Supplementary Table 1. Target trial specification and emulation using observational data

Protocol component	Specification	Emulation using observational data
Eligible criteria	Age ≥ 18 years, who received oral antiviral treatment within 5 days of a COVID-19 infection, during inclusion period[1] Excluded patients who: - had a history of COVID-19 infection before index date - with contraindications to nirmatrelvir-ritonavir or molnupiravir[2] The index date was defined as the date of nirmatrelvir-ritonavir or molnupiravir prescription.	Same as for specification. Date of COVID-19 infection was ascertained by the date of first positive polymerase chain reaction or rapid antigen test result during the inclusion period. Patients were considered non-hospitalised when they were not hospitalised on or before the index date. Patients were considered hospitalised when they were admitted to hospital within 5 days before or on index date. Those who had a prescription of both nirmatrelvir-ritonavir or molnupiravir during the study period were excluded.
Treatment strategy	Initiated molnupiravir *versus* Initiated nirmatrelvir-ritonavir Patients were expected to complete one full course of molnupiravir or nirmatrelvir-ritonavir according to the regimen approved by U.S. Food and Drug Administration, unless clinical conditions prevented them from completing the treatment (e.g. oral intake no longer possible, severe adverse effects). Physicians were allowed to prescribe other concomitant treatments (e.g. steroids) as clinically indicated for patients in both treatment groups.	Same as for specification. It was assumed that once the patient initiated COVID-19 antiviral therapy, he or she had completed the full course of COVID-19 antiviral.
Treatment assignment	Individuals were randomly assigned to a treatment strategy at baseline and were aware of the treatment strategy they were assigned to.	Randomisation of treatment assignment were emulated by propensity score matching.
Outcomes	All-cause mortality (28-day) Intensive unit care admission or ventilatory support (28-day) Hospitalisation (28-day)	Same as for specification.
Follow-up	From baseline until the earliest of occurrence of outcomes, 28 days after baseline.	Same as for specification.
Statistical analysis	Intention-to-treat analysis	Interaction effects of treatment with baseline age, gender, vaccination status at baseline, and Charlson Comorbidity Index were tested.

[1]Inclusion period commenced from 16 March 2022 (when both nirmatrelvir-ritonavir and molnupiravir became available in Hong Kong) to 31 December 2022 (to allow 28 days of follow-up)

[2]Patients with contraindications to nirmatrelvir-ritonavir include severe liver impairment (cirrhosis, hepatocellular carcinoma, or liver transplant), chronic kidney disease, and use of interacting drugs (i·e·, amiodarone, apalutamide, rifampicin, rifapentine, carbamazepine, primidone, phenobarbital, or phenytoin, direct oral anticoagulants) within 90 days before index date[3,4]

References

1. HKSAR Government. LCQ7: Introduction of new drugs for treating Coronavirus Disease 2019. 2022. https://www.info.gov.hk/gia/general/202202/23/P2022022300303.htm (accessed 16 June 2023).
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3. U.S. Food & Drug Administration. Fact Sheet For Healthcare Providers: Emergency Use Authorization For Paxlovid. 2023. https://www.fda.gov/media/155050/download (accessed 16 June 2023).
4. U·S· Food & Drug Administration. Fact Sheet for Healthcare Providers: Emergency Use Authorization for Lagevrio (molnupiravir) Capsules. 2023. https://www.fda.gov/media/155054/download (accessed 16 June 2023).

Supplementary Table 2. Baseline characteristics of COVID-19 patients before one-to-one propensity score matching

