Supplemental materials

Nirmatrelvir/Ritonavir Regimen for Mild/Moderately Severe COVID-19: A Rapid Review With Meta-Analysis and Trial Sequential Analysis

George N. Okoli, MD, PhD[1,2]

Nicole Askin, MLIS[3]

Rasheda Rabbani, PhD[1]

[1]George and Fay Yee Centre for Healthcare Innovation, Max Rady College of Medicine, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada

[2]College of Pharmacy, Rady Faculty of Health Sciences, University of Manitoba, Winnipeg, Manitoba, Canada

[3]Neil John Maclean Health Sciences Library, University of Manitoba, Winnipeg, Manitoba, Canada

Supplemental Appendix. Search strategy for Ovid MEDLINE® and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations and Daily <January 2022 to May 23, 2023>

1	exp Coronavirus/ or Coronavirus Infections/ or exp COVID-19/ or exp COVID-19 testing/ or exp COVID-19 vaccines/ or COVID-19 Drug Treatment/	245983
2	(coronavir* or corona vir* or betacorona* or OC43 or NL63 or D614G or 229E or HKU1 or hcov* or ncov* or covid* or sarscov* or sars cov* or sarscoronavir* or sars coronavir* or 2019ncov* or 19ncov* or novel cov* or 2019novel cov* or longcovid* or postcovid* or postcoronavir* or postsars*).mp.	379005
3	(COVID-19 or SARS-CoV-2).rx,px,ox,rn.	16123
4	(COVID-19 or COVID-19 serotherapy or ORF7b protein, SARS-CoV-2 or ORF6 protein, SARS-CoV-2 or ORF8 protein, SARS-CoV-2 or pediatric multisystem inflammatory disease, COVID-19 related or envelope protein, SARS-CoV-2 or ORF7a protein, SARS-CoV-2 or spike protein, SARS-CoV-2 or ORF3a protein, SARS-CoV-2 or severe acute respiratory syndrome coronavirus 2 or membrane protein, SARS-CoV-2 or ORF1ab polyprotein, SARS-CoV-2 or nucleocapsid protein, Coronavirus or COVID-19 vaccine).os,ps,rn,rs.	26356
5	(variant* adj2 (alpha or beta or delta or gamma or kappa or lambda or mu or omicron or "b.1.1.7" or "b.1.351" or "p.1" or "b.1.617.2" or "b.1.1.529" or "c.37" or "b.1.621" or india or indian or south africa* or uk or british or english or brazil*)).mp.	12134
6	or/1-5	385139
7	(paxlovid or pf07321332 or "pf 07321332" or nirmatrelvir* or ritonavir plus pf* or ritnonavirpf* or ritonavirnirmatrelvir).mp.	720
8	exp clinical trial/ or exp "clinical trials as topic"/ or random allocation/ or single-blind method/ or double-blind method/ or placebos/ or control groups/	1375654
9	(random* or rct* or blind* or placebo* or trial* or control or controlled).ti,ab.	5219498
10	8 or 9	5645684
11	6 and 7 and 10	157
12	limit 11 to (english language and yr="2022 -Current")	149

Supplemental Table 1. Additional Characteristics of the Included RCTs

Study	Inclusion	Swab type	No. intervention	No. comparator
Balykova 2022	18 to 80 years old, a positive laboratory test for the presence of SARS-CoV-2 RNA using nucleic acid amplification methods (NAAT) or SARS-CoV-2 antigen using an immunochromatographic analysis, mild or moderate infection caused by SARSCoV-2 with at least one of the following symptoms characteristic of COVID-19: nasal congestion or a running nose, a sore throat, shortness of breath on exertion, cough, fatigue, muscle or body pain, headache pain, chills, fever (body temperature >38°C), nausea, vomiting, diarrhoea, loss of smell (anosmia), loss of taste sensation (ageusia), onset of the disease (appearance of the first symptom) no more than 5 days before randomization, patient is willing and able to take oral medications, patient's consent to use reliable methods of contraception throughout the study and for 3 weeks after the end of the study	Nasopharynx and/or oropharynx	132	132
Hammond 2022	≥18 years with confirmed SARS-CoV-2 infection by reverse-transcriptase–polymerase-chain-reaction assay and symptom onset no more than 5 days before randomization, with at least one sign or symptom of Covid-19 on the day of randomization and to have at least one characteristic or coexisting condition associated with high risk of progression to severe Covid-19	Nasopharyngeal or nasal	1120	1126
Liu 2023	18 to 90 years old, had severe comorbidities, confirmed SARSCoV-2 infection by positive of real-time polymerase-chain-reaction within the previous 48 hours, duration from symptoms onset to hospital admission less than 5 days or the SARS-CoV-2 nucleic acid Ct value ≤ 25 by reverse-transcriptase–polymerase-chain-reaction	Nasopharyngeal	132	132
*EPIC-SR [Double-blinded] (NCT05011513)	≥18 years with confirmed SARS-CoV-2 infection by reverse-transcriptase–polymerase-chain-reaction assay and symptom onset no more than 5 days before randomization, and if fertile, must agree to use a highly effective method of contraception	Nasopharyngeal or nasal	658	638

