Report on the Deliberation Results

December 24, 2021
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Lagevrio Capsules 200 mg
Non-proprietary Name	Molnupiravir (JAN*)
Applicant	MSD K.K.
Date of Application	December 3, 2021

Results of Deliberation

Under the current pandemic of disease caused by a novel coronavirus (severe acute respiratory syndrome coronavirus 2 [SARS-CoV-2]), the applicant has submitted an application for approval of the product on the understanding that the product is qualified for approval based on Article 14-3, Paragraph 1 of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of 1960, hereinafter referred to as the "Pharmaceuticals and Medical Devices Act").

In its meeting held on December 24, 2021, the Second Committee on New Drugs discussed whether the product was qualified for Special Approval for Emergency under Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. The Committee concluded that the product may be approved with the conditions listed below, and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The product is not classified as a biological product or a specified biological product. The re-examination period is 8 years. The drug product and its drug substance are both classified as powerful drugs.

**Japanese Accepted Name (modified INN)*

Approval Conditions

1. The applicant is required to develop and appropriately implement a risk management plan.
2. The applicant is required to request that physicians administer the product only to patients considered eligible for treatment with the product who, or whose legally acceptable representatives, have been provided with the efficacy and safety information of the product in written form, and have provided written informed consent before the treatment.
3. Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act, the grace period for data submission is 6 months after the approval. If newly submitted data, etc., necessitate a change in the approved product information, the change may be ordered in accordance with the provision in Article 74-2, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.

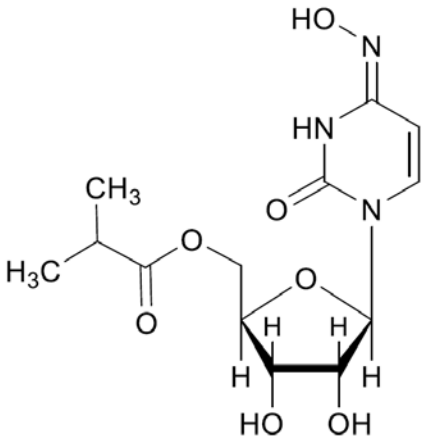
Report on Special Approval for Emergency

December 20, 2021
Pharmaceuticals and Medical Devices Agency

I. Product

Brand Name	Lagevrio Capsules 200 mg
Non-proprietary name	Molnupiravir
Applicant	MSD K.K.
Date of Application	December 3, 2021
Dosage Form/Strength	Each capsule contains 200 mg of molnupiravir.
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure



Molecular formula: $C_{13}H_{19}N_3O_7$

Molecular weight: 329.31

Chemical name: {(2*R*,3*S*,4*R*,5*R*)-3,4-Dihydroxy-5-[(4*Z*)-4-(hydroxyimino)-2-oxo-3,4-dihydropyrimidin-1(2*H*)-yl]oxolan-2-yl}methyl 2-methylpropanoate

Items Warranting Special Mention	The product is handled as a product that requires approval from the Minister of Health, Labour and Welfare prescribed in Article 14, Paragraph 1 of the Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 1 of the Act (PSEHB/PED Notification 1202-5, dated December 2, 2021, issued by the Director of the Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare). Priority Review based on "Policy on regulatory review of drugs, etc. against coronavirus disease (COVID-19) (No. 2)" (PSEHB/PED Notification No. 0617-9 and PSEHB/MDED Notification No. 0617-1, dated June 17, 2021)
Reviewing Office	Office of New Drug IV

Table of Contents

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information 3
2. Clinical Efficacy and Safety..... 4
3. Summary of the submitted data..... 17
4. Overall Evaluation 21

List of Abbreviations

See Appendix.

II. Summary of the submitted data

1. Origin or History of Discovery, Use in Foreign Countries, and Other Information

COVID-19 is a disease caused by SARS-CoV-2 infection. Main symptoms reported include pyrexia, cough, acute respiratory symptoms other than cough, and serious pneumonia.[1)] In Japan, the first patient infected with SARS-CoV-2 was identified on January 15, 2020. On February 1, 2020, COVID-19[2)] was classified as a Designated Infectious Disease[3)] pursuant to the Act on the Prevention of Infectious Diseases and Medical Care for Patients with Infectious Diseases (Infectious Diseases Control Act) and as a Quarantinable Infectious Disease[4)] pursuant to the Quarantine Act. In Japan, as of December 6, 2021, a total of 1,727,942 people have been infected (positive for polymerase chain reaction [PCR] test). Among them, 1,137 (including 29 with severe disease) required hospitalization for treatment, 1,708,711 were discharged or released from medical treatment, and 18,364 died.[5)]

Molnupiravir was discovered by Drug Innovation Ventures at Emory University (DRIVE), LLC, a non-profit organization in the United States (US), and developed by Ridgeback Biotherapeutics LP and Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc. Molnupiravir is hydrolyzed *in vivo* into *N*-hydroxycytidine (NHC), which is then intracellularly phosphorylated to form *N*-hydroxycytidine 5′-triphosphate (NHC-TP). NHC-TP acts as a substrate of the viral ribonucleic acid (RNA)-dependent RNA polymerase (RdRp) of SARS-CoV-2 and accumulates errors in the viral genome newly synthesized during a viral replication process, leading to inhibition of the replication.

In response to the Conditional Marketing Authorization issued in the United Kingdom (UK), Emergency Use Authorization filed with US FDA and recommendation gained from its Advisory Committee, and based on the preliminary data of the global phase II/III study (Study MK-4482-002), the applicant has submitted an application for Special Approval for Emergency of molnupiravir on the understanding that molnupiravir is qualified for approval based on Article 14, Paragraph 1 of the Pharmaceuticals and Medical Devices Act, pursuant to Article 14-3, Paragraph 1 of the Act. For this application, the applicant submitted the application data filed with US FDA for the Emergency Use Authorization, investigator's brochure, results of the foreign phase IIa study (Study MK-4482-006), and preliminary data of the global phase II/III study (Study MK-4482-002). This report contains the results of review conducted based on the data submitted by the applicant, in accordance with the "Handling of drugs intended to be submitted for Special Approval for Emergency (Request)" (PSEHB/PED Notification 1202-5, dated December 2, 2021).

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1) Symptoms of 29,601 patients reported to the National Epidemiological Surveillance of Infectious Diseases Program between February 1 and August 5, 2020 [Infectious Disease Weekly Report Japan, Vol. 22, No. 31 and 32 (combined issue): https://www.niid.go.jp/niid/images/idsc/idwr/IDWR2020/idwr2020-31-32.pdf (last accessed on December 6, 2021)]

2) Limited to the disease caused by coronavirus of genus *Betacoronavirus* that was reported as "transmissible to humans" from the People's Republic of China to WHO in January 2020.

3) The term Designated Infectious Disease means already known infectious diseases (excluding Class I Infectious Diseases, Class II Infectious Diseases, Class III Infectious Diseases, and Novel Influenza Infection, etc.) specified by Cabinet Order as a disease which would be likely to seriously affect the health of the public in the event of its spread if the provisions of the Infectious Diseases Control Act, in whole or in part, did not apply mutatis mutandis (Article 6 of the Infectious Diseases Control Act).

4) The term Quarantinable Infectious Disease means diseases specified by Cabinet Order as those which require inspection in order to prevent pathogens of infectious diseases not endemic to Japan from entering the country (Article 2, Item 3 of the Quarantine Act).

5) Ministry of Health, Labour and Welfare: https://www.mhlw.go.jp/stf/covid-19/kokunainohasseijoukyou.html (last accessed on December 6, 2021)

2. Clinical Efficacy and Safety

The applicant submitted results of the foreign phase IIa study (Study MK-4482-006) and preliminary data of the global phase II/III study (Study MK-4482-002) both in patients with COVID-19 as the main efficacy and safety data.

2.1 Foreign phase IIa study (Study MK-4482-006, June 2020 to February 2021)

A randomized, double-blind, placebo-controlled, parallel-group study[6)] was conducted in ≥18-year-old patients with COVID-19 (target sample size, 172[7)]) at 11 study sites in the US to investigate the antiviral activity and safety of molnupiravir. Table 1 shows main inclusion and exclusion criteria.

Table 1. Main inclusion and exclusion criteria

Inclusion criteria	1. Has a SARS-CoV-2-positive diagnostic test (confirmed by PCR test, etc., using a sample collected within 96 hours prior to randomization). 2. Is expected to start the study treatment within 168 hours[a)] after symptom onset. 3. Has a symptom of COVID-19 (pyrexia or respiratory symptom)[b)] at randomization. 4. Males willing and able to use effective contraception from the start of study treatment to 100 days after the end of study treatment or non-pregnant females willing and able to use effective contraception from the start of study treatment to 50 days after the end of study treatment
Exclusion criteria	1. Is required to be hospitalized or receive immediate treatment. 2. Has a hemoglobin value <10 g/dL for males and <9 g/dL for females. 3. Has a platelet count <100,000/μL[c)] or received platelet transfusion within 5 days prior to randomization. 4. Is on dialysis or has eGFR <30 mL/min/1.73 m^2[d)]. 5. Has AST or ALT >3 × the upper limit of normal. 6. Is being hospitalized or was hospitalized for COVID-19. 7. Has a history of renal disease (creatinine clearance <30 mL/min[e)]). 8. Has a history of hepatic disease or has active HBV or HCV infection. 9. Has HIV with CD4 count <200 cell/mm^3 or being treated with nucleoside analogues. 10. Has been vaccinated against COVID-19.

a) Time from symptom onset was revised from within 120 hours to within 168 hours in the Protocol version 2 (July 22, 2020).
b) A complaint of feeling feverish or chills was also deemed as pyrexia. Loss of smell, loss of taste, sore throat, cough, or shortness of breath was deemed as a respiratory symptom.
c) Platelet count was revised from <125,000/μL to <100,000/μL in the Protocol version 5 (November 15, 2020).
d) eGFR value was revised from <60 mL/min/1.73 m^2 to <30 mL/min/1.73 m^2 in the Protocol version 5 (November 15, 2020).
e) Creatinine clearance value was revised from <60 mL/min to <30 mL/min in the Protocol version 5 (November 15, 2020).