Characteristics	Non-hospitalised (N = 129,345)			Hospitalised (N = 18,962)		
	Nirmatrelvir-ritonavir (N = 96,758)	Molnupiravir (N = 32,587)	SMD†	Nirmatrelvir-ritonavir (N = 12,793)	Molnupiravir (N = 6,169)	SMD†
Age, year - mean (SD)	63·73 (14·3)	70·97 (14·1)	0·509	73·44 (15·12)	75·85 (15·78)	0·156
Sex, Male (%)	41,190 (42·6)	15,591 (47·8)	0·106	6,590 (51·5)	3,088 (50·1)	0·029
Charlson Comorbidity Index - mean (SD)	2·43 (1·6)	3·37 (1·8)	0·544	3·77 (2·01)	4·24 (2·17)	0·221
COVID-19 vaccination (%)			0·304			0·235
Unvaccinated	3,960 (4·1)	2,380 (7·3)		1,588 (12·4)	967 (15·7)	
1 dose	1,208 (1·2)	1,475 (4·5)		384 (3·0)	443 (7·2)	
2 doses	7,760 (8·0)	4,088 (12·5)		1,973 (15·4)	1,028 (16·7)	
≥3 doses	83,830 (86·6)	24,644 (75·6)		8,848 (69·2)	3,731 (60·5)	
Pre-existing comorbidities (%)						
Cancer	4,524 (4·7)	2,239 (6·9)	0·094	1,237 (9·7)	602 (9·8)	0·003
Respiratory disease	2,563 (2·6)	1,615 (5·0)	0·121	985 (7·7)	532 (8·6)	0·034
Diabetes	19,283 (19·9)	9,396 (28·8)	0·209	3,594 (28·1)	1,998 (32·4)	0·094
Myocardial infarction	586 (0·6)	776 (2·4)	0·147	250 (2·0)	384 (6·2)	0·217
Cerebrovascular disease	4,413 (4·6)	3,565 (10·9)	0·240	1,598 (12·5)	1,229 (19·9)	0·203
Hypertension	36,794 (38·0)	16,743 (51·4)	0·271	6,544 (51·2)	3,377 (54·7)	0·072
Medication use within 90 days (%)						
Renin-angiotensin-system agents	20,197 (20·9)	10,953 (33·6)	0·289	3,811 (29·8)	2,137 (34·6)	0·104
Beta blockers	11,248 (11·6)	7,395 (22·7)	0·297	2,280 (17·8)	1,558 (25·3)	0·182
Calcium channel blockers	28,757 (29·7)	14,449 (44·3)	0·306	5,205 (40·7)	2,813 (45·6)	0·099
Diuretics	3,161 (3·3)	2,701 (8·3)	0·216	1,112 (8·7)	904 (14·7)	0·186
Nitrates	3,114 (3·2)	2,784 (8·5)	0·228	889 (6·9)	729 (11·8)	0·168
Lipid lowering agents	32,538 (33·6)	17,085 (52·4)	0·387	5,217 (40·8)	3,114 (50·5)	0·196
Insulins	1,734 (1·8)	1,473 (4·5)	0·157	633 (4·9)	546 (8·9)	0·154
Antidiabetic drugs	15,786 (16·3)	8,074 (24·8)	0·211	2,846 (22·2)	1,633 (26·5)	0·099
Antiplatelets	12,302 (12·7)	9,285 (28·5)	0·398	3,170 (24·8)	2,322 (37·6)	0·280
Immuno-suppressants	501 (0·5)	653 (2·0)	0·133	114 (0·9)	178 (2·9)	0·147
Corticosteroids	1,087 (1·1)	1,136 (3·5)	0·158	693 (5·4)	481 (7·8)	0·096
Proton pump inhibitors	12,472 (12·9)	8,761 (26·9)	0·356	3,179 (24·8)	2,424 (39·3)	0·313
Histamine H_2 receptor antagonists	15,436 (16·0)	7,621 (23·4)	0·188	2,774 (21·7)	1,525 (24·7)	0·072
Tocilizumab	0 (0·0)	0 (0·0)	<0·001	1 (0·0)	1 (0·0)	0·008
Baricitinib	0 (0·0)	0 (0·0)	<0·001	9 (0·1)	1 (0·0)	0·026
Remdesivir	0 (0·0)	0 (0·0)	<0·001	65 (0·5)	36 (0·6)	0·010
Interferon beta-1b	0 (0·0)	0 (0·0)	<0·001	2 (0·0)	2 (0·0)	0·011

SMD=Standardised mean difference; SD=Standard deviation

Notes:
†SMD<0·1 indicates balance between groups

Supplementary Table 3. Subgroup analysis for ICU admission or ventilatory support and hospitalisation

