THE LANCET Infectious Diseases

Supplementary appendix 2

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Khoo SH, FitzGerald R, Saunders G, et al. Molnupiravir versus placebo in unvaccinated and vaccinated patients with early SARS-CoV-2 infection in the UK (AGILE CST-2): a randomised, placebo-controlled, double-blind, phase 2 trial. *Lancet Infect Dis* 2022; published online Oct 19. https://doi.org/10.1016/S1473-3099(22)00644-2.

Supplementary material

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			Molnupiravir			Placebo		Total
		Vaccinated	Unvaccinated	Total	Vaccinated	Unvaccinated	Total	
		(n=44)	(n=46)	(n=90)	(n=46)	(n =44)	(n=90)	n=180
Age at consent (years)	Ν	44	46	90	46	44	90	180
	Mean	39.9	46.0	43.0	40.1	44.0	42.0	42.5
	Standard Deviation	15.41	14.90	15.38	14.49	14.74	14.67	15.00
	Median	39.0	50.0	45.0	38.0	47.5	43.0	43.0
	Quartiles	24.0 to 50.0	33.0 to 55.0	31.0 to 55.0	27.0 to 50.0	30.5 to 55.5	28.0 to 54.0	28.0 to 55.0
	Range	18·0 to 71·0	19·0 to 81·0	18·0 to 81·0	20.0 to 78.0	20·0 to 67·0	20.0 to 78.0	18·0 to 81·0
Gender - n (%)	Female	23 (52.3%)	29 (63.0%)	52 (57.8%)	26 (56.5%)	25 (56.8%)	51 (56.7%)	103 (57.2%)
	Male	21 (47.7%)	17 (37.0%)	38 (42.2%)	20 (43.5%)	19 (43.2%)	39 (43.3%)	77 (42.8%)
Ethnicity - n (%)	White- English / Welsh / Scottish / Northern Irish / British	38 (86.4%)	35 (76.1%)	73 (81.1%)	40 (87.0%)	38 (86.4%)	78 (86.7%)	151 (83.9%)
	Any other White background	3 (6.8%)	10 (21.7%)	13 (14.4%)	3 (6.5%)	4 (9.1%)	7 (7.8%)	20 (11.1%)
	Asian / Asian British- Indian	1 (2.3%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	1 (2.3%)	1 (1.1%)	2 (1.1%)
	Mixed / Multiple ethnic groups- White and Black African	1 (2.3%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
	Mixed / Multiple ethnic groups- White and Asian	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	0 (0.0%)	1 (1.1%)	1 (0.6%)
	Black / African / Caribbean / Black British- Caribbean	1 (2.3%)	0 (0.0%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
	Asian / Asian British- Pakistani	0 (0.0%)	0 (0.0%)	0 (0.0%)	0(0.0%)	1 (2.3%)	1 (1.1%)	1 (0.6%)
	Asian / Asian British- Chinese	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	0 (0.0%)	1 (1.1%)	1 (0.6%)
	Any other Black / African / Caribbean background	0 (0.0%)	1 (2.2%)	1 (1.1%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (0.6%)
	Any other Asian background	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.2%)	0 (0.0%)	1 (1.1%)	1 (0.6%)

TABLE S1 Participant characteristics at baseline by vaccinated status (ITT population)

			Molnupiravir			Placebo		Total
		Vaccinated (n=44)	Unvaccinated (n=46)	Total (n=90)	Vaccinated (n=46)	Unvaccinated (n=44)	Total (n=90)	n=180
BMI	Ν	44	46	90	46	44	90	180
	Mean	29.2	28.6	28.9	28.1	29.0	28.6	28.7
	Standard Deviation	5.91	5.39	5.63	6.24	6.32	6.26	5.94
	Median	29.6	27.1	28.2	27.1	27.1	27.1	27.4
	Quartiles	23.7 to 32.8	24.8 to 31.5	24·2 to 32·2	23.0 to 30.8	24.0 to 33.8	23.6 to 31.6	24.0 to 32.0
	Range	18·1 to 41·7	20.9 to 44.5	18·1 to 44·5	20·7 to 50·0	21.5 to 45.2	20·7 to 50·0	18·1 to 50·0
WHO score (Day 1) - n (%)	2. Ambulatory mild disease, symptomatic; independent	44 (100%)	46 (100%)	90 (100%)	46 (100%)	44 (100%)	90 (100%)	180 (100%)
Time from symptom onset to randomisation (days)	N	44	46	90	46	44	90	180
	Mean	3.4	3.4	3.4	3.3	3.3	3.3	3.3
	Standard Deviation	1.08	0.95	1.01	1.06	1.02	1.03	1.02
	Median	4.0	3.0	3.5	3.0	3.0	3.0	3.0
	Quartiles	3.0 to 4.0	$3 \cdot 0$ to $4 \cdot 0$	3.0 to 4.0	3.0 to 4.0	$3 \cdot 0$ to $4 \cdot 0$	3.0 to 4.0	$3 \cdot 0$ to $4 \cdot 0$
	Range	1.0 to 5.0	1.0 to 5.0	1.0 to 5.0	1.0 to 5.0	1.0 to 5.0	1.0 to 5.0	$1 \cdot 0$ to $5 \cdot 0$
NEWS2 score	Ν	44	46	90	46	44	90	180
	Mean	0.3	0.3	0.3	0.2	0.3	0.3	0.3
	Standard Deviation	0.54	0.55	0.55	0.48	0.55	0.51	0.53
	Median	0.0	0.0	0.0	0.0	0.0	0.0	0.0
	Quartiles	0.0 to 0.0	0.0 to 1.0	0.0 to 0.0	0.0 to 0.0	0.0 to 0.5	0.0 to 0.0	0.0 to 0.0
	Range	0.0 to 2.0	0.0 to 2.0	0.0 to 2.0	0.0 to 2.0	0.0 to 2.0	0.0 to 2.0	0.0 to 2.0