Subjects orally received molnupiravir 200, 400, or 800 mg or the placebo twice daily for 5 days.

Of 204 randomized subjects, 202 (23 in the molnupiravir 200 mg group, 62 in the 400 mg group, 55 in the 800 mg group, and 62 in the placebo group) who received at least 1 dose of the study drug were included in the safety analysis. Of the 204 randomized subjects, 198 (23 in the molnupiravir 200 mg group, 61 in the 400 mg group, 53 in the 800 mg group, and 61 in the placebo group) who received at least 1 dose of the study drug and provided reverse transcription PCR (RT-PCR) test results (from a nasopharyngeal swab) at ≥1 time points were included in the modified intent-to-treat (MITT) population and antiviral activity analysis set.

6) The sponsor members who were not directly involved in the study were allowed to evaluate data on antiviral activity under a blinded condition to make decisions such as addition of a dose.
7) The study was initiated to administer molnupiravir 200 mg or the placebo in accordance with Protocol version 1 (May 29, 2020) (target sample size, 44 [22 per group]). Then, the Protocol version 3 (August 27, 2020) additionally included 4 parts (Parts 2-5) to administer molnupiravir at high doses not exceeding 800 mg or the placebo, and accordingly changed the target sample size to 108 (including 16 for each of Parts 2-5 [12 in the molnupiravir group and 4 in the placebo group]). The Protocol version 5 (November 15, 2020) further included 4 parts (Parts 6-9) and thus changed the target sample size to 172 (including 16 for each of Parts 6-9 [12 in the molnupiravir group and 4 in the placebo group]). In addition, it allowed enrollment of a new subject in the study to replace the subject who discontinued the study and provided no data on antiviral activity, where applicable, but did not allow the overall sample size to exceed 204.

A total of 7 subjects (3 in the 400 mg group, 3 in the 800 mg group, and 1 in the placebo group) discontinued the study owing to adverse events in 3 subjects (1 in the 400 mg group, 1 in the 800 mg group, and 1 in the placebo group), lost to follow-up in 1 subject (in the 400 mg group), decision of the investigator[8)] in 1 subject (in the 800 mg group), and withdrawal in 2 subjects (1 each in the 400 mg and 800 mg groups).

Table 2 and Figure 1 show the antiviral activity results on the primary endpoint of time from start of the study treatment to day of collection of a sample that tested negative by RT-PCR for the first time (time to viral clearance).[9)]

Table 2. Time to viral clearance by RT-PCR test (nasopharyngeal swab) (MITT population)

	Molnupiravir 200 mg (n = 23)	Molnupiravir 400 mg (n = 61)	Molnupiravir 800 mg (n = 53)	Placebo (n = 61)
Number of events[a)]	21	48	49	49
Median [95% CI] (days)	22.0 [15.0, 28.0]	27.0 [15.0, 28.0]	14.0 [13.0, 14.0]	15.0 [15.0, 27.0]

a) Onset of the event was defined as a case where 2 consecutive samples tested negative by RT-PCR, and day of onset of the event was the day when the first of these negative samples was collected. In the case where only the last sample tested negative by RT-PCR, onset of the event was deemed as the day when the last sample was collected.

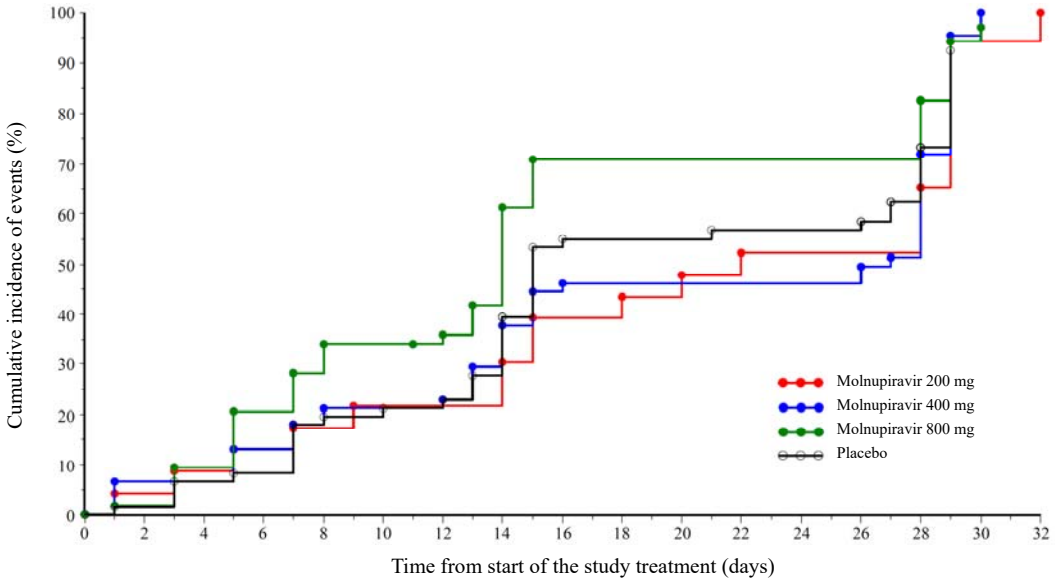

Figure 1. Kaplan-Meier curve of time to viral clearance by RT-PCR test (nasopharyngeal swab) (MITT population)

For safety,[10)] adverse events and adverse drug reactions[11)] occurred in 47.8% (11 of 23) and 17.4% (4 of 23) of subjects in the molnupiravir 200 mg group, 32.3% (20 of 62) and 21.0% (13 of 62) of subjects in the 400 mg group, 20.0% (11 of 55) and 1.8% (1 of 55) of subjects in the 800 mg group, and 29.0% (18 of 62) and 12.9% (8 of 62) of subjects in the placebo group, respectively. Table 3 shows adverse events and adverse drug reactions reported by ≥2 subjects in any group.

8) A reason for the decision was a concern about compliance with the treatment.
9) A nasopharyngeal swab in which an amount of SARS-CoV-2 RNA was determined to be below the lower limit of quantitation (1,018 copies/mL) by RT-PCR was deemed to be negative. Nasopharyngeal swabs for RT-PCR test were collected before the start of study drug administration (baseline), 2, 3, 4, 5, 7, 10, 14, and 28 days after randomization (Days 2, 3, 4, 5, 7, 10, 14, and 28), and at discontinuation of the study. The collection of samples on Days 2, 4, and 10 was removed in the Protocol version 4 (September 10, 2020).
10) Adverse events and adverse drug reactions that occurred within 14 days after end of the study treatment
11) Adverse events assessed as causally related to the study drug by the investigator

Table 3. Adverse events and adverse drug reactions reported by ≥2 subjects in any group (safety analysis population)

Event term	Adverse events				Adverse drug reactions			
	Molnupiravir 200 mg (n = 23)	Molnupiravir 400 mg (n = 62)	Molnupiravir 800 mg (n = 55)	Placebo (n = 62)	Molnupiravir 200 mg (n = 23)	Molnupiravir 400 mg (n = 62)	Molnupiravir 800 mg (n = 55)	Placebo (n = 62)
Overall	11 (47.8)	20 (32.3)	11 (20.0)	18 (29.0)	4 (17.4)	13 (21.0)	1 (1.8)	8 (12.9)
Headache	1 (4.3)	3 (4.8)	2 (3.6)	3 (4.8)	0	2 (3.2)	0	0
Dizziness	2 (8.7)	1 (1.6)	0	0	1 (4.3)	0	0	0
Paraesthesia	0	2 (3.2)	0	0	0	0	0	0
ALT increased	0	2 (3.2)	2 (3.6)	2 (3.2)	0	2 (3.2)	1 (1.8)	2 (3.2)
AST increased	0	1 (1.6)	2 (3.6)	1 (1.6)	0	1 (1.6)	1 (1.8)	1 (1.6)
Blood creatinine increased	0	3 (4.8)	0	0	0	3 (4.8)	0	0
Nausea	1 (4.3)	2 (3.2)	0	1 (1.6)	1 (4.3)	2 (3.2)	0	1 (1.6)
Abdominal pain	0	1 (1.6)	0	2 (3.2)	0	0	0	1 (1.6)
Cough	0	2 (3.2)	1 (1.8)	0	0	0	0	0
Insomnia	2 (8.7)	1 (1.6)	1 (1.8)	4 (6.5)	2 (8.7)	1 (1.6)	0	3 (4.8)

n (%), MedDRA ver. 23.0

There were no adverse events leading to death.

