Report on the Deliberation Results

February 10, 2022
Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau
Ministry of Health, Labour and Welfare

Brand Name	Paxlovid PACK
Non-proprietary Name	Nirmatrelvir (JAN*) and Ritonavir (JAN*)
Applicant	Pfizer Japan Inc.
Date of Application	January 14, 2022

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 February 10, 2022, 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 substance, nirmatrelvir, is not classified as a poisonous drug or a powerful drug, and its drug product is classified as a powerful drug.

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 7 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.

**Japanese Accepted Name (modified INN)*

Report on Special Approval for Emergency

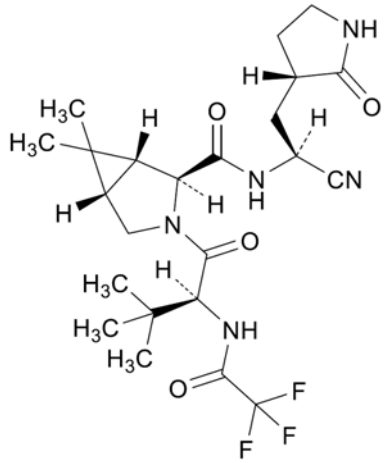
February 7, 2022
Pharmaceuticals and Medical Devices Agency

I. Product

Brand Name	Paxlovid PACK
Non-proprietary name	Nirmatrelvir (JAN*) and Ritonavir (JAN*)
Applicant	Pfizer Japan Inc.
Date of Application	January 14, 2022
Dosage Form/Strength	Each daily blister card contains 4 film-coated tablets each containing 150 mg of nirmatrelvir and 2 film-coated tablets each containing 100 mg of ritonavir.
Application Classification	Prescription drug, (1) Drug with a new active ingredient

Chemical Structure

Nirmatrelvir



Molecular formula: $C_{23}H_{32}F_3N_5O_4$

Molecular weight: 499.53

Chemical name: (1*R*,2*S*,5*S*)-*N*-{(1*S*)-1-Cyano-2-[(3*S*)-2-oxopyrrolidin-3-yl]ethyl}-3-[(2*S*)-3,3-dimethyl-2-(2,2,2-trifluoroacetamido)butanoyl]-6,6-dimethyl-3-azabicyclo[3.1.0]hexane-2-carboxamide

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

	0113-4, dated January 13, 2022, 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

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List of Abbreviations

See Appendix.

II. Summary of the submitted data

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

Coronavirus disease 2019 (COVID-19) is a disease caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection. Common symptoms include fever, 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 February 2, 2022, a total of 2,811,050 people have been infected (positive for polymerase chain reaction [PCR] test). Among them, 624,145 (including 886 with severe disease) needed hospitalization for treatment, 2,144,690 were discharged or released from medical treatment, and 18,871 died.[5]

Nirmatrelvir is an inhibitor of the SARS-CoV-2 main protease (Mpro), also known as 3C-like (3CL) protease, or nsp5, which was discovered by Pfizer Inc., and prevents cleavage of polyprotein, thereby inhibiting viral replication. In addition, ritonavir (hereinafter, referred to as "RTV") does not exert antiviral activity against SARS-CoV-2 but inhibits cytochrome P450 (CYP) 3A, the main metabolizing enzyme of nirmatrelvir, thereby maintaining the increased plasma concentrations of nirmatrelvir. RTV-containing products approved in Japan include Norvir Tablets 100 mg, Kaletra Combination Tablets, and Kaletra Combination Oral solution. Paxlovid is expected to exert its intended therapeutic effect when nirmatrelvir is co-administered with RTV. Paxlovid consisting of nirmatrelvir tablets and RTV tablets co-packaged in blister packs is available outside Japan. To enable such drug product to be marketed also in Japan, an application for Special Approval for Emergency has been submitted for the two drugs handled as a single product.

In response to the Emergency Use Authorization (EUA) granted to Paxlovid by the US Food and Drug Administration (FDA) and based on data from a global phase II/III study (Study C4671005), the applicant has submitted the application for Special Approval for Emergency of Paxlovid on the understanding that the product 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 regulatory submission, the applicant submitted the application data filed with the US FDA for the EUA, the FACT SHEET FOR HEALTHCARE PROVIDERS[6] prepared under the EUA by the US FDA, investigator's brochure, and the results of the global phase II/III study (Study C4671005). This report contains the results of review conducted based on the data submitted by the applicant, in

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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, Nos. 31 and 32 (combined issue): https://www.niid.go.jp/niid/images/idsc/idwr/IDWR2020/idwr2020-31-32.pdf (last accessed on February 2, 2022)]

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 February 2, 2022)

6 Document that contains information equivalent to that in the label used in the US

accordance with the "Handling of drugs intended to be submitted for Special Approval for Emergency (Request)" (PSEHB/PED Notification 0113-4, dated January 13, 2022).