Subgroups	Non-hospitalised (N = 63,522)										
	Nirmatrelvir-ritonavir (N = 31,761)				Molnupiravir (N = 31,761)						
	Events	Rate (%)	Follow-up (days)	Incidence rate (per 10,000 person days)	Events	Rate (%)	Follow-up (days)	Incidence rate (per 10,000 person days)	ARR (95% CI) (%)	Adjusted HR (95% CI)†	p-value for interaction
ICU admission or ventilatory support											
Age, years											0·64
<70	14	0·09	418,333	0·33 (0·18, 0·56)	13	0·09	393,081	0·33 (0·18, 0·57)	0·00 (-0·07, 0·07)	1·09 (0·51, 2·34)	
≥70	57	0·34	468,766	1·22 (0·92, 1·58)	78	0·44	491,338	1·59 (1·25, 1·98)	0·10 (-0·03, 0·23)	0·95 (0·67, 1·35)	
Sex											0·49
Male	35	0·23	425,808	0·82 (0·57, 1·14)	57	0·37	423,645	1·35 (1·02, 1·74)	0·14 (0·02, 0·27)	0·74 (0·48, 1·13)	
Female	36	0·22	461,291	0·78 (0·55, 1·08)	34	0·21	460,774	0·74 (0·51, 1·03)	-0·01 (-0·11, 0·09)	1·36 (0·84, 2·21)	
CCI											0·50
0-3	24	0·13	533,948	0·45 (0·29, 0·67)	19	0·11	486,702	0·39 (0·24, 0·61)	-0·02 (-0·09, 0·05)	1·22 (0·66, 2·25)	
≥4	47	0·37	353,151	1·33 (0·98, 1·77)	72	0·50	397,717	1·81 (1·42, 2·28)	0·13 (-0·03, 0·29)	0·89 (0·61, 1·29)	
COVID-19 vaccination											0·71
0-1 dose	11	0.58	52,438	2.10 (1.05, 3.75)	21	0.97	59,688	3.52 (2.18, 5.38)	0.39 (-0.15, 0.92)	0.93 (0.43, 1.99)	
≥2 doses	60	0.20	834,661	0.72 (0.55, 0.93)	70	0.24	824,731	0.85 (0.66, 1.07)	0.04 (-0.04, 0.11)	1.02 (0.72, 1.45)	
Hospitalisation											
Age, years											0·017
<70	441	2·95	411,933	10·71 (9·73, 11·75)	695	4·95	382,169	18·19 (16·86, 19·59)	2·00 (1·55, 2·45)	0·66 (0·59, 0·75)	
≥70	1,412	8·40	443,392	31·85 (30·21, 33·55)	2,342	13·22	449,724	52·08 (49·99, 54·23)	4·82 (4·17, 5·48)	0·77 (0·72, 0·82)	
Sex											0·50
Male	903	5·92	410,484	22·00 (20·59, 23·48)	1,407	9·25	399,877	35·19 (33·37, 37·07)	3·33 (2·73, 3·92)	0·73 (0·67, 0·79)	
Female	950	5·75	444,841	21·36 (20·02, 22·76)	1,630	9·85	432,016	21·36 (20·02, 22·76)	4·10 (3·52, 4·68)	0·70 (0·65, 0·76)	
CCI											0·017
0-3	525	2·75	525,319	9·99 (9·16, 10·89)	754	4·33	474,051	15·91 (14·79, 17·08)	1·58 (1·20, 1·96)	0·66 (0·59, 0·74)	
≥4	1,328	10·48	330,006	40·24 (38·11, 42·47)	2,283	15·90	357,842	63·80 (61·21, 66·47)	5·42 (4·62, 6·22)	0·76 (0·70, 0·81)	
COVID-19 vaccination											0·70
0-1 dose	224	11·88	48,417	46·26 (40·40, 52·74)	445	20·45	52,481	46·26 (40·40, 52·74)	8·57 (6·33, 10·80)	0·69 (0·58, 0·81)	
≥2 doses	1,629	5·45	806,908	20·19 (19·22, 21·19)	2,592	8·76	779,412	33·26 (31·99, 34·56)	3·31 (2·90, 3·72)	0·72 (0·67, 0·76)	