Serious adverse events occurred in 2 subjects in the molnupiravir 400 mg group (oxygen saturation decreased and cerebrovascular accident in 1 subject each), 1 in the 800 mg group (acute respiratory failure), and 1 in the placebo group (hypoxia). For any of these events, a causal relationship to the study drug was denied.

Adverse events leading to discontinuation of the treatment occurred in 1 subject in the molnupiravir 400 mg group (oxygen saturation decreased), 1 in the 800 mg group (acute respiratory failure), and 1 in the placebo group (hypoxia). For any of these events, a causal relationship to the study drug was denied.

2.2 Global phase II/III study (Study MK-4482-002, ongoing since October 2020)

2.2.1 Phase II part (data cut-off on March 2021)

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in ≥18-year-old patients with COVID-19 (target sample size, 300 [75 per group][12)]) at 82 study sites in 12 countries including the US, Russia, and Colombia to investigate the efficacy and safety of molnupiravir. Table 4 shows main inclusion and exclusion criteria.

12) On the assumption that each group includes 60 subjects, a change in viral RNA from baseline (log_{10} copies/mL) differs between each of the molnupiravir groups and the placebo group by −0.75 to −1.25, and the standard deviation (SD) in each group is 1.25 to 1.75, the power is calculated to be 64% to >99% with a one-sided significance level of 2.5%.

Table 4. Main inclusion and exclusion criteria

Inclusion criteria	1. Has a SARS-CoV-2-positive diagnostic test (confirmed by PCR test, etc., using a sample collected within 7 days prior to randomization). 2. Has initial onset of symptoms[a)] attributable to COVID-19 within 7 days prior to randomization and ≥1 symptoms[b)] attributable to COVID-19 on the day of randomization. 3. Has moderate COVID-19 or mild COVID-19 with ≥1 risk factors for severe COVID-19 defined below. Definitions used to determine severity of COVID-19 are as follows: [Mild] (a) and (b) are met. (a) All of the following conditions are observed. Respiratory rate <20 breaths/min, heart rate <90 beats/min, and SpO_2 >93%[c)] (b) None of the following conditions is observed. Shortness of breath at rest or with exertion, respiratory failure,[d)] shock,[e)] and multiple organ dysfunction[f)] [Moderate] All of (a) to (c) are met. (a) ≥1 of the following conditions are observed. Shortness of breath with exertion, respiratory rate ≥20 to <30 breaths/min, and heart rate ≥90 to <125 beats/min (b) Any of the following conditions is observed. • SpO_2 >93%[c)] • On supplemental oxygen at ≤2 L/min since onset of COVID-19 regardless of SpO_2 (c) None of the following conditions is observed. Shortness of breath at rest, respiratory failure,[d)] shock,[e)] and multiple organ dysfunction[f)] Risk factors for severe COVID-19 are as listed below: • Age >60 years • Active cancer (excluding minor cancers not associated with immunosuppression or significant mortality such as basal cell carcinomas) • Chronic kidney disease • Chronic obstructive pulmonary disease • Immunocompromised state from solid organ transplant • Obesity (BMI ≥30 kg/m^2) • Serious heart conditions (cardiac failure, coronary artery disease, cardiomyopathy, etc.) • Sickle cell disease • Diabetes mellitus 4. Males willing and able to use effective contraception for at least 90 days after end of the study treatment or non-pregnant females willing and able to use effective contraception for 28 days after start of the study treatment[g)]
Exclusion criteria	1. Is currently hospitalized or is expected to need hospitalization for COVID-19 within 48 hours of randomization. 2. Is on dialysis or has eGFR <30 mL/min/1.73 m^2. 3. Has HIV with a recent RNA viral load >50 copies/mL or CD4 count <200 cell/mm^3. 4. Chemotherapy required within 6 weeks prior to randomization 5. Has a neutrophil count <500/mm^3. 6. Autologous or allogeneic hematopoietic stem cell transplant recipient 7. Has a history of HBV or HCV with any of the following: hepatic cirrhosis, end-stage liver disease, hepatocellular carcinoma, and AST or ALT >3 × upper limit of normal at screening. 8. Has a platelet count <100,000/μL or received platelet transfusion within 5 days prior to randomization. 9. Has a history of chronic pancreatitis or has a history of acute pancreatitis within 3 months prior to randomization. 10. Has a baseline heart rate of <50 beats/min at rest. 11. Was vaccinated for COVID-19.

a) No specific symptoms defined.
b) Cough, sore throat, nasal congestion, runny nose, shortness of breath or difficulty breathing with exertion, muscle or body aches, fatigue, fever >38.0°C, chills, headache, nausea, vomiting, diarrhoea, loss of smell, or loss of taste
c) SpO_2 >93% on room air or on supplemental oxygen for a reason other than COVID-19 which has not increased since onset of COVID-19 symptoms
d) Respiratory failure is defined as a condition requiring at least 1 of the following (a) to (d): (a) endotracheal intubation and mechanical ventilation; (b) oxygen delivered by high-flow nasal cannula (at flow rates >20 L/min with fraction of delivered oxygen ≥0.5); (c) noninvasive positive pressure ventilation; and (d) extracorporeal membrane oxygenation (ECMO).
e) Shock is defined as a condition with systolic blood pressure <90 mmHg, diastolic blood pressure <60 mmHg, or requiring vasopressors.
f) Multiple organ dysfunction is defined as an acute failure or dysfunction, at the discretion of the investigators, of at least 1 of the following organ systems: respiratory, cardiovascular, renal, hematological, hepatic, and/or central nervous systems.
g) The contraception period for females was revised from 7 months after the last dose of study treatment to 28 days after the first dose of study treatment in the Protocol Amendment version 1 (December 17, 2020).

Subjects orally received molnupiravir 200, 400, or 800 mg or the placebo twice daily[13] for 5 days.

In the phase II part of this study, 2 interim analyses were planned.[14] The first analysis was to be performed to evaluate the dose and other aspects of molnupiravir when 300 subjects combined in this study (phase II part) and the global phase II/III study (Study MK-4482-001, phase II part)[15] completed the study treatment. The second analysis was to be performed to determine the dose in the phase III part and other aspects of molnupiravir when 300 subjects in this study (phase II part) completed the follow-up through Day 29. This section presents results from the second interim analysis (final analysis results from the phase II part).

Of 302 randomized subjects (75 in the molnupiravir 200 mg group, 77 in the 400 mg group, 76 in the 800 mg group, and 74 in the placebo group), 299 (74 in the molnupiravir 200 mg group, 77 in the 400 mg group, 74 in the 800 mg group, and 74 in the placebo group) who received at least 1 dose of the study drug were included in the safety analysis and MITT population, which also served as the efficacy analysis population.

A total of 16 subjects (5 in the molnupiravir 200 mg group, 4 in the 400 mg group, 4 in the 800 mg group, and 3 in the placebo group) discontinued the study owing to adverse events in 4 subjects (3 in the 800 mg group and 1 in the placebo group), poor compliance with study treatment in 4 subjects (2 in the 200 mg group, 1 in the 400 mg group, and 1 in the placebo group), decision of the investigator in 2 subjects (in the 400 mg group), withdrawal in 4 subjects (1 in the 200 mg group, 1 in the 400 mg group, 1 in the 800 mg group, and 1 in the placebo group), and others in 2 subjects (in the 200 mg group).

Table 5 shows results of the primary efficacy endpoint, proportion of subjects with all-cause hospitalization[16] or death by Day 29 in the MITT population (hereinafter referred to as “event”).

[13] Subjects received the study drug at an interval of 12 hours (±2 hours).
[14] The interim analyses were performed by the external data monitoring committee (eDMC) and standing internal data monitoring committee (siDMC) comprising sponsor members not directly involved in this study.
[15] In the study, ≥18-year-old inpatients with COVID-19 orally received molnupiravir 200, 400, or 800 mg or the placebo twice daily for 5 days.
[16] Hospitalization was defined as cases where acute care was provided for ≥24 hours in a hospital or similar acute care facility.

Table 5. Proportion of subjects with all-cause hospitalization or death by Day 29[a] (MITT population)

		Molnupiravir 200 mg	Molnupiravir 400 mg	Molnupiravir 800 mg	Placebo
Overall	Incidence of events	1.4% (1 of 74 subjects)	3.9% (3 of 77 subjects)	4.1% (3 of 74 subjects)	5.4% (4 of 74 subjects)
	Difference vs. placebo [95% CI][b]	-4.1 [-12.2, 2.5]	-1.5 [-9.9, 6.2]	-1.3 [-9.6, 6.4]	—
Age >60 years	Incidence of events	0% (0 of 18 subjects)	5.9% (1 of 17 subjects)	5.0% (1 of 20 subjects)	21.4% (3 of 14 subjects)
	Difference vs. placebo [95% CI][c]	-21.4 [-48.0, -1.2]	-15.5 [-43.5, 10.1]	-16.4 [-44.0, 6.8]	—
Had risk factors for severe COVID-19	Incidence of events	1.8% (1 of 56 subjects)	5.0% (3 of 60 subjects)	5.6% (3 of 54 subjects)	7.4% (4 of 54 subjects)
	Difference vs. placebo [95% CI][c]	-5.6 [-16.1, 3.0]	-2.4 [-13.3, 7.5]	-1.9 [-12.9, 8.8]	—
Received the first dose within 5 days after onset of COVID-19 symptoms	Incidence of events	2.0% (1 of 51 subjects)	3.8% (2 of 52 subjects)	2.1% (1 of 48 subjects)	8.0% (4 of 50 subjects)
	Difference vs. placebo [95% CI][c]	-6.0 [-17.2, 3.3]	-4.2 [-15.6, 6.2]	-5.9 [-17.1, 3.9]	—
Had risk factors for severe COVID-19 and received the first dose within 5 days after onset of COVID-19 symptoms	Incidence of events	2.6% (1 of 38 subjects)	5.3% (2 of 38 subjects)	3.2% (1 of 31 subjects)	11.8% (4 of 34 subjects)
	Difference vs. placebo [95% CI][c]	-9.1 [-24.5, 3.5]	-6.5 [-22.3, 7.5]	-8.5 [-24.1, 6.1]	—