*= Unpublished data (available online, but have not been peer-reviewed)
EPIC-SR = Evaluation of Protease Inhibition for COVID-19 in Standard-Risk Patients

Supplemental Table 2. Risk of Bias Assessment for the Included Randomized Controlled Trials

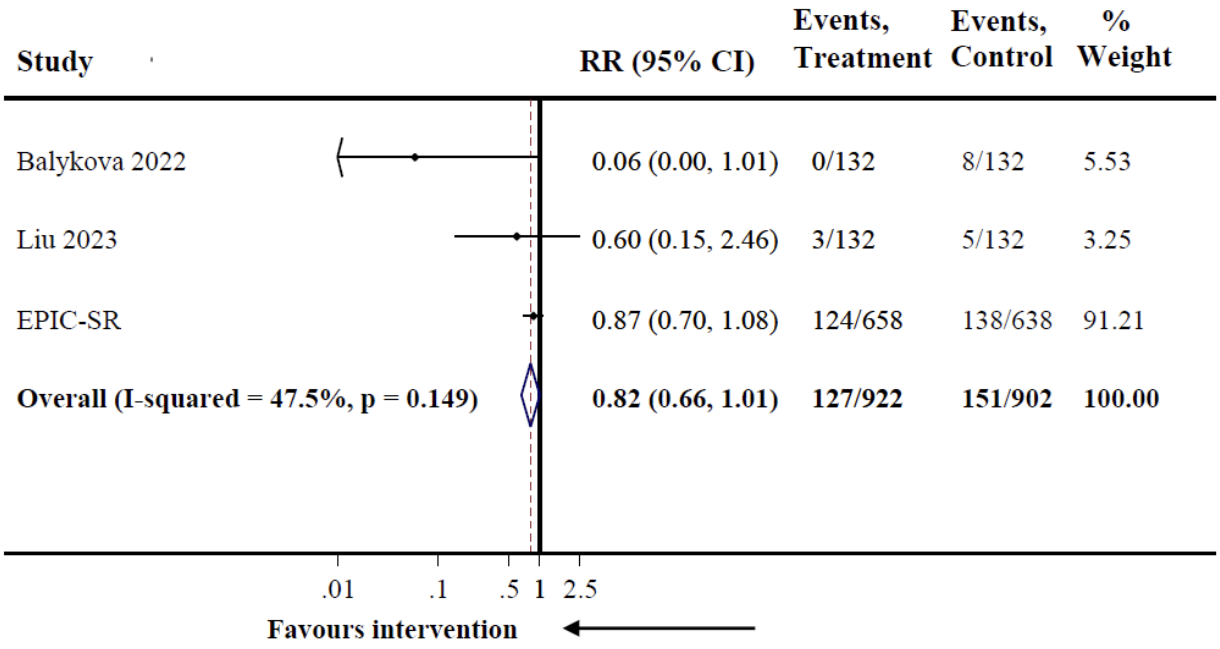
Article	Comparisons	Randomisation process	Deviations from the intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported result	Overall assessment			
Balykova 2022	Nirmatrelvir 300 mg and ritonavir 100 mg over 5 days versus no treatment	+	!	+	!	+	!		+	**Low risk**
Hammond 2022	Nirmatrelvir 300 mg and ritonavir 100 mg over 5 days versus placebo	+	+	!	+	+	!		!	**Some concerns**
Liu 2023	Nirmatrelvir 300 mg and ritonavir 100 mg over 5 days versus no treatment	+	!	+	+	+	!		-	**High risk**
EPIC-SR	Nirmatrelvir 300 mg and ritonavir 100 mg over 5 days versus placebo	+	+	+	+	+	+			

EPIC-SR = Evaluation of Protease Inhibition for COVID-19 in Standard-Risk Patients