	Hospitalised (N = 11,784)										
	Nirmatrelvir-ritonavir (N = 5,892)				Molnupiravir (N = 5,892)						
	Events	Rate (%)	Follow-up (days)	Incidence rate (per 10,000 person days)	Events	Rate (%)	Follow-up (days)	Incidence rate (per 10,000 person days)	ARR (95% CI) (%)	Adjusted HR (95% CI)†	p-value for interaction
ICU admission or ventilatory support											
Age, years											0·32
<70	4	0·24	45,911	0·87 (0·24, 2·23)	7	0·42	45,458	1·54 (0·62, 3·17)	0·18 (-0·21, 0·57)	0·63 (0·18, 2·27)	
≥70	22	0·52	116,135	1·89 (1·19, 2·87)	17	0·40	114,170	1·49 (0·87, 2·38)	-0·12 (-0·41, 0·17)	1·25 (0·66, 2·37)	
Sex											0·63
Male	20	0·68	80,761	2·48 (1·51, 3·82)	17	0·58	80,072	2·12 (1·24, 3·40)	-0·10 (-0·51, 0·30)	1·19 (0·62, 2·28)	
Female	6	0·20	81,285	0·74 (0·27, 1·61)	7	0·24	79,556	0·88 (0·35, 1·81)	0·04 (-0·21, 0·27)	0·93 (0·31, 2·83)	
CCI											0·14
0-3	4	0·19	57,384	0·70 (0·19, 1·78)	10	0·54	51,514	1·94 (0·93, 3·57)	0·35 (-0·04, 0·73)	0·38 (0·12, 1·26)	
≥4	22	0·57	104,662	2·10 (1·32, 3·18)	14	0·35	108,114	1·29 (0·71, 2·17)	-0·22 (-0·53, 0·07)	1·56 (0·79, 3·06)	
COVID-19 vaccination											0·24
0-1 dose	7	0·81	23,491	2·98 (1·20, 6·14)	3	0·35	22,769	1·32 (0·27, 3·85)	-0·46 (-1·17, 0·26)	2·50 (0·62, 10·13)	
≥2 doses	19	0·38	138,555	1·37 (0·83, 2·14)	21	0·42	136,859	1·53 (0·95, 2·35)	0·04 (-0·21, 0·29)	0·93 (0·50, 1·73)	

ARR=Absolute risk reduction; CI=Confidence interval; HR=Hazard ratio; CCI= Charlson Comorbidity Index; ICU=Intensive care unit

Notes: †Hazard ratios were obtained from Cox proportional hazard regression adjusted by sex, age, Charlson Comorbidity Index and vaccination status, pre-existing comorbidities, and medication use within 90 days at baseline

Supplementary Table 4. Sensitivity analysis on the risk of outcomes for COVID-19 patients receiving nirmatrelvir-ritonavir compared with molnupiravir using within three rather than five days periods between treatment and COVID-19 infection

Outcomes	Non-hospitalised (N = 59,870)									
	Nirmatrelvir-ritonavir (N = 29,935)				Molnupiravir (N = 29,935)				ARR (95% CI) (%)	Adjusted HR (95% CI)[†]
	Events	Rate (%)	Follow-up (days)	Incidence rate (per 10,000 person days)	Events	Rate (%)	Follow-up (days)	Incidence rate (per 10,000 person days)		
Effectiveness outcomes										
All-cause mortality	74	0·25	837,097	0·88 (0·69, 1·11)	262	0·88	834,704	3·14 (2·77, 3·54)	0·63 (0·51, 0·75)	0·44 (0·34, 0·58)
ICU admission or ventilatory support	72	0·24	835,877	0·86 (0·67, 1·08)	86	0·29	833,445	1·03 (0·83, 1·27)	0·05 (-0·04, 0·13)	1·04 (0·76, 1·44)
Hospitalisation	1,751	5·85	805,922	21·73 (20·72, 22·77)	2,923	9·76	782,746	37·34 (36·00, 38·72)	3·91 (3·49, 4·34)	0·70 (0·66, 0·74)
	Hospitalised (N = 11,370)									
	Nirmatrelvir-ritonavir (N = 5,685)				Molnupiravir (N = 5,685)				ARR (95% CI) (%)	Adjusted HR (95% CI)[†]
	Events	Rate (%)	Follow-up (days)	Incidence rate (per 10,000 person days)	Events	Rate (%)	Follow-up (days)	Incidence rate (per 10,000 person days)		
Effectiveness outcomes										
All-cause mortality	172	3·03	156,630	10·98 (9·40, 12·75)	308	5·42	154,491	19·94 (17·77, 22·29)	2·39 (1·65, 3·13)	0·61 (0·51, 0·74)
ICU admission or ventilatory support	27	0·47	156,303	1·73 (1·14, 2·51)	23	0·40	154,185	1·49 (0·95, 2·24)	-0·07 (-0·31, 0·17)	1·18 (0·67, 2·06)