2. Clinical Efficacy and Safety

The applicant submitted the results of the global phase II/III study (Study C4671005) in patients with COVID-19 as the main efficacy and safety data.

2.1 Global phase II/III study (Study C4671005, ongoing since July 2021, data cut-off in October 2021)

A randomized, double-blind, placebo-controlled, parallel-group study was conducted at 322 sites in 20 countries or regions including the US, Bulgaria, Mexico, India, Ukraine, and Japan to evaluate the efficacy and safety of nirmatrelvir/RTV in patients aged ≥18 years with COVID-19 (target sample size, 3,100 [1,550 per group][7]). Table 1 summarizes main inclusion and exclusion criteria.

[7] The primary endpoint was the proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28. On the hypothesis that the proportion in the placebo group was 7%, and a difference in the proportion between the nirmatrelvir and RTV combination (nirmatrelvir/RTV) group and placebo group was 3.5%, the number of participants required to ensure 90% power at a two-sided significance level of 5% was calculated to be 1,779. On the assumption that 20% of the participants would be excluded from the primary efficacy analysis set because they received or were expected to receive COVID-19 monoclonal antibody treatment, the proportion of such participants to be enrolled was planned to be up to approximately 25%. In a similar manner, on the assumption that 25% of the participants had experienced the onset of COVID-19 symptoms >3 days prior to randomization, the number of such participants to be enrolled was limited to approximately 1,000. In addition to the above assumptions, on the hypothesis that approximately 5% of the participants would drop out of the study, the target sample size was determined to be 3,100.

Table 1. Main inclusion and exclusion criteria

Inclusion criteria	1. Confirmed SARS-CoV-2 infection (determined by PCR test, etc. using a specimen collected within 5 days prior to randomization[a)]) 2. Experienced the onset of COVID-19 symptoms[b)] within 5 days prior to randomization and has at least 1 of the COVID-19 symptoms[b)] at the time of randomization. 3. Has at least 1 of the following risk factors for severe COVID-19. • ≥60 years of age • Body mass index (BMI) >25 kg/m^2 • Smoker (smoking within the past 30 days and has a history of smoking of at least 100 cigarettes in his or her lifetime) • Immunosuppressive disease[c)] or prolonged use of immunosuppressive drugs[d)] • Chronic lung disease (including asthma that requires daily treatment with prescription drugs) • Diagnosis of hypertension • Cardiovascular disease (e.g., a history of myocardial infarction, cerebral stroke, transient ischemic attack, cardiac failure, angina pectoris with prescribed nitroglycerin, coronary artery bypass graft, percutaneous coronary intervention, carotid endarterectomy, or aortic bypass) • Type 1 or 2 diabetes mellitus • Chronic kidney disease • Sickle cell disease • Neurodevelopmental disorders (e.g., cerebral palsy, Down's syndrome) or other conditions that confer medical complexity (e.g., genetic disease, metabolic syndromes, severe congenital anomalies) • Active cancer other than localized skin cancer • Medically-related technological dependence (e.g., continuous positive airway pressure, not related to COVID-19)
Exclusion criteria	1. Has a history of hospitalization for treatment of COVID-19 2. Current need for hospitalization or anticipated need for hospitalization within 48 hours after randomization 3. Has a history of confirmed SARS-CoV-2 infection as determined by antigen or nucleic acid detection test before the current infection 4. Has a history of active liver disease (e.g., active liver disease such as chronic or active hepatitis B or C virus infection, primary biliary cirrhosis, Child-Pugh Class B or C, or acute hepatic failure, except for nonalcoholic fatty liver) 5. Receiving dialysis or has moderate to severe renal impairment (estimated glomerular filtration rate [eGFR] <45 mL/min/1.73 m^2 calculated from a serum creatinine value within 6 months prior to screening visit, according to the Chronic Kidney Disease Epidemiology Collaboration [CKD-EPI] equation) 6. Has human immunodeficiency virus (HIV) infection either with a viral load >400 copies/mL or using prohibited concomitant drugs for HIV treatment 7. Has received or is expected to receive a vaccine against SARS-CoV-2 before the Day 34 visit 8. Oxygen saturation <92% (at rest, on room air)[e)] within 24 hours prior to randomization

a) "Within 72 hours prior to randomization" was changed to "within 5 days prior to randomization" in the Protocol Amendment 1 (July 2, 2021).
b) Cough, shortness of breath or difficulty breathing, fever (>38°C) or feeling feverish, chill or shivering, fatigue, muscle or body aches, diarrhoea, nausea, vomiting, headache, sore throat, stuffy or runny nose
c) Bone marrow transplantation, organ transplantation, primary immunodeficiency, HIV infection with CD4 positive cells <200/μL and a viral load <400 copies/mL, etc.
d) Has received corticosteroid at a dose -equivalent to prednisone ≥20 mg/day for consecutive ≥14 days within 30 days prior to entry in the study; or has received biological products (infliximab, ustekinumab, etc.) or immunomodulatory drugs (methotrexate, mercaptopurine, azathioprine, etc.), or cancer chemotherapy within 90 days prior to entry in the study
e) Value on standard home oxygen therapy for a patient who receives chronic supplementary oxygen for an underlying lung condition

Participants orally received nirmatrelvir/RTV 300 mg/100 mg[8] or placebo twice daily[9] for 5 days.