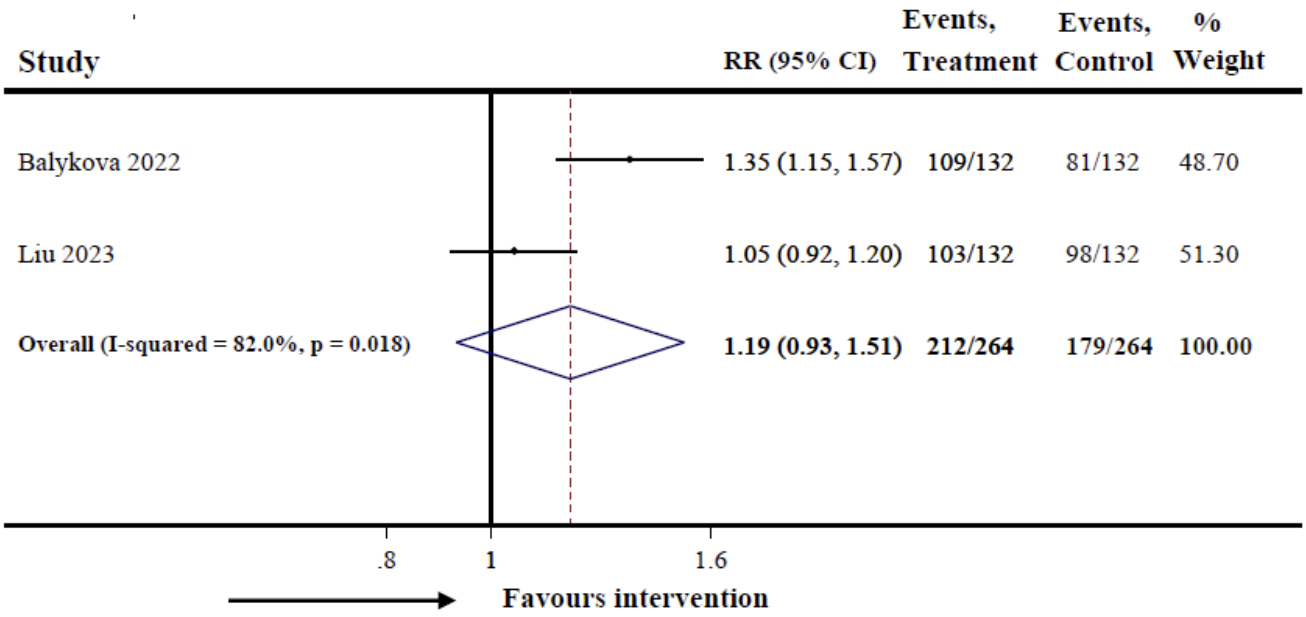
Supplemental Table 3. Study Quality Assessment for the Included Real-World Studies

Study	Research question/objective stated	Study population clearly specified/defined	Participation rate of eligible persons ≥50%	Subjects recruited from the same/similar populations	Sample size justification or testing	Exposures measured prior to the outcomes	Sufficient timeframe for measured association	Measured different levels of the exposure	Clearly defined exposure measures	Exposures assessed more than once over time	Clearly defined outcome measures	Outcome assessors blinded to exposure status	Loss of participants due to missing data ≤20%	Key potential confounders measured/adjusted
Aggarwal 2023	Yes	Yes	NA	Yes	No	NA	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes
Al-Obaidi 2023	Yes	Yes	NA	Yes	No	NA	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes
Bajema 2022	Yes	Yes	NA	Yes	No	NA	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes
Bhatia 2023	Yes	Yes	NA	Yes	No	NA	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes
Dryden-Peterson 2022	Yes	Yes	NA	Yes	No	NA	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes
Ganatra 2022	Yes	Yes	NA	Yes	No	NA	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes
Lewnard 2023	Yes	Yes	NA	Yes	No	NA	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes
Najjar-Debbiny 2023	Yes	Yes	NA	Yes	No	NA	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes
Paraskevis 2023	Yes	Yes	NA	Yes	No	NA	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes
Park 2022	Yes	Yes	NA	Yes	No	NA	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes
Schwartz 2023	Yes	Yes	NA	Yes	No	NA	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes
Shah 2023	Yes	Yes	NA	Yes	No	NA	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes
Wai 2023	Yes	Yes	NA	Yes	No	NA	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes
Wong 2022	Yes	Yes	NA	Yes	No	NA	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes
Yip 2022	Yes	Yes	NA	Yes	No	NA	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes
Zhou 2022	Yes	Yes	NA	Yes	No	NA	Yes	Yes	Yes	NA	Yes	NA	Yes	Yes