ARR=Absolute risk reduction; CI=Confidence interval; HR=Hazard ratio; ICU=Intensive care unit

Notes:
[†]Hazard ratios were obtained from Cox proportional hazard regression adjusted by gender, age, Charlson Comorbidity Index, vaccination status, pre-existing comorbidities, and medication use within 90 days at baseline

Supplementary Table 5. Sensitivity analysis on the risk of outcomes for COVID-19 patients receiving nirmatrelvir-ritonavir compared with molnupiravir by excluding patients with pre-existing myocardial infarction

Outcomes	Non-hospitalised (N = 62,060)									
	Nirmatrelvir-ritonavir (N = 31,030)				Molnupiravir (N = 31,030)				ARR (95% CI) (%)	Adjusted HR (95% CI)[†]
	Events	Rate (%)	Follow-up (days)	Incidence rate (per 10,000 person days)	Events	Rate (%)	Follow-up (days)	Incidence rate (per 10,000 person days)		
Effectiveness outcomes										
All-cause mortality	71	0·23	867,813	0·82 (0·64, 1·03)	252	0·81	865,456	2·91 (2·56, 3·29)	0·58 (0·47, 0·70)	0·44 (0·33, 0·57)
ICU admission or ventilatory support	68	0·22	866,622	0·78 (0·61, 0·99)	86	0·28	864,187	1·00 (0·80, 1·23)	0·06 (-0·02, 0·14)	1·00 (0·72, 1·38)
Hospitalisation	1,762	5·68	836,452	21·07 (20·09, 22·07)	2,909	9·37	813,833	35·74 (34·46, 37·07)	3·69 (3·28, 4·11)	0·71 (0·66, 0·75)
	Hospitalised (N = 11,066)									
	Nirmatrelvir-ritonavir (N = 5,533)				Molnupiravir (N = 5,533)				ARR (95% CI) (%)	Adjusted HR (95% CI)[†]
	Events	Rate (%)	Follow-up (days)	Incidence rate (per 10,000 person days)	Events	Rate (%)	Follow-up (days)	Incidence rate (per 10,000 person days)		
Effectiveness outcomes										
All-cause mortality	155	2·80	152,609	10·16 (8·62, 11·89)	299	5·40	150,423	19·88 (17·69, 22·26)	2·60 (1·87, 3·34)	0·56 (0·46, 0·69)
ICU admission or ventilatory support	19	0·34	152,356	1·25 (0·75, 1·95)	24	0·43	150,106	1·60 (1·02, 2·38)	0·09 (-0·14, 0·32)	0·81 (0·44, 1·48)

ARR=Absolute risk reduction; CI=Confidence interval; HR=Hazard ratio; ICU=Intensive care unit

Notes:
[†]Hazard ratios were obtained from Cox proportional hazard regression adjusted by sex, age, Charlson Comorbidity Index and vaccination status, pre-existing comorbidities, and medication use within 90 days at baseline

Supplementary Table 6. E-value of eligible COVID-19 patients who received nirmatrelvir-ritonavir or molnupiravir

Outcomes	Non-hospitalised Received COVID-19 treatment
Effectiveness outcomes	
All-cause mortality	4·08
ICU admission or ventilatory support	1·16
Hospitalisation	2·12
	Hospitalised **Received COVID-19 treatment**
Effectiveness outcomes	
All-cause mortality	2·78
ICU admission or ventilatory support	1·40

ICU=Intensive care unit