

Supplementary materials

Title: Safety and effectiveness of molnupiravir in Japanese patients with COVID-19: final report of post-marketing surveillance in Japan

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Supplementary Table 1. Summary of fatal cases due to adverse events and adverse drug reactions (safety analysis set)

	Number of patients	
	N = 3,179	
	Adverse event	Adverse drug reaction
Any event ^a	323 (10.16)	175 (5.50)
Any serious event	89 (2.80)	7 (0.22)
Any fatal event	39 (1.23)	3 (0.09)
COVID-19	9	0
Pneumonia	4	0
Lymphoma	2	0
Hypoxia	2	1
Cardiac failure congestive	1	1
Emphysematous cystitis	1	0
Acute respiratory failure	1	1
Acute myeloid leukaemia	1	0
Diet refusal	1	0
Respiratory disorder	1	0
Respiratory failure	1	0
Pneumonia aspiration	1	0
Pneumonia bacterial	1	0
Shock haemorrhagic	1	0
Cardiac failure	1	0
Neuroblastoma	1	0
Small cell lung cancer extensive stage	1	0
Prostate cancer stage IV	1	0
Diabetic ketoacidosis	1	0
Breast cancer	1	0
Sepsis	1	0
Lung adenocarcinoma stage IV	1	0
End stage renal disease	1	0
Asthenia	1	0
Bladder cancer stage IV	1	0
Pancreatic carcinoma	1	0

Values are given as n (%) or n.

^aObservation period: mean, 38.3 days; median, 30.0 days.

COVID-19, coronavirus disease 2019

Supplementary Table 2. Serious adverse drug reactions (safety analysis set)

	Number of patients	Number of events
Any serious ADR	7 (0.22)	7
Infections and infestations		
COVID-19	2 (0.06)	2
Cardiac disorders		
Cardiac failure congestive	1 (0.03)	1
Respiratory, thoracic and mediastinal disorders		
Acute respiratory failure	1 (0.03)	1
Hypoxia	1 (0.03)	1
Hepatobiliary disorders		
Hepatic function abnormal	1 (0.03)	1
Skin and subcutaneous tissue disorders		
Rash	1 (0.03)	1

Values are given as n (%) or n.

ADR, adverse drug reaction; COVID-19, coronavirus disease 2019

Supplementary Table 3. Baseline characteristics associated with adverse drug reactions (safety analysis set)

Item	Number of patients, n	Patients with ADR, n (%)	<i>P</i> value
Sex			
Male	1,663	92 (5.53)	1.000 ^a
Female	1,516	83 (5.47)	
Age, years			
18 to < 65	1257	78 (6.21)	0.106 ^b
65 to < 75	751	45 (5.99)	
≥ 75	1,118	52 (4.65)	
COVID-19 symptoms			
No	80	1 (1.25)	0.129 ^a
Yes	3,099	174 (5.61)	
History of COVID-19			
No	3,155	174 (5.52)	0.620 ^a
Yes	17	1 (5.88)	
COVID-19 severity at MOV initiation			
Mild	2,748	153 (5.57)	0.610 ^b
Moderate I	325	17 (5.23)	
Moderate II	95	4 (4.21)	
Severe	1	0 (0.00)	
Comorbidities			
No	489	27 (5.52)	1.000 ^a
Yes	2,653	147 (5.54)	
Risk factors for severe COVID-19 illness			
No	136	7 (5.15)	1.000 ^a
Yes	3,043	168 (5.52)	
Prior treatment for COVID-19			
No	2,952	169 (5.72)	0.275 ^a
Yes	150	5 (3.33)	
Other medications			
No	2,282	126 (5.52)	0.723 ^a
Yes	817	48 (5.88)	
SARS-CoV-2 vaccination			
No	276	10 (3.62)	0.135 ^a
Yes	2,619	158 (6.03)	
Hepatic impairment			
No	3,082	167 (5.42)	0.095 ^a
Yes	67	7 (10.45)	
Renal impairment			
No	2,863	154 (5.38)	0.276 ^a
Yes	286	20 (6.99)	
Hemodialysis			
No	3,025	169 (5.59)	0.653 ^a
Yes	95	6 (6.32)	
Use of oxygen or mechanical ventilation			
No	2,988	169 (5.66)	0.410 ^a
Yes	114	4 (3.51)	

^aFisher's exact test.^bWilcoxon rank sum test.