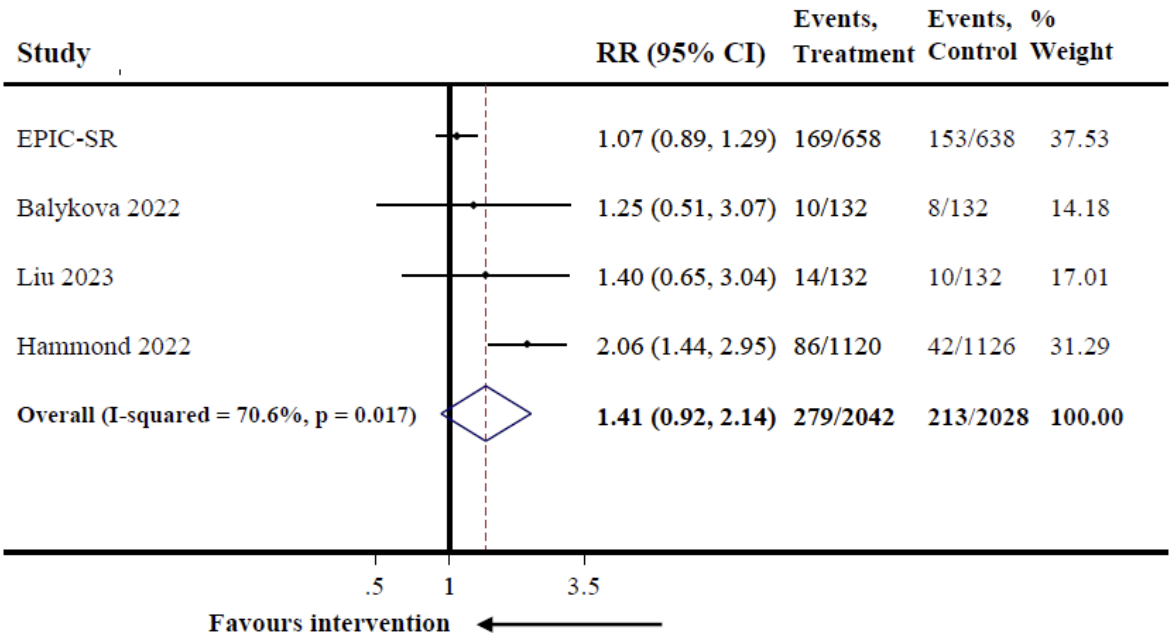
Supplemental Figure 1. Forest plot of nirmatrelvir/ritonavir versus no treatment/placebo for reducing worsening severity among adults with laboratory-confirmed mild/moderately severe COVID-19 (RCTs).



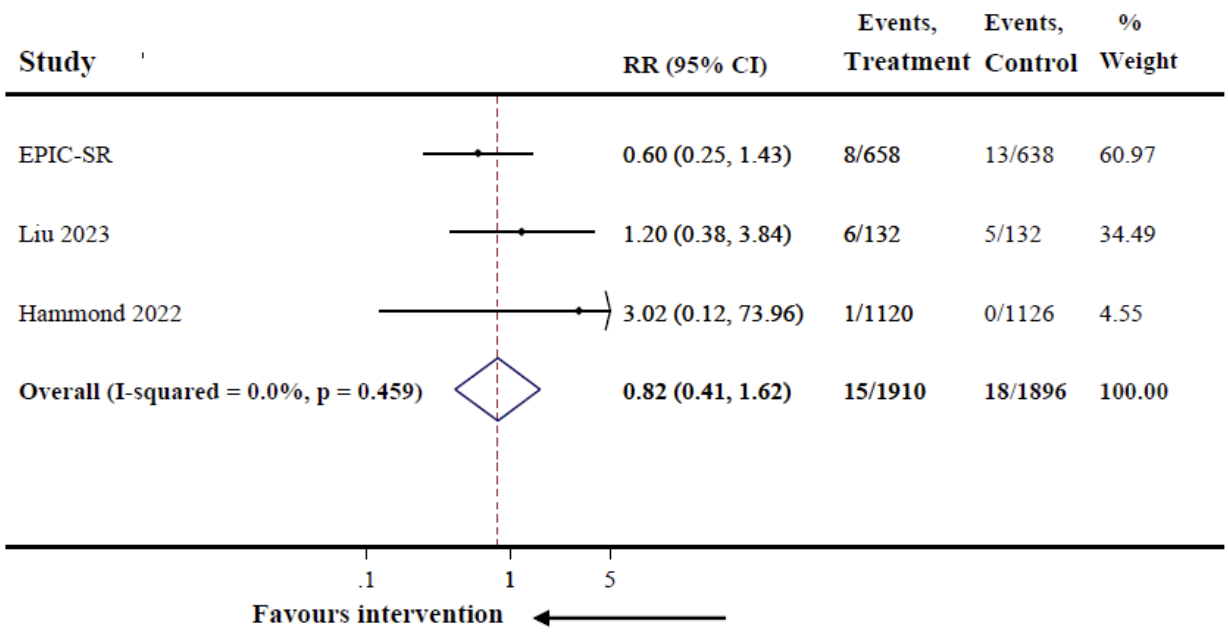
Supplemental Figure 2. Forest plot of nirmatrelvir/ritonavir versus no treatment/placebo for viral clearance among adults with laboratory-confirmed mild/moderately severe COVID-19 (RCTs).