—: Not applicable

a) No deaths occurred until Day 29, and all the events occurred as hospitalization. Unknown survival status on Day 29 was handled as an event, and early discontinuation from the study with known survival status on Day 29 of being alive but unknown hospitalization status on Day 29 was handled as non-event.

b) Calculated by the stratified Miettinen and Nurminen method using time from onset of COVID-19 (≤5 days vs. >5 days) and risk factors for severe COVID-19 (presence vs. absence) as stratification factors

c) Calculated by the Miettinen and Nurminen method

According to data on viral genome sequence at baseline obtained from 155 subjects, predominant SARS-CoV-2 clades[17] were 20A (23.9%), 20B (38.1%), 20C (12.9%), 20E (5.2%), and 20G (15.5%), while 20D, 20I (Alpha), and 20H (Beta) were detected in 0.6%, 0.6%, and 3.2% of the subjects, respectively.

For safety,[18] adverse events and adverse drug reactions[19] occurred in 33.8% (25 of 74) and 5.4% (4 of 74) of subjects in the molnupiravir 200 mg group, 24.7% (19 of 77) and 7.8% (6 of 77) of subjects in the 400 mg group, 39.2% (29 of 74) and 5.4% (4 of 74) of subjects in the 800 mg group, and 37.8% (28 of 74) and 6.8% (5 of 74) of subjects in the placebo group, respectively. Table 6 shows adverse events and adverse drug reactions reported by ≥2 subjects in any group.

[17] Nextstrain Clade (https://nextstrain.org/)

[18] Adverse events and adverse drug reactions that occurred within 14 days after end of the study treatment

[19] Adverse events assessed to be causally related to the study drug by the investigator

Table 6. Adverse events and adverse drug reactions reported by ≥2 subjects in any group (safety analysis population)

Event term	Adverse events				Adverse drug reactions			
	Molnupiravir 200 mg (n = 74)	Molnupiravir 400 mg (n = 77)	Molnupiravir 800 mg (n = 74)	Placebo (n = 74)	Molnupiravir 200 mg (n = 74)	Molnupiravir 400 mg (n = 77)	Molnupiravir 800 mg (n = 74)	Placebo (n = 74)
Overall	25 (33.8)	19 (24.7)	29 (39.2)	28 (37.8)	4 (5.4)	6 (7.8)	4 (5.4)	5 (6.8)
Neutrophilia	0	2 (2.6)	0	0	0	1 (1.3)	0	0
Palpitations	0	2 (2.6)	0	1 (1.4)	0	0	0	0
Abdominal pain	1 (1.4)	2 (2.6)	0	0	1 (1.4)	0	0	0
Abdominal pain upper	0	1 (1.3)	2 (2.7)	1 (1.4)	0	1 (1.3)	1 (1.4)	1 (1.4)
Constipation	0	1 (1.3)	0	2 (2.7)	0	0	0	0
Diarrhoea	3 (4.1)	2 (2.6)	2 (2.7)	4 (5.4)	2 (2.7)	2 (2.6)	1 (1.4)	2 (2.7)
Uvulitis	0	0	0	2 (2.7)	0	0	0	0
COVID-19	3 (4.1)	2 (2.6)	2 (2.7)	5 (6.8)	0	0	0	0
COVID-19 pneumonia	1 (1.4)	3 (3.9)	4 (5.4)	3 (4.1)	0	0	0	0
Pneumonia	1 (1.4)	0	3 (4.1)	0	0	0	0	0
Body temperature increased	2 (2.7)	0	0	1 (1.4)	0	0	0	0
C-reactive protein increased	1 (1.4)	0	1 (1.4)	2 (2.7)	0	0	0	0
Back pain	2 (2.7)	1 (1.3)	0	1 (1.4)	1 (1.4)	0	0	0
Dizziness	2 (2.7)	0	0	0	0	0	0	0

n (%), MedDRA ver 23.1

An adverse event leading to death occurred in 1 subject in the placebo group (COVID-19 pneumonia), and for this event, a causal relationship to the study drug was denied.

Serious adverse events occurred in 1 subject in the molnupiravir 200 mg group (COVID-19 pneumonia), 3 in the 400 mg group (COVID-19 pneumonia in 2 subjects and pulmonary embolism in 1 subject), and 4 in the 800 mg group (COVID-19 pneumonia in 3 subjects and pneumonia in 1 subject), and 4 in the placebo group (COVID-19 in 1 subject, COVID-19 pneumonia in 2 subjects, diabetic metabolic decompensation in 1 subject, and peripheral vascular disorder in 1 subject). For any of these events, a causal relationship to the study drug was denied.

Adverse events leading to discontinuation of the treatment occurred in 3 subjects in the molnupiravir 800 mg group (COVID-19 pneumonia in 2 subjects, hypoaesthesia in 1 subject, and insomnia in 1 subject [some subjects had more than 1 event]) and 1 in the placebo group (diarrhoea), and for the event in the placebo group, a causal relationship to the study drug could not be ruled out, and the outcome was “recovery.”

2.2.2 Phase III part (data cut-off on September 2021, preliminary data)

A randomized, double-blind, placebo-controlled, parallel-group study was conducted in ≥18-year-old patients with COVID-19 (target sample size, 1,550 [775 per group]) to investigate the efficacy and safety of molnupiravir at 146 study sites in 21 countries or regions including Colombia, Russia, South Africa, the US, and Japan. Table 7 shows main inclusion and exclusion criteria.

Table 7. Main inclusion and exclusion criteria

Inclusion criteria	1. Has a SARS-CoV-2-positive diagnostic test (confirmed by PCR test, etc., using a sample collected within 5 days prior to randomization). 2. Has initial onset of symptoms[a)] attributable to COVID-19 within 5 days prior to randomization and ≥1 symptoms[b)] attributable to COVID-19 on the day of randomization. 3. Has mild or moderate COVID-19 defined below. Definitions used to determine severity of COVID-19 are as follows: [Mild] (a) and (b) are met. (a) All of the following conditions are observed. Respiratory rate <20 breaths/min, heart rate <90 beats/min, and SpO_2 >93%[c)] (b) None of the following conditions is observed. Shortness of breath at rest or with exertion, respiratory failure,[d)] shock,[e)] and multiple organ dysfunction[f)] [Moderate] All of (a) to (c) are met. (a) ≥1 of the following conditions are observed. Shortness of breath with exertion, respiratory rate ≥20 to <30 breaths/min, and heart rate ≥90 to <125 beats/min (b) Any of the following conditions is observed. • SpO_2 >93%[c)] • On supplemental oxygen at ≤4 L/min since onset of COVID-19 regardless of SpO_2 (c) None of the following conditions is observed. Shortness of breath at rest, respiratory failure,[d)] shock,[e)] and multiple organ dysfunction[f)] 4. Has at least 1 of the following risk factors for severe COVID-19: • Age >60 years • Active cancer (excluding minor cancers not associated with immunosuppression or significant mortality such as basal cell carcinomas) • Chronic kidney disease • Chronic obstructive pulmonary disease • Obesity (BMI ≥30 kg/m^2) • Serious heart conditions (cardiac failure, coronary artery disease, or cardiomyopathy) • Diabetes mellitus 5. Males willing and able to use effective contraception for at least 4 days after end of the study treatment or non-pregnant females willing and able to use effective contraception for at least 4 days after end of the study treatment
Exclusion criteria	1. Is currently hospitalized or is expected to need hospitalization for COVID-19 within 48 hours of randomization. 2. Is on dialysis or has eGFR <30 mL/min/1.73 m^2. 3. Has HIV with a recent RNA viral load >50 copies/mL or an AIDS-defining illness in the past 6 months. 4. Has a neutrophil count <500/mm^3. 5. Has a history of HBV or HCV with any of the following: hepatic cirrhosis, end-stage liver disease, hepatocellular carcinoma, and AST or ALT >3 × upper limit of normal at screening. 6. Has a platelet count <100,000/μL or received platelet transfusion within 5 days prior to randomization 7. Was vaccinated for COVID-19. 8. Previously received monoclonal antibodies to SARS-CoV-2, the target virus of the study drug.

a) No specific symptoms defined.
b) Cough, sore throat, nasal congestion, runny nose, shortness of breath or difficulty breathing with exertion, muscle or body aches, fatigue, fever >38.0°C, chills, headache, nausea, vomiting, diarrhoea, loss of smell, or loss of taste
c) SpO_2 >93% on room air or on supplemental oxygen for a reason other than COVID-19 which has not increased since onset of COVID-19 symptoms
d) Respiratory failure is defined as a condition requiring at least 1 of the following (a) to (d): (a) endotracheal intubation and mechanical ventilation; (b) oxygen delivered by high-flow nasal cannula (at flow rates >20 L/min with fraction of delivered oxygen ≥0.5); (c) noninvasive positive pressure ventilation; and (d) extracorporeal membrane oxygenation (ECMO).
e) Shock is defined as a condition requiring vasopressors.
f) Multiple organ dysfunction is defined as an acute failure or dysfunction, at the discretion of the investigators, of at least 1 of respiratory, cardiovascular, renal, hematological, hepatic, and/or central nervous systems.