In this study, 2 interim analyses were planned.[10] The first interim analysis was performed to investigate the efficacy, futility, and need for re-estimation of sample size when approximately 45% of participants in the modified intent-to-treat (mITT) population completed assessment at 28 days after randomization (Day 28). The second one was to be performed to investigate the efficacy and futility when approximately 70% of participants in the mITT population completed the Day 28 assessment. The external data monitoring committee (E-DMC) recommended the termination of the study because the results of the first interim analysis (data cut-off on October 26, 2021) met the predetermined efficacy criteria. In response to the recommendation, participant enrollment was discontinued on November 5, 2021. The second interim analysis was not performed. Then, all the enrolled participants were analyzed for efficacy through Day 28 and for safety through Day 34 (data cut-off on December

[8] The dosage regimen was determined based on the following estimation: the plasma trough concentration of free nirmatrelvir following twice-daily oral administration of nirmatrelvir/RTV 300 mg/100 mg was estimated to be above the *in vitro* 90% effective concentration against SARS-CoV-2 (EC_{90}, 90.4 ng/mL) in >95% of the participants on the assumption that an inter-individual variation was approximately 60% according to a population pharmacokinetic model developed using data from clinical studies in healthy adults.
[9] An interval between the first and second doses had to fall within a range from 4 hours to 12 hours, and subsequent intervals had to be 12 hours (± 30 minutes).
[10] The interim analysis was performed by the E-DMC.

11, 2021, preliminary data). This report, unless otherwise specified, presents the results of the first interim analysis (hereinafter referred to as “interim analysis”) that would primarily determine the success of the study.

Of 1,361 randomized participants (678 in the nirmatrelvir/RTV group and 683 in the placebo group), 1,349 (672 and 677, respectively) who received at least 1 dose of the study drug were included in the safety analysis set. Of those who were randomized and received at least 1 dose of the study drug, 774 (389 and 385, respectively) with at least 1 post-baseline visit through Day 28 who at baseline neither received nor were expected to receive COVID-19 monoclonal antibody treatment, and who received the study drug within 3 days after the onset of COVID-19 symptoms were included in the mITT population, which was used for efficacy analysis.

A total of 107 participants (50 in the nirmatrelvir/RTV group and 57 in the placebo group) discontinued the study treatment through Day 34. The reasons for discontinuation were deaths in 10 participants (0 and 10, respectively), lost to follow-up in 16 participants (9 and 7, respectively), participant-requested withdrawal in 63 participants (31 and 32, respectively), and other reasons (10 and 8, respectively).

As efficacy data, Table 2 shows the primary endpoint/outcome, the proportion of participants with COVID-19 related hospitalization or death from any cause (hereinafter referred to as “event”) through Day 28 (mITT population). The outcome showed a statistically significant difference between the nirmatrelvir/RTV group and placebo group. Figure 1 shows a Kaplan-Meier curve on the cumulative proportion of participants with the event as the primary endpoint. Of the participants with the event, 3 in the nirmatrelvir/RTV group and 27 in the placebo group were hospitalized owing to COVID-19-related conditions and 0 and 7, respectively, died from any cause (participants who were hospitalized and then died were counted twice).

Table 2. Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 (mITT population)

	Nirmatrelvir/RTV	Placebo
Proportion of participants with the event	0.8% (3 of 389 participants)	7.0% (27 of 385 participants)
Difference vs. placebo [95% CI][a),b)]	−6.317% [-9.041%, −3.593%]	
P value[a),b),c)]	<0.0001	

a) Participants who had completed the Day 28 assessment were censored at the Day 34 visit or their last visits, and those who had discontinued the study treatment before the Day 28 assessment or are lost to follow-up were censored at the date of the last record.
b) A difference between the groups was calculated from the proportion of participants with the event estimated using the Kaplan-Meier method, and variances were calculated according to the Greenwood's formula. A confidence interval (CI) was calculated by a normal approximation method.
c) Wald test. The O'Brien-Fleming-type alfa-spending function was used to adjust multiplicity of the hypothesis testing in the interim analysis with a two-sided significance level of 0.2% and overall two-sided significance level of 5%.