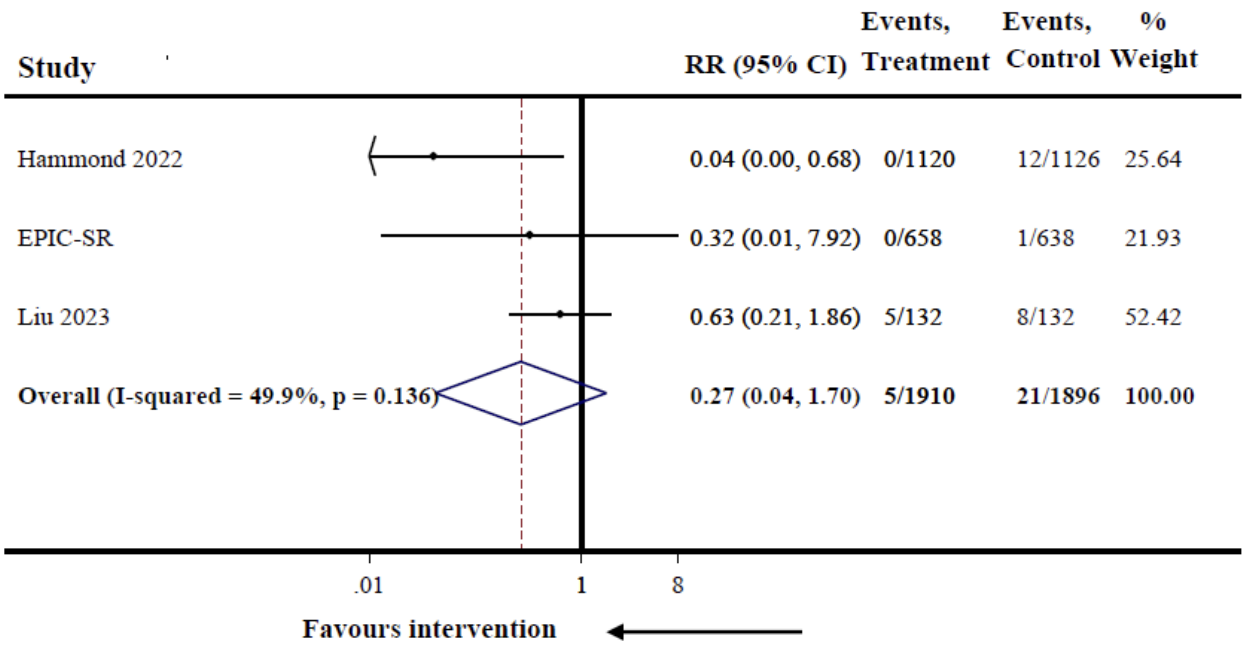
Supplemental Figure 3. Forest plot of nirmatrelvir/ritonavir versus no treatment/placebo for adverse events among adults with laboratory-confirmed mild/moderately severe COVID-19 (RCT



Supplemental Figure 4. Forest plot of nirmatrelvir/ritonavir versus no treatment/placebo for serious adverse events among adults with laboratory-confirmed mild/moderately severe COVID-19 (RCTs).



Supplemental Figure 5. Forest plot of nirmatrelvir/ritonavir versus no treatment/placebo against all-cause mortality among adults with laboratory-confirmed mild/moderately severe COVID-19 (RCTs).