Subjects orally received molnupiravir 800 mg or the placebo twice daily[20)] for 5 days.

The phase III part was initiated after a dose for this part was selected from analysis on data from the completed phase II part [see Section 2.2.1]. In the phase III part of this study, 2 interim analyses were planned.[21)] The first analysis was planned to re-estimate the sample size when ≥30% of the initial target sample size (in total for both groups) were enrolled. The second analysis was planned to assess

[20)] Subjects received the study drug at an interval of 12 hours (±2 hours).
[21)] The results from the interim analysis were evaluated by the eDMC.

the efficacy data for study termination in the case of futility or early efficacy when 50% of the initial target sample size (in total for both groups) completed the follow-up through Day 29. The first and second interim analyses (hereinafter referred to as "interim analyses") were performed at the same time. Results from the interim analyses met the criteria for study termination for early efficacy, and thus new enrolment on October 2, 2021 and afterward was stopped as the efficacy of molnupiravir was recommended by the eDMC. In this section, the results from the concerned interim analyses are presented.

At the start of the study, the target sample size of 1,150 (575 per group) was estimated as the number of subjects required to ensure the power of 92% with a one-sided significance level of 2.5% for data on the primary endpoint, proportion of subjects with all-cause hospitalization or death by Day 29, on the assumption that the proportion was expected to differ between the molnupiravir and placebo groups by 6%. After results from the phase II part were obtained, the Protocol was revised. In the Protocol Amendment version 2 (April 4, 2021), the target sample size of 1,550 (775 per group) was re-estimated as the number of subjects required to ensure the power of 97% with a one-sided significance level of 2.5% for data on the primary endpoint, the expected proportion, on the assumption that the proportion was 6% in the molnupiravir group and 12% in the placebo group with an expected difference of 6%.

Of 775 randomized subjects (387 in the molnupiravir group and 388 in the placebo group), 765 (386 in the molnupiravir group and 379 in the placebo group) who received at least 1 dose of the study drug were included in the safety analysis. The safety analysis population comprises 762 subjects (385 in the molnupiravir group and 377 in the placebo group), excluding 13 subjects who were hospitalized before receiving the first dose of the study drug and was handled as the MITT population, which also served as the efficacy analysis population. The interim analysis did not include Japanese.

By Day 29, 38 subjects (17 in the molnupiravir group and 21 in the placebo group) discontinued the study[22] owing to deaths in 8 subjects (8 in the placebo group), lost to follow-up in 8 subjects (5 in the molnupiravir group and 3 in the placebo group), withdrawal in 21 subjects (12 in the molnupiravir group and 9 in the placebo group), and others in 1 subject (1 in the placebo group).

Table 8 shows results on the primary efficacy endpoint, proportion of subjects with all-cause hospitalization[23] or death by Day 29 in the MITT population (hereinafter referred to as "event"), and a comparison of the endpoint between the molnupiravir and placebo groups presented a statistically significant difference. Figure 2 shows a Kaplan-Meier curve on the primary endpoint or cumulative incidence of the event. Of the subjects who experienced the event, 28 in molnupiravir group and 52 in the placebo group experienced all-cause hospitalization; 0 in the molnupiravir group and 8 in the placebo group died of any cause; and 0 in the molnupiravir group and 1 in the placebo group experienced an unknown event (subjects who died after hospitalization were counted twice).[24]

[22] Discontinuation of subjects who received at least 1 dose of the study drug
[23] Cases where acute care was provided for ≥24 hours in a hospital or similar acute care facility.
[24] Hospitalization or death considered attributable to COVID-19 by the investigator, etc. occurred in 6.5% (25 of 385) of subjects in the molnupiravir group and 13.3% (50 of 377) of subjects in the placebo group.

Table 8. Proportion of subjects with all-cause hospitalization or death by Day 29 (MITT population)

	Molnupiravir	Placebo
Incidence of events	7.3% (28 of 385 subjects)	14.1% (53 of 377 subjects)
Difference vs. placebo [95% CI][a)]	-6.8 [-11.3, -2.4]	
One-sided *P* value[a),b)]	0.0012	

Unknown survival status on Day 29 was handled as an event, and early discontinuation from the study with known survival status on Day 29 of being alive but unknown hospitalization status on Day 29 was handled as non-event.

a) Stratified Miettinen and Nurminen method using time from symptom onset to randomization (≤3 days vs. >3 days) as a stratification factor (*Stat. Med.* 1985;4:213-26)

b) The Gamma family spending function with $\gamma = -1$ was used to adjust multiplicity of the hypothesis test in the interim analysis with a one-sided significance level of 0.0092 and overall one-sided significance level of 2.5%.

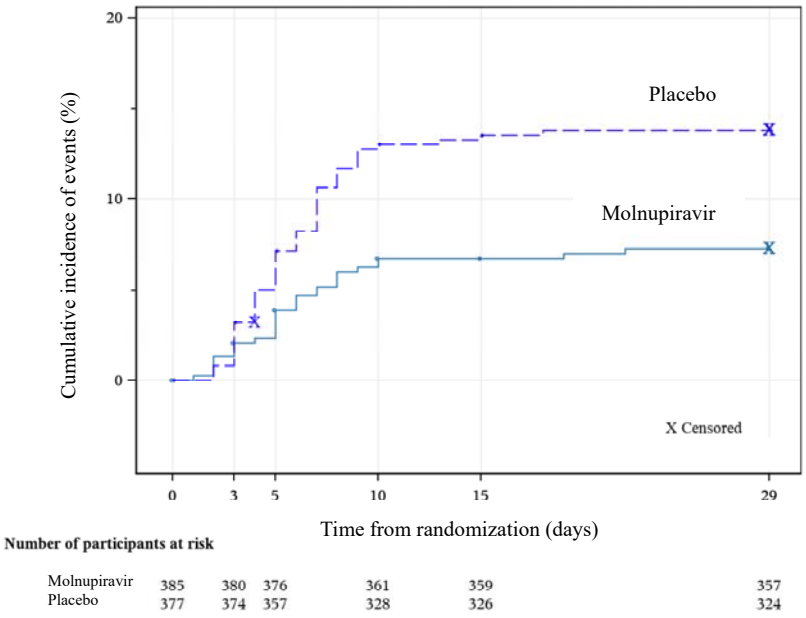

Figure 2. Cumulative incidence of events defined for the primary endpoint (MITT population)

Table 9 shows results from a subgroup analysis.

Table 9. Proportion of subjects with all-cause hospitalization or death by Day 29 (MITT population)

			Molnupiravir	Placebo
Anti-SARS-CoV-2 antibody at baseline	Present	Incidence of events	2.9% (2 of 70 subjects)	2.9% (2 of 69 subjects)
		Difference vs. placebo [95% CI][a)]	-0.0 [-7.5, 7.3]	
	Absent	Incidence of events	7.7% (23 of 299 subjects)	17.1% (49 of 287 subjects)
		Difference vs. placebo [95% CI][a)]	-9.4 [-14.9, -4.1]	
Severity of COVID-19	Mild	Incidence of events	5.4% (12 of 222 subjects)	10.3% (21 of 203 subjects)
		Difference vs. placebo [95% CI][a)]	-4.9 [-10.5, 0.2]	
	Moderate	Incidence of events	9.9% (16 of 161 subjects)	17.9% (31 of 173 subjects)
		Difference vs. placebo [95% CI][a)]	-8.0 [-15.5, -0.5]	
	Severe	Incidence of events	0% (0 of 2 subjects)	0 of 0 subjects
		Difference vs. placebo [95% CI][a)]	—	

Unknown survival status on Day 29 was handled as an event, and early discontinuation from the study with known survival status on Day 29 of being alive but unknown hospitalization status on Day 29 was handled as non-event.

a) Stratified Miettinen and Nurminen method using time from symptom onset to randomization (≤3 days vs. >3 days) as a stratification factor (*Stat. Med.* 1985;4:213-26)

Table 10 shows changes over time in viral load. On Day 3 and at end of the treatment (Day 5), the viral load was lower in the molnupiravir group than in the placebo group.

Table 10. Changes over time in viral load[a)] (nasopharyngeal swab)

	Molnupiravir	Placebo
Baseline	6.85 ± 1.658 (n = 314)	6.99 ± 1.616 (n = 304)
Day 3	5.82 ± 1.822 (n = 301)	6.16 ± 1.659 (n = 290)
Day 5	4.80 ± 1.547 (n = 285)	5.29 ± 1.703 (n = 286)
Day 10	3.70 ± 1.217 (n = 267)	3.86 ± 1.303 (n = 263)
Day 15	3.20 ± 0.852 (n = 266)	3.32 ± 0.952 (n = 245)
Day 29	2.90 ± 0.490 (n = 186)	2.91 ± 0.549 (n = 193)

Viral load, $\log_{10}$ copies/mL; Mean ± SD
Number of subjects who provided data on viral load at each time point
a) Detection limit, 500 copies/mL; the result below the detection limit was handled as 499 copies/mL.