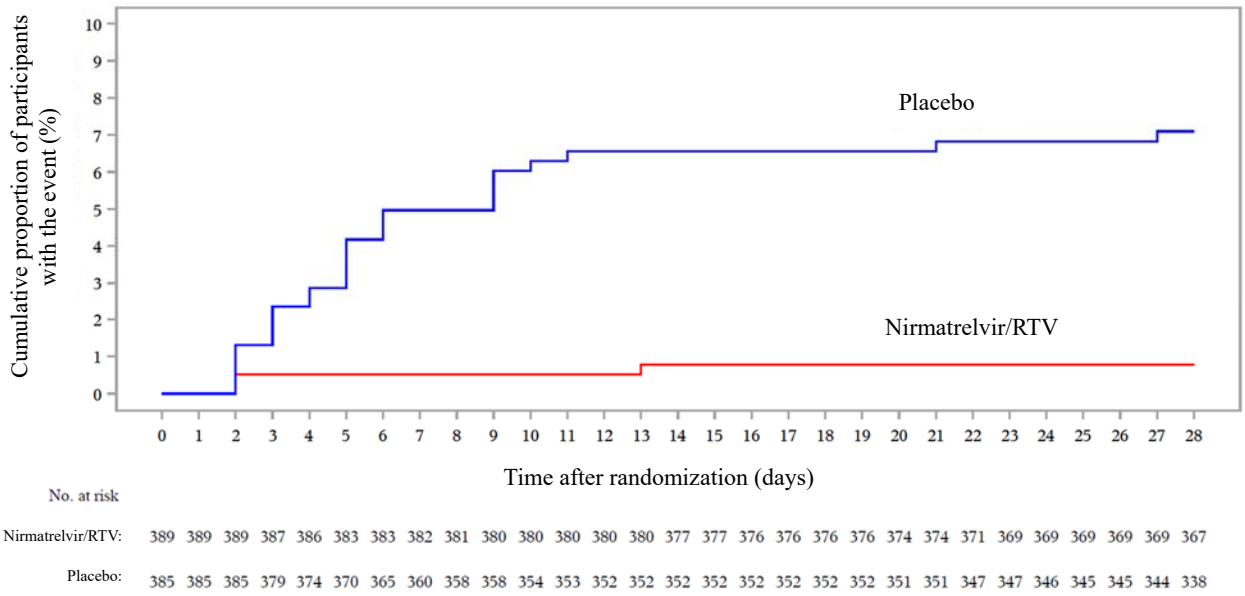

Figure1. Cumulative proportion of participants with the event of primary endpoint (mITT population)

Table 3 shows the proportions of participants with the event, the primary endpoint, in 2 analysis sets. One is the population of participants who were randomized and received at least 1 dose of the study drug, with at least 1 post-baseline visit through Day 28, and who at baseline neither received nor were expected to receive COVID-19 monoclonal antibody treatment (mITT1 population). The other is the population of participants who were randomized and received at least 1 dose of the study drug, with at least 1 post-baseline visit through Day 28 (mITT2 population). The results for the 2 analysis sets were not considerably different from the results of analysis in the mITT population.

Table 3. Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28

		Nirmatrelvir/RTV	Placebo
mITT1 population	Proportion of participants with the event[a)]	1.0% (6 of 607 participants)	6.7% (41 of 612 participants)
	Difference vs. placebo [95% CI][b),c)]	-5.765% [-7.917%, -3.613%]	
mITT2 population	Proportion of participants with the event[a)]	1.1% (7 of 661 participants)	6.4% (43 of 669 participants)
	Difference vs. placebo [95% CI][b),c)]	−5.425% [-7.460%, −3.390%]	

a) Details of participants with the event (subjects who were hospitalized and then died were counted twice)
mITT1 population: Hospitalization occurred in 6 participants in the nirmatrelvir/RTV group and 41 participants in the placebo group; and deaths in 0 and 10 participants, respectively.
mITT2 population: Hospitalization occurred in 7 and 43 participants, respectively; and deaths in 0 and 10 participants, respectively.
b) Participants who had completed the Day 28 assessment were censored at the Day 34 visit or their last visit, and those who had discontinued the study treatment before the Day 28 assessment or are lost to follow-up were censored at the date of the last record.
c) A difference between the groups was calculated from the proportion of participants with the event estimated using the Kaplan-Meier method, and variances were calculated according to the Greenwood's formula. A confidence interval (CI) was calculated by a normal approximation method.

Table 4 shows the proportions of participants with the event, the primary endpoint, in major subgroups.

Table 4. Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 (mITT population)

			Nirmatrelvir/RTV	Placebo
Age	<65 years	Proportion of participants with the event	0.6% (2 of 345 participants)	5.4% (18 of 334 participants)
		Difference vs. placebo [95% CI][a),b)]	−4.880% [−7.465%, −2.295%]	
	≥65 years	Proportion of participants with the event	2.3% (1 of 44 participants)	17.6% (9 of 51 participants)
		Difference vs. placebo [95% CI][a),b)]	−15.374% [−26.726%, −4.023%]	
Sex	Male	Proportion of participants with the event	1.0% (2 of 198 participants)	8.5% (17 of 201 participants)
		Difference vs. placebo [95% CI][a),b)]	−7.505% [−11.625%, −3.385%]	
	Female	Proportion of participants with the event	0.5% (1 of 191 participants)	5.4% (10 of 184 participants)
		Difference vs. placebo [95% CI][a),b)]	−4.990% [−8.467%, −1.513%]	
Anti SARS-CoV-2 serological status	Negative	Proportion of participants with the event	1.8% (3 of 168 participants)	13.7% (24 of 175 participants)
		Difference vs. placebo [95% CI][a),b)]	−12.173% [−17.739%, −6.607%]	
	Positive	Proportion of participants with the event	0% (0 of 217 participants)	1.5% (3 of 204 participants)
		Difference vs. placebo [95% CI][a),b)]	−1.478% [−3.138%, 0.182%]	