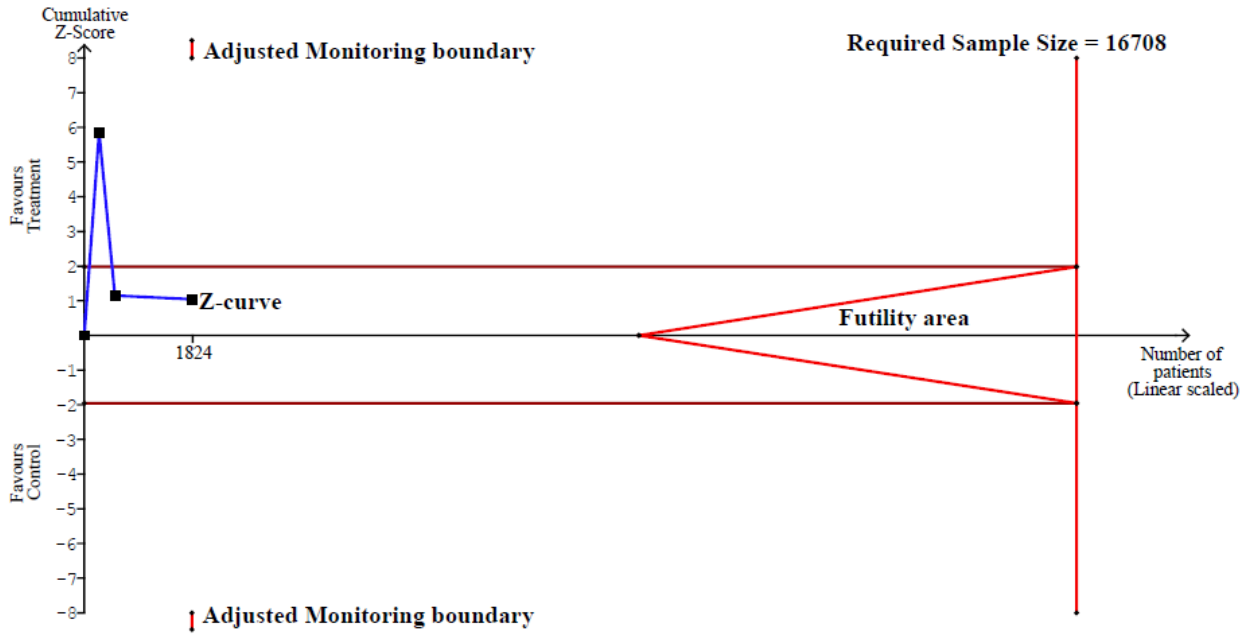


Supplemental Table 4. Grading of the Evidence for the Outcomes From Randomised Controlled Trials (RCTs)

