospital	Ankara, Turkey
Vahed, Yacoob	MERC Welkom	Welkom, South Africa
Varkonyi, Istvan	Debreceni Egyetem Klinikai Kozpont Infektologiai Klinika	Debrecen, Hungary
Vasylyev, Marta	Regional Information and Analytical Center of Medical Statistics,	Lviv, Ukraine
Vico, Marisa	Instituto de Investigaciones Clinicas Zarate	Zarate, Buenos Aires, Argentina
Victoria, Rafaelito	Atella Clinical Research	La Palma, CA, USA
Vyshnyvetsky, Ivan	Hospital #1 of Zhytomyr City Council	Zhytomyr, Ukraine
Warshoff, Neal	Advanced Pulmonary Research Institute	Loxahatchee, FL, USA
Wever, David	Cahaba Research	Pelham, AL, USA
Winnie, Michael	South Texas Clinical Research	Corpus Christi, TX, USA
Yakovenko, Oleh	Volyn Regional Clinical Hospital #2	Volyn, Ukraine
Yamato, Masaya	Rinku General Medical Center	Izumisano, Osaka, Japan
Zilahi, Zsolt	Medifarma-98	Nyiregyhaza, Hungary

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

2. Detection and quantification of SARS-CoV-2 viral load

As measured by the Abbott Real-Time (rt) Quantitative SARS-CoV-2 assay, a reverse transcriptase polymerase chain reaction (PCR) test utilizing reagents and equivalent application specifications of the Abbott rt SARS-CoV-2 Qualitative Emergency Use Authorization assay, modified in collaboration with Abbott Molecular, to quantitate SARS-CoV-2 nucleic acid in nasopharyngeal, oropharyngeal and nasal swab samples.

3. Tables

Table S1. EPIC-HR Swab collection site by treatment and visit. From ref.²

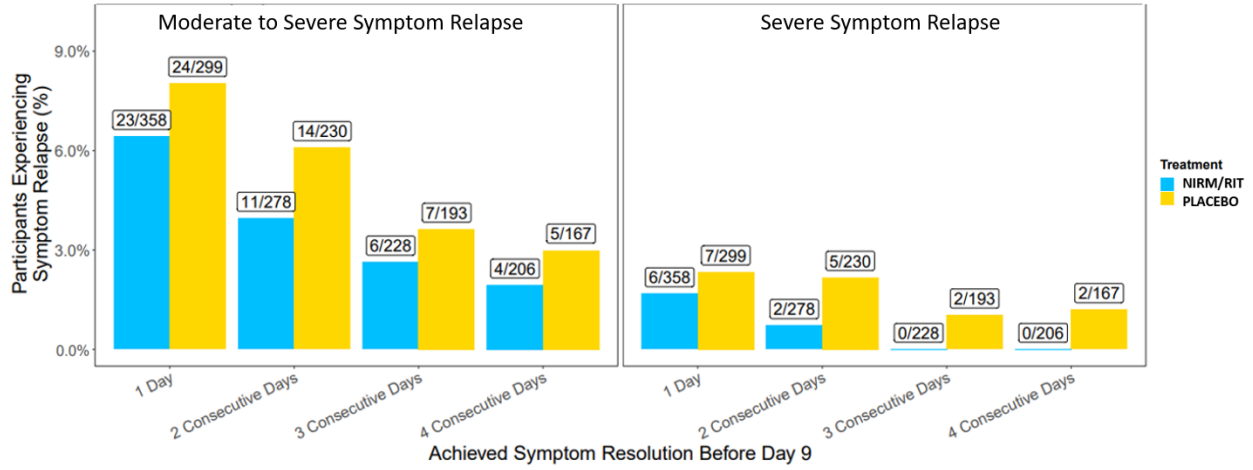
TREATMENT ARMS	A VISIT	NASOPHARYNX	NOSTRIL	MISSING
PLACEBO	Baseline	1086 (N=1086; 100%)	0 (N=1086; 100%)	0 (N=1086; 0%)
Nirmatrelvir 300 mg + Ritonavir 100 mg	Baseline	1078 (N=1080; 99.8%)	2 (N=1080; 0.2%)	0 (N=1080; 0%)
PLACEBO	Day 3	995 (N=1040; 95.7%)	45 (N=1040; 4.3%)	0 (N=1040; 0%)
Nirmatrelvir 300 mg + Ritonavir 100 mg	Day 3	983 (N=1038; 94.7%)	54 (N=1038; 5.2%)	1 (N=1038; 0.1%)
PLACEBO	Day 5	997 (N=1001; 99.6%)	4 (N=1001; 0.4%)	0 (N=1001; 0%)
Nirmatrelvir 300 mg + Ritonavir 100 mg	Day 5	995 (N=1002; 99.3%)	5 (N=1002; 0.5%)	2 (N=1002; 0.2%)
PLACEBO	Day 10	870 (N=962; 90.4%)	92 (N=962; 9.6%)	0 (N=962; 0%)
Nirmatrelvir 300 mg + Ritonavir 100 mg	Day 10	888 (N=989; 89.8%)	100 (N=989; 10.1%)	1 (N=989; 0.1%)
PLACEBO	Day 14	930 (N=1006; 92.4%)	76 (N=1006; 7.6%)	0 (N=1006; 0%)
Nirmatrelvir 300 mg + Ritonavir 100 mg	Day 14	928 (N=1009; 92%)	81 (N=1009; 8%)	0 (N=1009; 0%)