According to data on viral genome sequence at baseline obtained from 277 subjects, the predominant SARS-CoV-2 clade[25)] was 21H (mu) (31.1% [41 of 132] of subjects in the molnupiravir group and 38.6% [56 of 145] of subjects in the placebo group) followed by 21A (delta) (25.0% [33 of 132 subjects] and 20.0% [29 of 145 subjects]) and 20J (gamma) (20.5% [27 of 132 subjects] and 24.1% [35 of 145 subjects]).

For safety,[26)] adverse events and adverse drug reactions[27)] occurred in 35.0% (135 of 386) and 12.4% (48 of 386) of subjects in the molnupiravir group and 39.6% (150 of 379) and 11.1% (42 of 379) of subjects in the placebo group. Table 11 shows adverse events and adverse drug reactions reported by ≥2 subjects in any group.

25) Nextstrain Clade (https://nextstrain.org/)
26) Adverse events and adverse drug reactions that occurred within 14 days after end of the study treatment
27) Adverse events assessed to be causally related to the study drug by the investigator

Table 11. Adverse events and adverse drug reactions reported by ≥2 subjects in any group (safety analysis population)

Event term	Adverse events		Adverse drug reactions	
	Molnupiravir (n = 386)	Placebo (n = 379)	Molnupiravir (n = 386)	Placebo (n = 379)
Overall	135 (35.0)	150 (39.6)	48 (12.4)	42 (11.1)
COVID-19	31 (8.0)	56 (14.8)	0	0
COVID-19 pneumonia	19 (4.9)	34 (9.0)	0	0
Diarrhoea	15 (3.9)	17 (4.5)	12 (3.1)	12 (3.2)
Nausea	11 (2.8)	5 (1.3)	9 (2.3)	4 (1.1)
Pneumonia bacterial	8 (2.1)	3 (0.8)	0	0
ALT increased	6 (1.6)	6 (1.6)	3 (0.8)	4 (1.1)
Hypertension	6 (1.6)	5 (1.3)	0	0
Dizziness	5 (1.3)	5 (1.3)	5 (1.3)	1 (0.3)
Rash	5 (1.3)	1 (0.3)	3 (0.8)	1 (0.3)
Respiratory failure	4 (1.0)	8 (2.1)	0	0
Platelet count increased	4 (1.0)	4 (1.1)	0	0
Pneumonia viral	4 (1.0)	4 (1.1)	0	0
Hyperkalaemia	4 (1.0)	2 (0.5)	0	0
Headache	4 (1.0)	1 (0.3)	4 (1.0)	0
Renal impairment	3 (0.8)	3 (0.8)	1 (0.3)	1 (0.3)
Vomiting	3 (0.8)	2 (0.5)	2 (0.5)	2 (0.5)
Vertigo	3 (0.8)	2 (0.5)	2 (0.5)	0
Anxiety	3 (0.8)	2 (0.5)	2 (0.5)	0
Diabetes mellitus	3 (0.8)	1 (0.3)	0	1 (0.3)
Gastroenteritis	3 (0.8)	0	1 (0.3)	0
Abdominal pain upper	2 (0.5)	5 (1.3)	2 (0.5)	4 (1.1)
Pneumonia	2 (0.5)	5 (1.3)	0	0
Insomnia	2 (0.5)	3 (0.8)	1 (0.3)	3 (0.8)
Blood glucose increased	2 (0.5)	3 (0.8)	0	0
Dyspepsia	2 (0.5)	2 (0.5)	2 (0.5)	2 (0.5)
Amylase increased	2 (0.5)	2 (0.5)	1 (0.3)	1 (0.3)
Lipase increased	2 (0.5)	2 (0.5)	1 (0.3)	1 (0.3)
Abdominal pain	2 (0.5)	2 (0.5)	0	1 (0.3)
Glomerular filtration rate decreased	2 (0.5)	2 (0.5)	0	0
Pruritus	2 (0.5)	1 (0.3)	1 (0.3)	1 (0.3)
Pharyngitis	2 (0.5)	0	0	0
AST increased	1 (0.3)	5 (1.3)	1 (0.3)	2 (0.5)
Dyspnoea	1 (0.3)	4 (1.1)	0	0
Blood creatine phosphokinase increased	1 (0.3)	3 (0.8)	1 (0.3)	0
Gastritis	1 (0.3)	3 (0.8)	1 (0.3)	0
Back pain	1 (0.3)	2 (0.5)	1 (0.3)	0
Chest pain	1 (0.3)	2 (0.5)	0	0
Platelet count decreased	1 (0.3)	2 (0.5)	0	1 (0.3)
Diabetes mellitus inadequate control	1 (0.3)	2 (0.5)	0	0
Cough	0	5 (1.3)	0	0
Dry mouth	0	4 (1.1)	0	3 (0.8)
Myalgia	0	3 (0.8)	0	1 (0.3)
Hepatic enzyme increased	0	2 (0.5)	0	1 (0.3)
Oral candidiasis	0	2 (0.5)	0	0
Body temperature increased	0	2 (0.5)	0	0
Acute respiratory failure	0	2 (0.5)	0	0
Pneumomediastinum	0	2 (0.5)	0	0
Pulmonary embolism	0	2 (0.5)	0	0
Hypotension	0	2 (0.5)	0	0

n (%), MedDRA ver 24.0

Adverse events leading to death occurred in 10 subjects in the placebo group (COVID-19 in 7 subjects, COVID-19 pneumonia in 3 subjects, respiratory failure in 2 subjects, and septic shock, staphylococcal bacteraemia, metastases to lung, and acute respiratory failure in 1 subject each [some subjects had more than 1 event]). For any of the events, a causal relationship to the study drug was denied.

Serious adverse events occurred in 28 subjects in the molnupiravir group (COVID-19 in 22 subjects, COVID-19 pneumonia in 15 subjects, respiratory failure in 4 subjects, pneumonia bacterial in 2 subjects, and anal abscess, peritonsillitis, pneumonia, pneumonia fungal, pneumonia staphylococcal, diabetic ketoacidosis, pneumonia aspiration, and shock in 1 subject each [some subjects had more than 1 event]); and 53 subjects in the placebo group (COVID-19 in 45 subjects; COVID-19 pneumonia in 28 subjects; respiratory failure in 8 subjects; pneumonia, pneumonia bacterial, and acute respiratory failure in 2 subjects each; and acute myocardial infarction, atrial flutter, pneumonia haemophilus, septic shock, staphylococcal bacteraemia, diabetic ketoacidosis, diabetic metabolic decompensation, type 2 diabetes mellitus, metastases to lung, acute kidney injury, cough, dyspnoea, hiccups, hypoxia, pneumomediastinum, pulmonary embolism, pulmonary hypertension, and respiratory distress in 1 subject each [some subjects had more than 1 event]). For any of the events, a causal relationship to the study drug was denied.

Adverse events leading to discontinuation of the treatment occurred in 5 subjects in the molnupiravir group (nausea and vomiting in 2 subjects each, and vision blurred, fatigue, peritonsillitis, tonsillitis, dizziness, and headache in 1 subject each [some subjects had more than 1 event]); and 13 subjects in the placebo group (COVID-19 in 7 subjects, COVID-19 pneumonia in 3 subjects, abdominal pain upper and diarrhoea in 2 subjects each, and chest discomfort, diabetic metabolic decompensation, myalgia, insomnia, and hiccups in 1 subject each [some subjects had more than 1 event]). For the events in 3 subjects in the molnupiravir group (vision blurred, nausea, vomiting, fatigue, dizziness, and headache in 1 subject each [some subjects had more than 1 event]) and ones in 3 subjects in the placebo group (abdominal pain upper and diarrhoea in 2 subjects each, and chest discomfort and insomnia in 1 subject each [some subjects had more than 1 event]), a causal relationship to the study drug could not be ruled out, and their outcome was “recovery” or “recovering.”

After the interim analysis, preliminary efficacy and safety data in all the 1,433 randomized subjects through Day 29 were published. The results are as shown below.[28),29)]

Table 12 shows results on the primary efficacy endpoint, proportion of subjects with all-cause hospitalization or death by Day 29 (hereinafter referred to as “event”). Of the subjects who experienced the event, 48 in molnupiravir group and 67 in the placebo group experienced all-cause hospitalization; 1 in the molnupiravir group and 9 in the placebo group died of any cause; and 0 in the molnupiravir group and 1 in the placebo group experienced an unknown event (subjects who died after hospitalization were counted twice).[30)]

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28) Material of US FDA Antimicrobial Drugs Advisory Committee Meeting November 30, 2021: https://www.fda.gov/media/154419/download, https://www.fda.gov/media/154422/download (last accessed on December 6, 2021)

29) Because the initially planned interim analysis indicated early termination for efficacy, the main results that lead to conclusion of this study should be data on the primary endpoint from the interim analysis, but data from the analysis in all the randomized subjects, of whom the number is greater than that of the subjects included in the interim analysis, also can support understanding of the efficacy of molnupiravir.

30) Hospitalization or death considered attributable to COVID-19 by the investigator, etc. occurred in 6.3% (45 of 709) of subjects in the molnupiravir group and 9.2% (64 of 699) of subjects in the placebo group.