a) Participants who had completed the Day 28 assessment were censored at the Day 34 visit or their last visit, and those who had discontinued the study treatment before the Day 28 assessment or are lost to follow-up were censored at the date of the last record.
b) A difference between the groups was calculated from the proportion of participants with the event estimated using the Kaplan-Meier method, and variances were calculated according to the Greenwood's formula. A confidence interval (CI) was calculated by a normal approximation method.

Table 5 shows the preliminary data of an analysis (performed after the interim analysis) on efficacy through Day 28 in all enrolled participants. The results do not tend to be considerably different from results of the interim analysis.

Table 5. Proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 (after interim analysis,[a)] preliminary data)

		Nirmatrelvir/RTV	Placebo
mITT population	Proportion of participants with the event[b)]	0.717% (5 of 697 participants)	6.452% (44 of 682 participants)
	Difference vs. placebo [95% CI][c),d)]	−5.807% [−7.777%, −3.837%]	
	P value[c),d),e)]	<0.0001	
mITT1 population	Proportion of participants with the event[b)]	0.770% (8 of 1,039 participants)	6.310% (66 of 1,046 participants)
	Difference vs. placebo [95% CI][c),d)]	−5.619% [−7.207%, −4.031%]	
mITT2 population	Proportion of participants with the event[b)]	0.812% (9 of 1,109 participants)	6.099% (68 of 1,115 participants)
	Difference vs. placebo [95% CI][c),d)]	−5.363% [−6.884%, −3.842%]	

mITT population: Participants who were randomized and received at least 1 dose of the study drug, who at baseline neither received nor were expected to receive COVID-19 monoclonal antibody treatment, and who received the study drug within 3 days after the onset of COVID-19 symptoms

mITT1 population: Participants who were randomized and received at least 1 dose of the study drug, and who at baseline neither received nor were expected to receive COVID-19 monoclonal antibody treatment

mITT2 population: Participants who were randomized and received at least 1 dose of the study drug

a) Results of the analysis on efficacy through Day 28 in all enrolled participants (an analysis performed after the interim analysis)

b) Details of participants with the event (participants who were hospitalized and then died were counted twice)
mITT population: Hospitalization occurred in 5 participants in the nirmatrelvir/RTV group and 44 participants in the placebo group, and deaths in 0 and 9 participants, respectively.
mITT1 population: Hospitalization occurred in 8 and 65 participants, respectively; and deaths in 0 and 12 participants, respectively.
mITT2 population: Hospitalization occurred in 9 and 67 participants, respectively; and deaths in 0 and 12 participants, respectively.

c) Participants who had completed the Day 28 assessment were censored at the Day 34 visit or their last visit, and those who had discontinued the study treatment before the Day 28 assessment or are lost to follow-up were censored at the date of the last record.

d) A difference between the groups was calculated from the proportion of participants with the event estimated using the Kaplan-Meier method, and variances were calculated according to the Greenwood's formula. A confidence interval (CI) was calculated by a normal approximation method.

e) Wald test

Changes in viral load from baseline to Day 5 (nasopharyngeal swabs)[11] were −2.81 ± 0.14 $\log_{10}$ copies/mL (233 participants) in the nirmatrelvir/RTV group and −1.85 ± 0.13 $\log_{10}$ copies/mL (266 participants) in the placebo group. A difference between the groups was −0.96 ± 0.12 $\log_{10}$ copies/mL.

Of 878 participants who gave specimens available for SARS-CoV-2 base sequencing, 98.53% were found to be infected with the Delta variant.

Analysis was performed for safety.[12] Adverse events and adverse drug reactions[13] occurred in 19.8% (133 of 672) of participants and 7.3% (49 of 672) of participants, respectively, in the nirmatrelvir/RTV group and in 22.3% (151 of 677) of participants and 4.3% (29 of 677) of participants, respectively, in the placebo group. Table 6 shows adverse events and adverse drug reactions reported by ≥1% of participants in either group.

[11] Data cut-off on September 30, 2021. Data are presented as least squares mean ± standard error (SE). Values below the lower detection limit (100 copies/mL) were handled as 50 copies/mL (1.69 $\log_{10}$ copies/mL). Analyses of covariance (ANCOVA) model using treatment group, baseline viral load, whether or not participants at baseline received or were expected to receive COVID-19 monoclonal antibody treatment, geographic region, baseline serological status, and time from symptom onset as covariates. The mITT2 population excluded participants with no data on baseline viral load or with no virus detected or those without the specimen collected using a specified swab.