ADR, adverse drug reaction; COVID-19, coronavirus disease 2019; MOV, molnupiravir; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2

Supplementary Table 4. Summary of cumulative incidence of events (effectiveness analysis set)

Item	Overall N = 2,988	Outpatients N = 2,006	Inpatients N = 925	Others N = 57
Age group				
≥ 80 years	759 (25.40)	350 (17.45)	357 (38.59)	52 (91.23)
< 80 years	2,177 (72.86)	1,633 (81.41)	539 (58.27)	5 (8.77)
Age unknown	52 (1.74)	23 (1.15)	29 (3.14)	0 (0.00)
All-cause death through day 29				
Alive	2,954 (98.86)	2,004 (99.90)	899 (97.19)	51 (89.47)
Dead	34 (1.14)	2 (0.10)	26 (2.81)	6 (10.53)
Age group				
≥ 80 years	24 (3.16 ^a)	2 (0.57 ^a)	16 (4.48 ^a)	6 (11.54 ^a)
< 80 years	9 (0.41 ^b)	0 (0.00 ^b)	9 (1.67 ^b)	0 (0.00 ^b)
Age unknown	1 (1.92 ^c)	0 (0.00 ^c)	1 (3.45 ^c)	-
Cause				
Related to COVID-19	12 (0.40)	0 (0.00)	10 (1.08)	2 (3.51)
Unrelated to COVID-19	22 (0.74)	2 (0.10)	16 (1.73)	4 (7.02)
Oxygen or mechanical ventilation use at molnupiravir initiation^d				
Oxygen	106 (3.55)	7 (0.35)	96 (10.38)	3 (5.26)
Mechanical ventilation	3 (0.10)	1 (0.05)	2 (0.22)	0 (0.00)
Unspecified respiratory support	2 (0.07)	1 (0.05)	1 (0.11)	0 (0.00)
Oxygen or mechanical ventilation initiation during or after molnupiravir treatment				
Oxygen	46 (1.54)	10 (0.50)	33 (3.57)	3 (5.26)
Mechanical ventilation	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)
Unspecified respiratory support	0 (0.00)	0 (0.00)	0 (0.00)	0 (0.00)

Values are given as n (%).

^aPercentage among patients aged ≥ 80 years.

^bPercentage among patients aged < 80 years.

^cPercentage among patients with unknown age.

^dPatients who used both oxygen and mechanical ventilation were included in the mechanical ventilation category.

COVID-19, coronavirus disease 2019

Supplementary Table 5. Baseline characteristics associated with outpatient hospitalization^a or all-cause death through day 29 (2,006 outpatients in effectiveness analysis set)

Item	Patients with events, n (%)	OR (95% CI)
Sex		
Female vs. Male	25/954 (2.62) vs. 22/1,052 (2.09)	1.26 (0.71, 2.25)
Age, years		
18 to < 65 vs. 65 to < 75	14/935 (1.50) vs. 5/520 (0.96)	1.57 (0.56, 4.37)
≥ 75 vs. 65 to < 75	28/528 (5.30) vs. 5/520 (0.96)	5.77 (2.21, 15.06)
BMI, kg/m ²		
≥ 30 vs. 18.5 to < 25	4/136 (2.94) vs. 10/456 (2.19)	1.35 (0.42, 4.38)
COVID-19 symptoms		
No vs. Yes	0/28 (0.00) vs. 47/1,978 (2.38)	< 0.01 (< 0.01, > 999.99)
History of COVID-19		
Yes vs. No	0/9 (0.00) vs. 47/1,996 (2.35)	< 0.01 (< 0.01, > 999.99)
COVID-19 severity at MOV initiation		
Moderate I vs. Mild	11/122 (9.02) vs. 34/1,860 (1.83)	5.32 (2.63, 10.79)
Moderate II vs. Mild	2/18 (11.11) vs. 34/1,860 (1.83)	6.71 (1.49, 30.35)
Comorbidities		
No vs. Yes	5/393 (1.27) vs. 42/1,583 (2.65)	0.47 (0.19, 1.20)
Risk factors for severe COVID-19 illness		
No vs. Yes	0/97 (0.00) vs. 47/1,909 (2.46)	< 0.01 (< 0.01, > 999.99)
Number of risk factors for severe COVID-19 illness		
2 vs. 1	17/599 (2.84) vs. 5/662 (0.76)	3.84 (1.41, 10.47)
3 vs. 1	11/409 (2.69) vs. 5/662 (0.76)	3.63 (1.25, 10.53)
≥ 4 vs. 1	14/239 (5.86) vs. 5/662 (0.76)	8.18 (2.91, 22.95)
Prior treatment for COVID-19		
Yes vs. No	3/91 (3.30) vs. 43/1,857 (2.32)	1.44 (0.44, 4.73)
Other medications		
Yes vs. No	20/407 (4.91) vs. 20/1,539 (1.30)	3.93 (2.09, 7.37)
SARS-CoV-2 vaccination		
No vs. Yes	5/151 (3.31) vs. 40/1,694 (2.36)	1.42 (0.55, 3.64)
SpO ₂ at MOV initiation, %		
94-95 vs. ≥ 96	5/72 (6.94) vs. 22/979 (2.25)	3.25 (1.19, 8.84)
≤ 93 vs. ≥ 96	5/21 (23.81) vs. 22/979 (2.25)	13.59 (4.57, 40.41)
Hepatic impairment		
Yes vs. No	2/37 (5.41) vs. 45/1,943 (2.32)	2.41 (0.56, 10.33)
Renal impairment		
Yes vs. No	13/90 (14.44) vs. 34/1,890 (1.80)	9.22 (4.68, 18.17)
Hemodialysis		
Yes vs. No	3/19 (15.79) vs. 44/1,948 (2.26)	8.11 (2.28, 28.86)