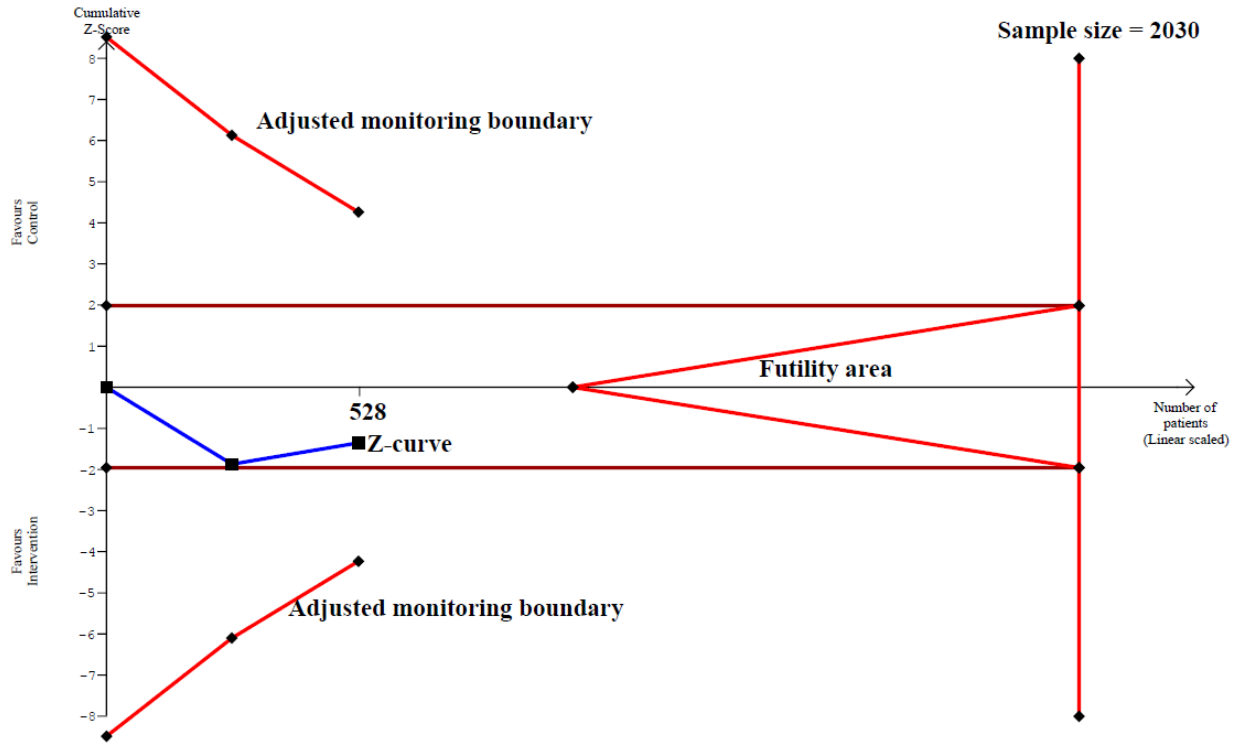
Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Nirmatrelvir/ ritonavir	No treatment or placebo	Relative (95% CI)	Absolute (95% CI)		
Hospitalisation												
2	RCTs	Not serious	Serious[b]	Not serious	Not serious	None	13/1,778 (0.7%)	75/1,764 (4.2%)	**RR 0.17** (0.10 to 0.31)	-	Moderate	Critical
Viral clearance												
2	RCTs	Serious[a]	Serious[b]	Not serious	Not serious	None	212/264 (80.3%)	179/264 (67.8%)	**RR 1.19** (0.93 to 1.51)	-	Low	Critical
Worsening severity												
3	RCTs	Serious[a]	Not serious	Not serious	Not serious	None	127/922 (13.8%)	151/902 (16.7%)	**RR 0.82** (0.66 to 1.01)	-	Moderate	Critical
Any adverse events												
4	RCTs	Serious[a]	Serious[b]	Not serious	Not serious	None	279/2,042 (13.7%)	213/2,028 (10.5%)	**RR 1.41** (0.92 to 2.14)	-	Low	Important
Serious adverse events												
3	RCTs	Serious[a]	Not serious	Not serious	Not serious	None	15/1,910 (0.8%)	18/1,896 (0.95%)	**RR 0.82** (0.41 to 1.62)	-	Moderate	Critical
All-cause mortality												
3	RCTs	Serious[a]	Not serious	Not serious	Not serious	None	5/1,910 (0.3%)	21/1,896 (1.1%)	**RR 0.27** (0.04 to 1.70)	-	Moderate	Important

RR: relative risk**; CI:** confidence interval; **a** = due to an unclear risk of bias; **b** = due to a high heterogeneity

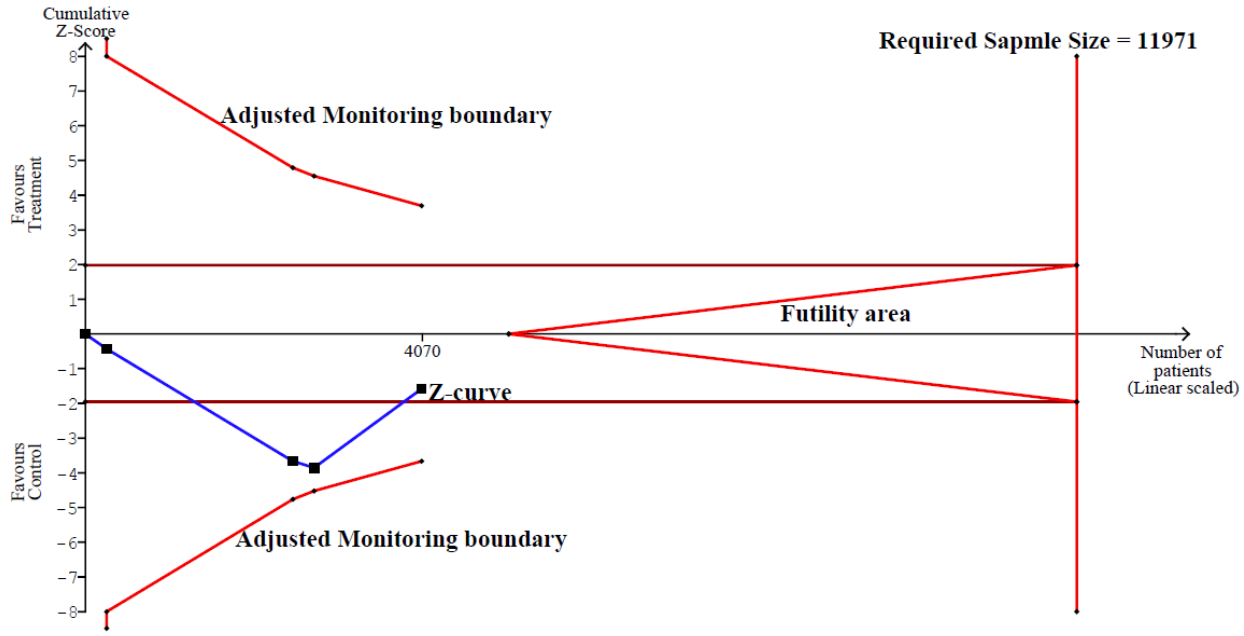
Supplemental Figure 6. Trial sequential analysis of nirmatrelvir/ritonavir versus no treatment/placebo for worsening COVID-19 severity in adults with laboratory-confirmed mild/moderately severe COVID-19 (RCTs).