[12] Adverse events and adverse drug reactions that occurred before the Day 34 visit

[13] Adverse events considered by the investigator, etc. to be related to the study drug

Table 6. Adverse events and/or adverse drug reactions reported by ≥1% of participants in either group (safety analysis set)

Event term	Adverse events		Adverse drug reactions	
	Nirmatrelvir/RTV (N = 672)	Placebo (N = 677)	Nirmatrelvir/RTV (N = 672)	Placebo (N = 677)
Any event	133 (19.8)	151 (22.3)	49 (7.3)	29 (4.3)
Dysgeusia	32 (4.8)	1 (0.1)	25 (3.7)	1 (0.1)
Diarrhoea	26 (3.9)	13 (1.9)	13 (1.9)	2 (0.3)
Nausea	13 (1.9)	14 (2.1)	6 (0.9)	7 (1.0)
Headache	10 (1.5)	11 (1.6)	1 (0.1)	1 (0.1)
Vomiting	9 (1.3)	2 (0.3)	5 (0.7)	1 (0.1)
Pyrexia	8 (1.2)	7 (1.0)	0	1 (0.1)
COVID-19 pneumonia	5 (0.7)	23 (3.4)	0	0
Alanine aminotransferase increased	4 (0.6)	10 (1.5)	0	1 (0.1)
COVID-19	3 (0.4)	12 (1.8)	0	0
Fibrin D dimer increased	3 (0.4)	11 (1.6)	0	1 (0.1)
Pneumonia	2 (0.3)	7 (1.0)	0	0

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Adverse events leading to death did not occur in the nirmatrelvir/RTV group but occurred in 10 participants in the placebo group (COVID-19 pneumonia in 5 participants; COVID-19 in 2; and hypoxia, acute respiratory distress syndrome, and acute respiratory failure in 1 each). For all of them, the causal relationship to the study drug was ruled out.

Serious adverse events occurred in 13 participants in the nirmatrelvir/RTV group (COVID-19 pneumonia in 4 participants; COVID-19 in 2; and palpitations, chest discomfort, abscess, pneumonia, sepsis, creatinine renal clearance decreased, haemoglobin decreased, oxygen saturation decreased, facial paralysis, and dyspnoea in 1 participant each [some participants experienced multiple events]) and 46 participants in the placebo group (COVID-19 pneumonia in 21 participants; COVID-19 and pneumonia in 7 each; acute respiratory failure in 4; hypoxia in 3; creatinine renal clearance decreased, dyspnoea, and pneumonitis in 2 each; and rectal haemorrhage, atypical pneumonia, craniocerebral injury, eye injury, hand fracture, road traffic accident, wrist fracture, alanine aminotransferase increased, colon adenoma, acute respiratory distress syndrome, interstitial lung disease, and respiratory failure in 1 each [some participants experienced multiple events]). For the events in 1 participant in the nirmatrelvir/RTV group (palpitations, chest discomfort, and dyspnoea in 1 participant each [this participant experienced multiple events]), the causal relationship to the study drug could not be ruled out. The outcomes of the events were “resolved.”

Adverse events leading to treatment discontinuation occurred in 16 participants in the nirmatrelvir/RTV group (nausea in 5 participants; vomiting in 4; creatinine renal clearance decreased in 2; and palpitations, abdominal pain lower, colitis, diarrhoea, chest discomfort, COVID-19, COVID-19 pneumonia, differential white blood cell count abnormal, haemoglobin decreased, oxygen saturation decreased, white blood cell count decreased, myalgia, dizziness, dysgeusia, vaginal haemorrhage, dyspnoea, and rash maculo-papular in 1 each [some participants experienced multiple events]) and 29 participants in the placebo group (COVID-19 pneumonia in 10 participants; COVID-19 in 4; nausea, glomerular filtration rate decreased, acute respiratory failure, and hypoxia in 2 each; and diarrhoea, pneumonia, blood glucose increased, creatinine renal clearance decreased, glomerular filtration rate abnormal, restless legs syndrome, insomnia, cough, interstitial lung disease, respiratory failure, and rash in 1 each [some participants experienced multiple events]). For the events

in 7 participants in the nirmatrelvir/RTV group (nausea in 4 participants; vomiting in 3; and palpitations, colitis, diarrhoea, chest discomfort, myalgia, dizziness, dysgeusia, dyspnoea, and rash maculo-papular in 1 each [some participants experienced multiple events]) and 3 participants in the placebo group (nausea, blood glucose increased, and rash in 1 participant each), the causal relationship to the study drug could not be ruled out. The outcomes of the events were "resolving or resolved."