			Molnupiravir			Placebo		Total
		Vaccinated (n=44)	Unvaccinated (n=46)	Total (n=90)	Vaccinated (n=46)	Unvaccinated (n=44)	Total (n=90)	n=180
COVID Variant - n (%)	Alpha	1 (2.3%)	16 (34.8%)	17 (18.9%)	4 (8.7%)	16 (36.4%)	20 (22.2%)	37 (20.6%)
	B.1.1.1	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.3%)	1 (1.1%)	1 (0.6%)
	B.1.177/EU1	0 (0.0%)	15 (32.6%)	15 (16.7%)	0 (0.0%)	13 (29.5%)	13 (14.4%)	28 (15.6%)
	BA.1	11 (25.0%)	4 (8.7%)	15 (16.7%)	8 (17.4%)	4 (9.1%)	12 (13.3%)	27 (15%)
	BA.2	4 (9.1%)	1 (2.2%)	5 (5.6%)	5 (10.9%)	1 (2.3%)	6 (6.7%)	11 (6.1%)
	Delta	28 (63.6%)	9 (19.6%)	37 (41.1%)	27 (58.7%)	8 (18.2%)	35 (38.9%)	72 (40%)
	XE	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (2.3%)	1 (1.1%)	1 (0.6%)
	Unknown	0 (0.0%)	1 (2.2%)	1 (1.1%)	2 (4.3%)	0 (0.0%)	2 (2.2%)	3 (1.7%)
Baseline Viral Load (Log10)	Ν	44	45	89	45	44	89	178
	Mean	7.5	6.6	7.1	7.1	7.7	7.4	7.2
	Standard Deviation	2.35	2.94	2.69	2.94	3.08	3.00	2.85
	Median	7.9	6.9	7.2	8.3	7.3	8.1	7.5
	Quartiles	5.6 to 9.5	4.9 to 9.3	5·3 to 9·5	5·4 to 9·0	5.4 to 9.5	5·4 to 9·3	5.4 to 9.3
	Range	2.7 to 11.6	0.4 to 11.4	0·4 to 11·6	0 to 11.7	0.6 to 13.8	0.0 to 13.8	0.0 to 13.8
Was the patient vaccinated? • $n (\%)^*$	No	0 (0.0%)	46 (100%)	46 (51.1%)	0 (0.0%)	44 (100%)	44 (48.9%)	90 (50%)
	Yes	44 (100%)	0 (0.0%)	44 (48.9%)	46 (100%)	0 (0.0%)	46 (51.1%)	90 (50%)
irst vaccine received – n %)	Ν	44	46	90	46	44	90	180
,	Pfizer	21 (48%)	0 (0.0%)	21 (24%)	26 (57%)	0 (0.0%)	26 (29%)	47 (26%)

			Molnupiravir			Placebo		Total
		Vaccinated (n=44)	Unvaccinated (n=46)	Total (n=90)	Vaccinated (n=46)	Unvaccinated (n=44)	Total (n=90)	n=180
	Astra Zeneca	21 (48%)	0 (0.0%)	21 (24%)	17 (37%)	0 (0.0%)	17 (19%)	38 (21%)
	Novavax	1 (2%)	0 (0.0%)	1 (1%)	0 (0%)	0 (0.0%)	0 (0%)	1 (1%)
	Unknown	1 (2%)	0 (0.0%)	1 (1%)	3 (7%)	0 (0.0%)	3 (3%)	4 (2%)
Second vaccine received – n (%)	Ν	35	N/A	N/A	34	N/A	N/A	N/A
	Pfizer	15 (43%)	N/A	N/A	22 (65%)	N/A	N/A	N/A
	Astra Zeneca	17 (49%)	N/A	N/A	11 (32%)	N/A	N/A	N/A
	Novavax	1 (3%)	N/A	N/A	0 (0%)	N/A	N/A	N/A
	Unknown	2 (6%)	N/A	N/A	1 (3%)	N/A	N/A	N/A
Third vaccine received – n (%)	N	12	N/A	N/A	7	N/A	N/A	N/A
	Pfizer	12 (100%)	N/A	N/A	6 (86%)	N/A	N/A	N/A
	Moderna	0 (0%)	N/A	N/A	1 (14%)	N/A	N/A	N/A