Table 12. Proportion of subjects with all-cause hospitalization or death by Day 29 (MITT population)

	Molnupiravir	Placebo
Incidence of events	6.8% (48 of 709 subjects)	9.7% (68 of 699 subjects)
Difference vs. placebo [95% CI][a)]	-3.0 [-5.9, -0.1]	
One-sided *P* value[a)]	0.0218	

Unknown survival status on Day 29 was handled as an event.

a) Stratified Miettinen and Nurminen method using time from symptom onset to randomization (≤3 days vs. >3 days) as a stratification factor (*Stat. Med.* 1985;4:213-26)

For safety,[26)] adverse events and adverse drug reactions[27)] occurred in 30.4% (216 of 710) and 8.0% (57 of 710) of subjects in the molnupiravir group and 33.0% (231 of 701) and 8.4% (59 of 701) of subjects in the placebo group. Adverse events reported by ≥2% of subjects in either group were diarrhoea (2.3% [16 of 710] of subjects in the molnupiravir group and 3.0% [21 of 701] of subjects in the placebo group), COVID-19 (7.9% [56 of 710] and 9.8% [69 of 701]), COVID-19 pneumonia (6.3% [45 of 710] and 9.6% [67 of 701]), and pneumonia bacterial (2.0% [14 of 710] and 1.6% [11 of 701]). Adverse drug reactions reported by ≥1% of subjects in either group were diarrhoea (1.7% [12 of 710] of subjects in the molnupiravir group and 2.1% [15 of 701] of subjects in the placebo group), nausea (1.4% [10 of 710] and 0.7% [5 of 701]), and dizziness (1.0% [7 of 710] and 0.7% [5 of 701]). Adverse events leading to death occurred in 2 subjects in the molnupiravir group and 12 in the placebo group. Serious adverse events occurred in 49 subjects in the molnupiravir group and 67 in the placebo group. Adverse events leading to discontinuation of the treatment occurred in 10 subjects in the molnupiravir group and 20 in the placebo group.

In this study, 8 Japanese subjects (5 in the molnupiravir group and 3 in the placebo group) were enrolled,[31)] and of these 7 received at least 1 dose of the study drug (5 in the molnupiravir group and 2 in the placebo group) For efficacy, all-cause hospitalization or death by Day 29, the primary endpoint, occurred in 1 subject (molnupiravir group, hospitalization). For safety, adverse events occurred in 2 subjects in the molnupiravir group (hypoxia and vessel puncture site haemorrhage in 1 subject each) and 1 subject in the placebo group (blood sodium decreased). The adverse event of hypoxia in 1 subject was serious and also led to discontinuation of the treatment. For any of the adverse events, a causal relationship to the study drug was denied, and the outcome was “recovery.” No deaths occurred.

3. Summary of the submitted data

3.1 Efficacy

In vitro, NHC, a major metabolite of molnupiravir, was demonstrated to have an antiviral activity not only against a SARS-CoV-2 clinical isolate (USA-WA1/2020) with the half maximal effective concentration (EC_{50}) of 0.78-2.03 μmol/L (Vero E6 cells) but also against SARS-CoV-2 variants, B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), and B.1.617.2 (Delta) with the EC_{50} values of 1.59, 1.77, 1.32, and 1.68 μmol/L (Vero E6 cells), respectively, which were similar to the EC_{50} value against the clinical isolate. In addition, in *in vivo* models infected with SARS-CoV-2 clinical isolate (USA-WA1/2020) such as SARS-CoV-2-infected human lung tissue grafted in mice, turbinate in SARS-CoV-2-infected ferret, and lung tissue in SARS-CoV-2-infected hamster, molnupiravir was demonstrated to reduce the infectious viral load. On the basis of the non-clinical data, molnupiravir can be expected to have an antiviral activity against SARS-CoV-2.

31) Not included in the interim analysis.

In addition, the interim analysis of the phase III part of the global phase II/III study (Study MK-4482-002) in patients with COVID-19 [see Section 2.2.2] showed a statistically significant difference in the primary endpoint, proportion of subjects with all-cause hospitalization or death by Day 29, between the molnupiravir and placebo groups. Molnupiravir, therefore, can be expected to be effective in treatment of COVID-19 [see Section 2.2.2]. The difference in results through Day 29[32] between the molnupiravir and placebo groups was smaller in the analysis including all the randomized subjects than in the interim analysis. The applicant investigated causes for the smaller difference by comparing patient characteristics,[33] study environment, and other conditions before and after the interim analysis but could not identify definite causes. The smaller difference may have been a consequence of accumulated various factors after the interim analysis, but data through Day 29 in all the randomized subjects still show the lower proportion of subjects with all-cause hospitalization or death in the molnupiravir group than in the placebo group, not denying the efficacy of molnupiravir.

In view of the above findings, molnupiravir is expected to have efficacy in treatment of COVID-19. In the global phase II/III study (Study MK-4482-002), however, the phase III part only provided the preliminary data, and experience with molnupiravir in Japanese subjects is extremely limited. The applicant, therefore, should collect information continuously even after market launch and provide new findings to healthcare professionals immediately when they become available. In addition, information about the effectiveness of molnupiravir against variants and possible development of variants resistant to molnupiravir through its treatment can be critical for the efficacy of molnupiravir. The applicant, therefore, should collect the concerned information continuously even after market launch and provide new findings to healthcare professionals immediately when they become available.

3.2 Safety

Table 13 shows the summary of safety profile in the phase II part and phase III part up to the interim analysis in the global phase II/III study (Study MK-4482-002). No considerable differences were observed in incidence of adverse events, etc. between the molnupiravir and placebo groups. In the molnupiravir group, adverse events leading to death did not occur, and a causal relationship to the study drug was denied for the serious adverse events. For the adverse events leading to discontinuation of the treatment in 3 subjects (vision blurred, nausea, vomiting, fatigue, dizziness, and headache in 1 subject each [some subjects had more than 1 event]) in the phase III part, a causal relationship to the study drug could not be ruled out, and the outcome was “recovery.”

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[32] Because the initially planned interim analysis indicated early termination for efficacy, the main results that lead to conclusion of this study should be data on the primary endpoint from the interim analysis, but data from the analysis in all the randomized subjects, of whom the number is greater than that of the subjects included in the interim analysis, also can support understanding of the efficacy of molnupiravir.

[33] Characteristics compared were sex, age, race, region, ethnic group, time from COVID-19 symptom onset to randomization, risk factors for severe COVID-19, severity of COVID-19 at baseline, presence or absence of detectable SARS-CoV-2 RNA at baseline, presence or absence of anti-SARS-CoV-2 antibody at baseline, and variant type.

Table 13. Safety summary in global phase II/III study
(Study MK-4482-002, phase II part and phase III part up to the interim analysis)

	Study MK-4482-002 (phase II part)				Study MK-4482-002 (phase III part)	
Treatment	Molnupiravir 200 mg (n = 74)	Molnupiravir 400 mg (n = 77)	Molnupiravir 800 mg (n = 74)	Placebo (n = 74)	Molnupiravir 800 mg (n = 386)	Placebo (n = 379)
Adverse events	25 (33.8)	19 (24.7)	29 (39.2)	28 (37.8)	135 (35.0)	150 (39.6)
Adverse drug reactions	4 (5.4)	6 (7.8)	4 (5.4)	5 (6.8)	48 (12.4)	42 (11.1)
Serious adverse events	1 (1.4)	3 (3.9)	4 (5.4)	4 (5.4)	28 (7.3)	53 (14.0)
Adverse events leading to death	0	0	0	1 (1.4)	0	10 (2.6)
Adverse events leading to discontinuation of the treatment	0	0	3 (4.1)	1 (1.4)	5 (1.3)	13 (3.4)

n (%)

For safety in Japanese, according to the data in 8 Japanese subjects enrolled in the global phase II/III study (Study MK-4482-002) [see Section 2.2.2] and preliminary data from the Japanese phase I study in healthy Japanese adults (Study MK-4482-008[34)], adverse events occurred in 1 of 6 subjects in the molnupiravir 200 mg group (dermatitis) and 1 of 6 subjects in the 400 mg group (amylase increased and lipase increased in 1 subject each [some subjects had more than 1 event]) in the single-dose part; and 4 of 15 subjects in the 400 mg group (orthostatic hypotension in 2 subjects, and amylase increased and dizziness postural in 1 subject each), 8 of 15 subjects in the 800 mg group (toxic skin eruption[35)] in 3 subjects, blood creatine phosphokinase increased in 2 subjects, and postural orthostatic tachycardia syndrome, stomatitis, alanine aminotransferase [ALT] increased, dyshidrotic eczema, and eczema nummular in 1 subject each [some subjects had more than 1 event]), and 1 of 10 subjects in the placebo group (haemoglobin decreased) in the multiple-dose part. For the events in 1 subject in the 400 mg group (amylase increased and lipase increased) in the single-dose part as well as 1 subject in the 400 mg group (amylase increased) and 5 subjects in the 800 mg group (toxic skin eruption in 3 subjects and blood creatine phosphokinase increased in 2 subjects) in the multiple-dose part, a causal relationship to the study drug could not be ruled out. An adverse event leading to discontinuation of the treatment occurred in 1 subject in the molnupiravir 800 mg group (toxic skin eruption) in the multiple-dose part. Neither serious adverse events nor deaths occurred.