In addition, according to the preliminary data of the analysis (performed after the interim analysis) on safety through Day 34 in all enrolled participants, adverse events[14] occurred in 22.6% (251 of 1,109) of participants in the nirmatrelvir/RTV group and 23.9% (266 of 1,115) of participants in the placebo group. Table 7 shows adverse events reported by ≥1% of participants in either group. Adverse events leading to death occurred in 0 participants in the nirmatrelvir/RTV group and in 13 participants in the placebo group. Serious adverse events occurred in 1.6% (18 of 1,109) of participants in the nirmatrelvir/RTV group and 6.6% (74 of 1,115) of participants in the placebo group. Adverse events leading to treatment discontinuation occurred in 2.1% (23 of 1,109) of participants in the nirmatrelvir/RTV group and in 4.2% (47 of 1,115) of participants in the placebo group.[15]

Table 7. Adverse events reported by ≥1% of participants in either group (safety analysis set, after the interim analysis,[a)] preliminary data)

Event term	Nirmatrelvir/RTV (N = 1,109)	Placebo (N = 1,115)
Any event	251 (22.6)	266 (23.9)
Dysgeusia	62 (5.6)	3 (0.3)
Diarrhoea	34 (3.1)	18 (1.6)
Fibrin D dimer increased	21 (1.9)	31 (2.8)
Alanine aminotransferase increased	17 (1.5)	27 (2.4)
Nausea	16 (1.4)	19 (1.7)
Headache	15 (1.4)	14 (1.3)
Creatinine renal clearance decreased	16 (1.4)	18 (1.6)
Vomiting	12 (1.1)	9 (0.8)
Aspartate aminotransferase increased	10 (0.9)	14 (1.3)
C-reactive protein increased	9 (0.8)	13 (1.2)
Activated partial thromboplastin time prolonged	9 (0.8)	12 (1.1)
COVID-19 pneumonia	7 (0.6)	41 (3.7)
COVID-19	3 (0.3)	14 (1.3)
Pneumonia	2 (0.2)	15 (1.3)

n (%), MedDRA ver.24.1
a) Results of the analysis (performed after the interim analysis) on safety through Day 34 in all enrolled participants

Six Japanese participants (4 in the nirmatrelvir/RTV group and 2 in the placebo group)[16] were included in the analysis performed after the interim analysis.[17] Of the participants, 1 in the nirmatrelvir/RTV group was also included in the interim analysis. According to the efficacy analysis, none of the 4 Japanese participants in the nirmatrelvir/RTV group experienced COVID-19 related hospitalization or death from any cause through Day 28, and 1 of the 2 Japanese participants in the placebo group experienced COVID-19 related hospitalization. According to the safety analysis, adverse events occurred in 2 Japanese participants in the nirmatrelvir/RTV group (haemoptysis in 1 participant and dysgeusia in 2 [some participants experienced multiple events]) and 1 Japanese participant in the placebo group (hepatic enzyme abnormal and pulmonary embolism in 1 each [this

[14] No information on assessment of the causal relationship to the study drug has been submitted.
[15] No information on specific event terms has been submitted.
[16] Participants registered at the study site in Japan
[17] Analyses on efficacy through Day 28 and on safety through Day 34 in all enrolled participants were performed after the interim analysis.

participant experienced multiple events]). For dysgeusia in the nirmatrelvir/RTV group, the causal relationship to the study drug could not be ruled out. The outcome of the event was "resolved." Serious adverse events did not occur in the nirmatrelvir/RTV group but occurred in 1 Japanese participant in the placebo group (pulmonary embolism). For this event, the causal relationship to the study drug was ruled out. The outcome of the event was "resolved." No adverse events leading to death or treatment discontinuation occurred in either group.

3. Summary of the submitted data

3.1 Efficacy

Nirmatrelvir was shown to have *in vitro* antiviral activity against a SARS-CoV-2 clinical isolate (USA-WA1/2020 strain) (EC_{50} in differentiated normal human bronchial epithelial [dNHBE] cells, 61.8 nmol/L; EC_{50} in Vero E6 cells expressing transmembrane serine protease 2 [Vero E6-TMPRSS2 cells], 38 or 71.2 nmol/L). In addition, the EC_{50} values against SARS-CoV-2 variants, B.1.1.7 (Alpha), B.1.351 (Beta), P.1 (Gamma), B.1.617.2 (Delta), C.37 (Lambda), and B.1.1.529 (Omicron), were 170, 217, 204, 82.2, 93, and 23 nmol/L (Vero E6-TMPRSS2 cells), respectively, which were not considerably different from that against the SARS-CoV-2 clinical isolate (USA-WA1/2020). *In vivo* data showed that nirmatrelvir reduced viral titers in the lungs of mice infected with mouse-adapted SARS-CoV-2-MA10. Based on the above, non-clinical data could support the antiviral activity of nirmatrelvir against SARS-CoV-2.