^aHospitalization for reasons other than isolation or assessment.

BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; MOV, molnupiravir; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SpO₂, peripheral oxygen saturation

Supplementary Table 6. Baseline characteristics associated with inpatient oxygen initiation or all-cause death through day 29 (826 inpatients^a in effectiveness analysis set)

Item	Patients with events, n (%)	OR (95% CI)
Sex		
Female vs. Male	18/398 (4.52) vs. 20/428 (4.67)	0.97 (0.50, 1.85)
Age, years		
18 to < 65 vs. 65 to < 75	4/232 (1.72) vs. 7/176 (3.98)	0.42 (0.12, 1.47)
≥ 75 vs. 65 to < 75	27/393 (6.87) vs. 7/176 (3.98)	1.78 (0.76, 4.17)
BMI, kg/m ²		
≥ 30 vs. 18.5 to < 25	1/65 (1.54) vs. 17/398 (4.27)	0.35 (0.05, 2.68)
COVID-19 symptoms		
No vs. Yes	1/45 (2.22) vs. 37/781 (4.74)	0.46 (0.06, 3.41)
History of COVID-19		
Yes vs. No	0/6 (0.00) vs. 38/815 (4.66)	< 0.01 (< 0.01, > 999.99)
COVID-19 severity at MOV initiation		
Moderate I vs. Mild	11/141 (7.80) vs. 26/659 (3.95)	2.06 (0.99, 4.27)
Moderate II vs. Mild	1/23 (4.35) vs. 26/659 (3.95)	1.11 (0.14, 8.53)
Comorbidities		
No vs. Yes	0/59 (0.00) vs. 38/762 (4.99)	< 0.01 (< 0.01, > 999.99)
Risk factors for severe COVID-19 illness		
No vs. Yes	1/32 (3.13) vs. 37/794 (4.66)	0.66 (0.09, 4.97)
Number of risk factors for severe COVID-19 illness		
2 vs. 1	9/211 (4.27) vs. 8/210 (3.81)	1.12 (0.43, 2.97)
3 vs. 1	10/196 (5.10) vs. 8/210 (3.81)	1.36 (0.52, 3.51)
≥ 4 vs. 1	10/177 (5.65) vs. 8/210 (3.81)	1.51 (0.58, 3.92)
Prior treatment for COVID-19		
Yes vs. No	3/38 (7.89) vs. 35/788 (4.44)	1.84 (0.54, 6.29)
Other medications		
Yes vs. No	15/305 (4.92) vs. 23/521 (4.41)	1.12 (0.58, 2.18)
SARS-CoV-2 vaccination		
No vs. Yes	5/95 (5.26) vs. 32/656 (4.88)	1.08 (0.41, 2.85)
SpO ₂ at MOV initiation, %		
94-95 vs. ≥ 96	10/118 (8.47) vs. 24/622 (3.86)	2.31 (1.07, 4.96)
≤ 93 vs. ≥ 96	2/27 (7.41) vs. 24/622 (3.86)	1.99 (0.45, 8.91)
Hepatic impairment		
Yes vs. No	3/25 (12.00) vs. 35/799 (4.38)	2.98 (0.85, 10.42)
Renal impairment		
Yes vs. No	11/151 (7.28) vs. 27/673 (4.01)	1.88 (0.91, 3.88)
Hemodialysis		
Yes vs. No	9/64 (14.06) vs. 29/762 (3.81)	4.14 (1.87, 9.17)

^aInpatients who did not use oxygen or mechanical ventilation at baseline.

BMI, body mass index; CI, confidence interval; COVID-19, coronavirus disease 2019; MOV, molnupiravir; OR, odds ratio; SARS-CoV-2, severe acute respiratory syndrome coronavirus 2; SpO₂, peripheral oxygen saturation