* A patient is deemed has having a vaccinated status of 'Yes' if they received at least one coronavirus vaccine at least 14 days prior to commencing treatment.

TABLE S2 Clinical scores at day 15 and 29Day 15

		Molnupiravir	Placebo	Total
		(n=90)	(n=90)	(n=180)
WHO Score	Patients with available data	87 (97%)	85 (94%)	172 (96%)
	0. Uninfected, no viral RNA detected	6 (6.9%)	7 (8.2%)	13 (7.6%)
	1. Ambulatory mild disease, asymptomatic; viral RNA detected	31 (35.6%)	29 (34.1%)	60 (34.9%)
	2. Ambulatory mild disease, symptomatic; independent	50 (57.5%)	49 (57.6%)	99 (57.6%)
News Assessment score	Patients with available data	86 (96%)	84 (93%)	170 (94%)
	Mean	0.3	0.4	0.3
	Standard Deviation	0.56	0.78	0.68
	Median	0.0	0.0	0.0
	Quartiles	0.0 to 0.0	0.0 to 1.0	0.0 to 0.0
	Range	0.0 to 2.0	0.0 to 4.0	0.0 to 4.0
Change in NEWS2 Assessment score from baseline	Patients with available data	86 (96%)	84 (93%)	170 (94%)
	Mean	-0.1	0.2	0.1
	Standard Deviation	0.76	0.80	0.79
	Median	0.0	0.0	0.0
	Quartiles	0.0 to 0.0	0.0 to 0.0	0.0 to 0.0
	Range	-3.0 to 2.0	-1.0 to 4.0	-3.0 to 4.0
FluPRO overall score	Patients with available data	87 (97%)	85 (94%)	172 (96%)
	Mean	0.2	0.2	0.2
	Standard Deviation	0.23	0.29	0.26
	Range	0.0 to 1.2	0.0 to 1.8	0.0 to 1.8
	Median	0.1	0.2	0.1
	Quartiles	0.0 to 0.3	0.0 to 0.4	0.0 to 0.3
		0.1-	•	

The numbers in the table header relate to the number of randomised patients.

These statistics and percentages are calculated using the number of patients in each arm. All patients who have reached day 15 and had the assessment contribute to each score. Patients who died before day 15 are included in the WHO score only.

Day 29

		Molnupiravir	Placebo	Total
		(n=90)	(n=90)	(n=180)
WHO Score	Patients with available data	89 (99%)	84 (93%)	173 (96%)
	0. Uninfected, no viral RNA detected	19 (21.3%)	21 (25%)	40 (23.1%)
	1. Ambulatory mild disease, asymptomatic; viral RNA detected	43 (48.3%)	39 (46.4%)	82 (47.4%)
	2. Ambulatory mild disease, symptomatic; independent	27 (30.3%)	24 (28.6%)	51 (29.5%)
News Assessment score	Patients with available data	89 (99%)	83 (92%)	172 (96%)
	Mean	0.3	0.3	0.3
	Standard Deviation	0.60	0.50	0.55
	Median	0.0	0.0	0.0
	Quartiles	0.0 to 0.0	0.0 to 1.0	0.0 to 1.0
	Range	0.0 to 4.0	0.0 to 2.0	0.0 to 4.0
Change in NEWS2 Assessment score from baseline	Patients with available data	89 (99%)	83 (92%)	172 (96%)
	Mean	-0.1	0.1	0.0
	Standard Deviation	0.76	0.55	0.67
	Median	0.0	0.0	0.0
	Quartiles	0.0 to 0.0	0.0 to 0.0	0.0 to 0.0
	Range	-3.0 to 3.0	-2.0 to 1.0	-3.0 to 3.0
FluPRO overall score	Patients with available data	86 (96%)	86 (96%)	172 (96%)
	Mean	0.1	0.1	0.1
	Standard Deviation	0.19	0.24	0.22
	Range	0.0 to 0.9	0.0 to 1.3	0.0 to 1.3
	Median	0.0	0.1	0.1
	Quartiles	0.0 to 0.2	0.0 to 0.2	0.0 to 0.2

The numbers in the table header relate to the number of randomised patients. These statistics and percentages are calculated using the number of patients in each arm. All patients who have reached day 29 and had the assessment contribute to each score. Patients who died before day 29 are included in the WHO score only.