Table S2. Viral load log₁₀ transformed means (SD, n) and median (range). Total EPIC-HR mITT2 population: Nirmatrelvir-Ritonavir N=1109, Placebo N=1115. VLR sub-study population: Nirmatrelvir-Ritonavir N=990, Placebo N=980. Population for VLR sub-study utilized participants with matched Day 5, Day 10 and/or Day 14 samples.					
Visit Day	EPIC-HR mITT2 total population Mean (SD, n)	EPIC-HR mITT2 total population Median (Range)	VLR Subset Mean (SD, n)	VLR Subset Median (Range)	VLR Subset Proportion
Baseline					
Nirmatrelvir-Ritonavir	5.681 (2.100, 873)	5.990 (1.700, 9.160)	5.210 (2.555, 22)	5.840 (0.000, 8.460)	
Placebo	5.522 (2.168, 888)	5.910 (1.700, 9.150)	4.801 (2.260, 17)	5.190 (0.000, 7.860)	
Day 3					
Nirmatrelvir-Ritonavir	3.891 (2.169, 821)	4.030 (0.000, 8.570)	4.117 (2.294, 22)	3.880 (0.000, 8.550)	
Placebo	4.315 (2.390, 829)	4.660 (0.000, 9.540)	4.362 (2.458, 17)	5.240 (0.000, 7.500)	
Day 5					
Nirmatrelvir-Ritonavir	2.697 (1.835, 789)	2.690 (0.000, 7.820)	2.380 (1.783, 23)	2.120 (0.000, 5.760)	
Placebo	3.314 (2.263, 792)	3.125 (0.000, 8.700)	2.439 (1.731, 17)	2.420 (0.000, 5.030)	
Day 10					
Nirmatrelvir-Ritonavir	1.419 (1.592, 782)	1.700 (0.000, 7.340)	2.173 (2.042, 22)	1.700 (0.000, 6.610)	
Placebo	1.697 (1.740, 760)	1.700 (0.000, 7.630)	2.911 (2.223, 16)	3.285 (0.000, 7.170)	
Day 14					
Nirmatrelvir-Ritonavir	0.884 (1.258, 794)	0.000 (0.000, 8.090)	4.750 (1.496, 20)	4.505 (2.950, 8.090)	
Placebo	0.970 (1.302, 800)	0.000 (0.000, 6.540)	4.626 (1.453, 14)	4.685 (2.740, 7.020)	
Proportion of Present and Persistent VLR*					
Nirmatrelvir-Ritonavir					2.32% (23/990)
Placebo					1.73% (17/980)

*Statistical VLR definition: If Day 14 viral load was not available, Day 10 viral load change from Day 5 $\geq 0.5 \log_{10}$ copies/mL and Day 10 viral load $\geq 2.7 \log_{10}$ copies/mL, or If Day 14 viral load is available, Day 14 viral load change from Day 5 $\geq 0.5 \log_{10}$ copies/mL and Day 14 viral load $\geq 2.7 \log_{10}$ copies/mL.
Abbreviations: EPIC-HR, Evaluation of Protease Inhibition for COVID-19 in High-Risk Patients; mITT2, modified intention-to treat population; SD, standard deviation; VLR, viral load rebound.