For safety of molnupiravir, reaching a definite conclusion is difficult because the phase III part of the global phase II/III study (Study MK-4482-002) provided only the preliminary data, and experience with molnupiravir in Japanese is extremely limited. Nevertheless, in view of the adverse events in clinical studies [see Sections 2.1, 2.2, and 3.2], Conditional Marketing Authorization issued in the UK, and Emergency Use Authorization filed with US FDA and recommendation gained from the Advisory Committee, it is considered possible to control the safety risk of molnupiravir by including not only precautions as presented in the SUMMARY OF PRODUCT CHARACTERISTICS in the UK but also the following points in the package insert. In addition, the applicant should collect information about

34) A single dose of molnupiravir 200, 400, 800, or 1,600 mg or the placebo was orally administered, and molnupiravir 400, 800 mg, or the placebo was orally administered twice daily for 5.5 days.

35) Clinical courses of toxic skin eruption are as follows: Case 1: On Day 4 of the study treatment, moderate rash spread from the bilateral flanks to the back, accompanied by wheal and itching. With dermal steroid and oral antihistamine, the concerned adverse event resolved 10 days later. Case 2: On Day 4 of the study treatment, mild rash without subjective symptoms developed, and redness was observed on the bilateral flanks. With oral steroid and oral antihistamine, the concerned adverse event resolved 10 days later. Case 3: On Day 4 of the study treatment, mild rash accompanied by itching developed on the neck, left flank, and back. With oral steroid and oral antihistamine, the concerned adverse event resolved 12 days later.

the safety of molnupiravir in Japanese continuously even after market launch and provide new findings to healthcare professionals immediately when they become available.

3.2.1 Use in pregnant women or in women who may possibly be pregnant

Molnupiravir should be contraindicated in pregnant women and women who may possibly be pregnant in view of the following points:

- To evaluate reproductive and developmental toxicity of molnupiravir, a study for fertility and early embryonic development to implantation in rats and embryo-fetal development studies in rats and rabbits were conducted. Major toxicological findings were noted in the embryo-fetal development study in rats, including teratogenicity to the fetal external surface, viscera, and skeleton, low fetal weight, and low mean number of sacral vertebrae. Non-clinical studies have indicated no genotoxic risk of molnupiravir or NHC.
- Plasma NHC exposure values ($AUC_{0\text{-}24\ h}$) at the no observed adverse effect level (NOAEL) of molnupiravir for teratogenicity (500 mg/kg) and at the NOAEL for embryo-fetal development (250 mg/kg) were 217 μmol·h/L and 58.3 μmol·h/L, respectively, which were approximately 2.9 and 0.8 times the clinical plasma NHC exposure ($AUC_{0\text{-}24\ h}$ = 75.6 μmol- h/L[36]).
- Although no safety information in pregnant women are available because of the relevant exclusion criterion for clinical studies, non-clinical study results indicate that molnupiravir may have a teratogenicity risk in humans.
- Drugs for treatment of COVID-19 available for pregnant women are approved in Japan.

For use in nursing women, whether molnupiravir administered to nursing women is excreted in milk or not remains unknown, but a study for effects on pre- and postnatal development, including maternal function, in rats showed no effect of molnupiravir exposure on neonatal development. The use in nursing women is considered unlikely to raise safety concerns.

3.3 Indication, dosage and administration, and clinical positioning

In view of the preliminary data from the phase III part of the global phase II/III study (Study MK-4482-002), the indication of molnupiravir should be “Treatment of disease caused by SARS-CoV-2 infection (COVID-19),” and the dosage and administration should be “The usual dosage for patients aged ≥18 years is 800 mg of molnupiravir orally administered twice daily for 5 days.”

In addition, because the phase III part of the global phase II/III study (Study MK-4482-002) allowed enrollment of patients with mostly mild to moderate I[37] COVID-19, molnupiravir can serve as a treatment option for the concerned patient population. Although a randomized, double-blind, placebo-controlled, parallel-group study (global phase II/III study, Study MK-4482-001) was conducted in patients requiring hospitalization for treatment of COVID-19 to investigate the efficacy and safety of molnupiravir which was administered at 200, 400, or 800 mg twice daily for 5 days, results from the planned interim analysis did not indicate definite efficacy and resulted in early termination before enrollment in the phase III part. In view of the concerned early termination, the

[36] Estimated plasma NHC exposure ($AUC_{0\text{-}24\ h}$) at a steady state in patients with COVID-19 who received molnupiravir 800 mg at an interval of 12 hours (Study MK-4482-001 and phase II part of Study MK-4482-002) according to the population pharmacokinetic model

[37] Guidelines for Diagnosis and Treatment of COVID 19, ver. 6.0, Ministry of Health, Labour and Welfare

applicant should include in the package insert a cautionary statement to the effect that the efficacy of molnupiravir in patients with severe COVID-19 has not been established.

Although the phase III part of the global phase II/III study (Study MK-4482-002) included patients with risk factors for severe COVID-19, and molnupiravir should be mainly administered to patients with risk factors for severe COVID-19, it is still considered useful to make molnupiravir available for patients who may necessitate it irrespective of the risk factors, for example, those who present with considerable symptoms potentially causing severe illness, such as high fever and respiratory symptoms, because (a) there are no treatment options for patients with mild to moderate disease without risk factors for severe COVID-19 in Japan; (b) the above study demonstrated the anti-viral effect of molnupiravir in patients with risk factors for severe COVID-19, which can be predicted in patients without the risk factors; and (c) molnupiravir is an oral formulation suitable for administration to patients with mild to moderate disease.

4. Overall Evaluation

On the basis of the data submitted, PMDA has concluded that molnupiravir is expected to have efficacy in the treatment of COVID-19, and that the safety can be controlled by providing appropriate precautions based on the obtained information. Because a part of the application data was given a grace period for submission, the quality, efficacy, and safety of molnupiravir must be evaluated again.

In view of the above, the indication, dosage and administration, and approval conditions for emergency approval of molnupiravir should be specified as shown below. Since the product is a drug with a new active ingredient, the re-examination period is 8 years. The product is not classified as a biological product or a specified biological product. The drug product and its drug substance are both classified as powerful drugs.

Indication

Treatment of disease caused by SARS-CoV-2 infection (COVID-19)

Dosage and Administration

The usual dosage for patients aged ≥18 years is 800 mg of molnupiravir orally administered twice daily for 5 days.

Approval Conditions

1. The applicant is obliged to fulfill the following duties set forth in each Item of Article 28, Paragraph 3 of the Cabinet Order for Enforcement of Pharmaceuticals and Medical Devices Act, pursuant to the provisions of Article 14-3, Paragraph 2 of the Pharmaceuticals and Medical Devices Act.
   (1) Matters related to Item 1
   The product is granted approval with a part of the data of clinical studies left unevaluated. The complete data should be submitted as soon as additional data of clinical studies become available.

(2) Matters related to Item 2

When learning about diseases, disorders, or death suspected to be caused by the product, the applicant is required to report them promptly.

(3) Matters related to Item 3

The applicant is required to take necessary actions to ensure that healthcare professionals who use the product can understand, and appropriately explain to patients (or their legally acceptable representatives), that the product has been granted Special Approval for Emergency and the objectives of said approval.

(4) Matters related to Item 4

The applicant is required to report the quantity of the product sold or provided, as necessary.

2. The product is approved with the following conditions, based on the provisions of Article 79, Paragraph 1 of the Pharmaceuticals and Medical Devices Act:

(1) The applicant is required to develop and appropriately implement a risk management plan.

(2) The applicant is required to request that physicians administer the product only to patients considered eligible for treatment with the product who, or whose legally acceptable representatives, have been provided with the efficacy and safety information of the product in written form, and have provided written informed consent before the treatment.

(3) Under Article 41 of the Ministerial Ordinance for Enforcement of the Pharmaceuticals and Medical Devices Act, the grace period for data submission is 6 months after the approval. If newly submitted data, etc., necessitate a change in the approved product information, the change may be ordered in accordance with the provision in Article 74-2, Paragraph 3 of the Pharmaceuticals and Medical Devices Act.

3. The product is approved based on Article 14-3, Paragraph 1 of the Pharmaceuticals and Medical Devices Act. The approval may be withdrawn in accordance with the provision in Article 75-3 of the Act in a case where (1) the product does not conform to any Item of Article 14-3, Paragraph 1 of the Act or (2) the withdrawal is necessary to prevent the emergence or expansion of public health risks.

Appendix

List of Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
$AUC_{0\text{-}24\ h}$	Area under the concentration-time curve from 0 to 24 hours
BMI	Body mass index
Cabinet Order for Enforcement of Pharmaceuticals and Medical Devices Act	Cabinet Order for Enforcement of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Cabinet Order No. 11, dated February 1, 1961)
COVID-19	Coronavirus disease caused by SARS-CoV-2 infection
ECMO	Extracorporeal membrane oxygenation
EC_{50}	Half maximal effective concentration
eGFR	Estimated glomerular filtration rate
Ministerial Ordinance for Enforcement of Pharmaceuticals and Medical Devices Act	Enforcement Ordinance for the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Ordinance of the Ministry of Health and Welfare No. 1, dated February 1, 1961)
MITT	Modified intent-to-treat
Molnupiravir	Molnupiravir
NHC	*N*-hydroxycytidine
PCR	Polymerase chain reaction
Pharmaceuticals and Medical Devices Act	Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices (Act No. 145 of August 10, 1960)
RNA	Ribonucleic acid
RT-PCR	Reverse transcription PCR
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
The product	Lagevrio Capsules 200 mg