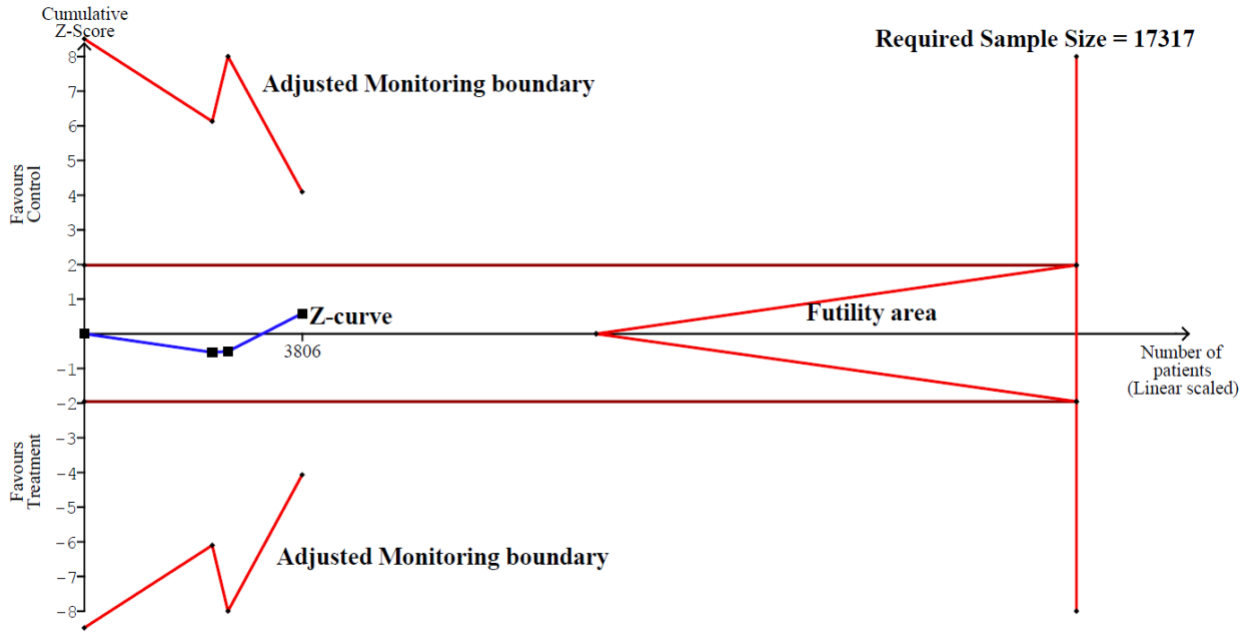
Supplemental Figure 7. Trial sequential analysis of nirmatrelvir/ritonavir versus no treatment/placebo for viral clearance in adults with laboratory-confirmed mild/moderately severe COVID-19 (RCTs).



Supplemental Figure 8. Trial sequential analysis of nirmatrelvir/ritonavir versus no treatment/placebo for adverse events in adults with laboratory-confirmed mild/moderately severe COVID-19 (RCTs).



Supplemental Figure 9. Trial sequential analysis of nirmatrelvir/ritonavir versus no treatment/placebo for serious adverse events in adults with laboratory-confirmed mild/moderately severe COVID-19 (RCTs).



Supplemental Figure 10. Trial sequential analysis of nirmatrelvir/ritonavir versus no treatment/placebo for reducing all-cause mortality in adults with laboratory-confirmed mild/moderately severe COVID-19 (RCTs).