4. Figures

A)



B)

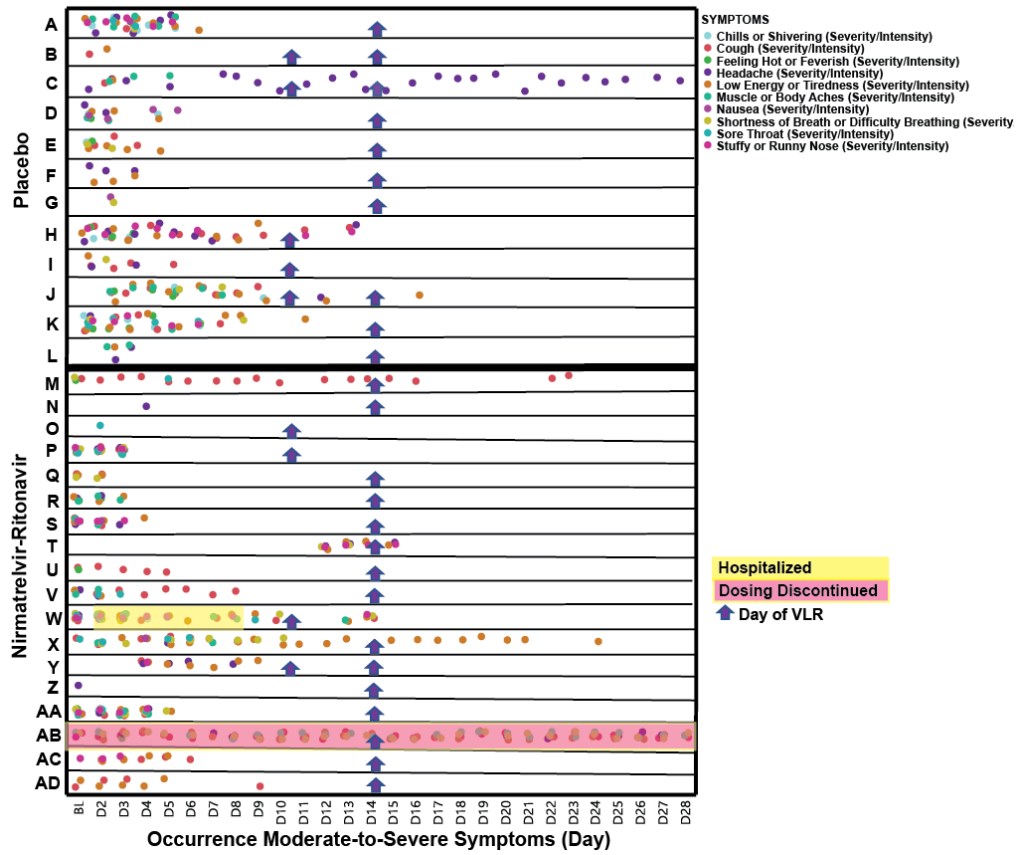


Figure S1. VLR is not associated with recurrence of severe disease. A) Participants on nirmatrelvir-ritonavir who achieved 3-4 consecutive days of symptom relief showed lower relapse during D8-D28 (0%) compared to placebo (1%). B) Individual moderate-severe symptoms in present and/or persistent VLR over 28 days. From ref.².

5. References

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2. Soares H, Baniecki ML, Cardin R, et al. Viral Load Rebound in Placebo and Nirmatrelvir-Ritonavir Treated COVID-19 Patients is not Associated with Recurrence of Severe Disease or Mutations. June 3, 2022 (<https://assets.researchsquare.com/files/rs-1720472/v1/d05313db-c500-4486-a678-2dd8c2423d3f.pdf>). preprint.