TABLE S3 Viral load reduction titre by vaccination status

	Molnupiravir	Placebo	Comparison between groups ³
All patients	(90)	(90)	
	(n=89)	(n=89)	
Baseline log10 viral load - mean (sd)	7.1 (2.69)	7.4 (3.00)	
Viral load reduction from baseline			
	(n=89)	(n=88)	
Day $3 - \text{mean}^1$ (sd ²)	-2.5 (2.22)	-2.0 (3.04)	-0.5 (0.40)
p-value			p=0.17
	(n=88)	(n=87)	
Day 5 – mean (sd)	-4.8 (2.58)	-3.9 (3.23)	-0.9 (0.44)
p-value			p=0.04
	(n=87)	(n=84)	
Day 8 – mean (sd)	-6.0 (2.80)	-5.8 (3.12)	0.2 (0.45)
p-value			p=0.66
Vaccinated patients ⁴			
	(n=44)	(n=45)	
Baseline log10 viral load – mean (sd)	7.5 (2.35)	7.1 (2.94)	
Viral load reduction from baseline			
	(n=44)	(n=45)	
Day 3 – mean (sd)	-2.8 (2.03)	-2.0 (2.67)	-0.8 (0.50)
p-value			p=0.12
	(n=43)	(n=45)	
Day 5 – mean (sd)	-5.4 (2.06)	-4.1 (3.12)	-1.3 (0.57)
p-value			p=0.03
	(n=43)	(n=43)	
Day 8 – mean (sd)	-6.5 (2.32)	-5.8 (3.13)	-0.7 (0.59)
p-value			p=0.25
Non-vaccinated patients ⁴			
	(n=45)	(n=44)	
Baseline log10 viral load – mean (sd)	6.6 (2.94)	7.7 (3.08)	
Viral load reduction from baseline			
	(n=45)	(n=43)	
Day 3 – mean (sd)	-2.3 (2.37)	-2.0 (3.42)	-0.3 (0.62)
p-value			p=0.63
	(n=45)	(n=42)	
Day 5 – mean (sd)	-4.2 (2.88)	-3.6 (3.37)	-0.6 (0.67)
p-value			p=0.38
	(n=44)	(n=41)	
Day 8 – mean (sd)	-5.6 (3.16)	-5.9 (3.15)	0.3 (0.69)
p-value			p=0.68

Estimated using the log10 average pseudo-concentration of the 3 genes (N, S and ORF, if amplified) taken away from the log10 baseline pseudo-concentration ¹Mean or difference in means in the last comparison column

² Standard deviation or standard error in the last comparison column

³ The comparison between groups column is the mean difference (associated standard error) or p-value (as indicated by the row) derived from a t-test between arms. ⁴A patient is deemed has having a vaccinated status of 'Yes' if they received at least one coronavirus vaccine at least 14 days

prior to commencing treatment

FIGURE S1 Probability distributions of the Hazard Ratio using a 2 point and a continuous prior (Bayesian Cox Proportional Model).

Probability of the hazard ratio being greater than 1 using	two-point priors
Probability of the hazard ratio being greater than 1 using two-point priors ¹	75.4%

¹Hazard ratio of more than 1 indicates effect in favour of EIDD-2801. The probability of the HR being greater than 1 is based on a two-point prior of a 50% probability that HR=1 and a 50% probability that HR=1.5.

Hazard Ratio using a Bayesian Cox proportional hazard model ¹			
Mean of posterior distribution for hazard ratio (95% credible interval) ²	1.30 (0.92, 1.71)		
Probability of the hazard ratio being greater than 1 (Used as supporting analysis)	94.7%		
Probability of the hazard ratio being greater than 1.5	16.6%		
Probability of the hazard ratio is between 0.9 and 1.1	14.6%		

¹Hazard ratios based on posterior distribution of the Bayesian Cox model derived from non-informative prior distributions.

² The credible interval is the highest posterior density interval.

Posterior distribution of the hazard ratio

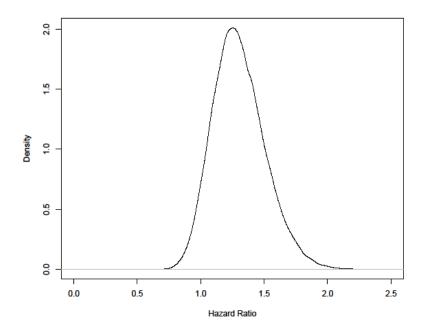


FIGURE S2 Viral Load by Treatment Arm