In addition, the interim analysis in the global phase II/III study in patients with COVID-19 (Study C4671005) shows a statistically significant difference between the nirmatrelvir/RTV group and placebo group in terms of the proportion of participants with COVID-19 related hospitalization or death from any cause through Day 28 as the primary endpoint. Thus, nirmatrelvir/RTV combination is expected to have efficacy in treatment of COVID-19 [see Section 2.1].

In view of the above findings, Paxlovid (nirmatrelvir/RTV) is expected to have efficacy in treatment of COVID-19, but experience with the use of Paxlovid in Japanese patients is extremely limited. The applicant, therefore, should collect information continuously in the post-marketing setting and communicate new findings to healthcare professionals immediately when they become available. In addition, information about the antiviral activity of Paxlovid against SARS-CoV-2 variants and the possible development of variants resistant to either drug can be critical for the efficacy of Paxlovid. The applicant, therefore, should collect information continuously in the post-marketing setting and communicate new findings to healthcare professionals immediately when they become available.

3.2 Safety

Table 8 shows the summary of safety profile in the global phase II/III study (Study C4671005). According to the interim analysis, the incidences of adverse events, serious adverse events, adverse events leading to death, and adverse events leading to treatment discontinuation did not tend to be higher in the nirmatrelvir/RTV group than in the placebo group, but the incidence of adverse drug reactions tended to be higher in the former group. Major adverse events and adverse drug reactions[18]

[18] Adverse events and adverse drug reactions that were reported by ≥1% of participants in the nirmatrelvir/RTV group and that were reported by ≥2 more participants in the nirmatrelvir/RTV group than those in the placebo group

that tended to occur more frequently in the nirmatrelvir/RTV group than in the placebo group were dysgeusia, diarrhoea, and vomiting [see Section 2.1]. Of these, dysgeusia and diarrhoea were both non-serious and their outcomes were "resolved." Vomiting was non-serious and its outcome was "resolving" or "resolved." No adverse events leading to death occurred in the nirmatrelvir/RTV group. For the serious adverse events in 1 participant (palpitations, chest discomfort, and dyspnoea) and adverse events leading to treatment discontinuation in 7 participants (nausea in 4 participants; vomiting in 3; and palpitations, colitis, diarrhoea, chest discomfort, myalgia, dizziness, dysgeusia, dyspnoea, and rash maculo-papular in 1 each [some participants experienced multiple events]), the causal relationship to the study drug could not be ruled out. The outcomes of the events were "resolving" or "resolved." In addition, the safety profile of nirmatrelvir/RTV presented by an analysis performed after the interim analysis did not tend to be considerably different from that demonstrated by the interim analysis.

Table 8. Summary of safety profile in global phase II/III study (Study C4671005)

	Interim analysis		Analysis performed after interim analysis (preliminary data)[a)]	
	Nirmatrelvir/RTV (N = 672)	Placebo (N = 677)	Nirmatrelvir/RTV (N = 1,109)	Placebo (N = 1,115)
Adverse events	133 (19.8)	151 (22.3)	251 (22.6)	266 (23.9)
Adverse drug reactions	49 (7.3)	29 (4.3)	-	-
Serious adverse events	13 (1.9)	46 (6.8)	18 (1.6)[b)]	74 (6.6)[b)]
Adverse events leading to death	0	10 (1.5)	0	13 (1.2)[b)]
Adverse events leading to treatment discontinuation	16 (2.4)	29 (4.3)	23 (2.1)[b)]	47 (4.2)[b)]

n (%)
-, Not submitted
a) Preliminary results of the analysis (performed after the interim analysis) on safety through Day 34 in all enrolled participants
b) No information about specific event terms has been submitted.

Besides safety data from the global phase II/III study (Study C4671005) [see Section 2.1], some safety data in Japanese subjects were available. Japanese subjects living outside Japan were enrolled in a foreign phase I study (Study C4671001) that was conducted in healthy adults.[19] In this study, adverse events occurred in 4 of 4 Japanese participants in the nirmatrelvir/RTV group (abdominal discomfort, abdominal pain upper, diarrhoea, fatigue, fall, blood thyroid stimulating hormone increased, dysgeusia, and insomnia in 1 participant each [some participants experienced multiple events]) and 2 of 2 Japanese participants in the placebo + RTV group (fatigue, medical device site irritation, blood thyroid stimulating hormone increased, and pain in extremity in 1 participant each [some participants experienced multiple events]). For the events in 2 participants in the nirmatrelvir/RTV group (blood thyroid stimulating hormone increased, and dysgeusia in 1 participant each) and 1 participant in the placebo + RTV group (blood thyroid stimulating hormone increased), the causal relationship to the study drug could not be ruled out. The outcomes of the events were all "resolved." None of adverse events leading to death, serious adverse events, and adverse events leading to treatment discontinuation were reported.

[19] Either the combination of nirmatrelvir 250 mg (suspension) and RTV 100 mg or the combination of placebo and RTV 100 mg was orally administered in the fasted state twice daily for 10 days. The formulation of nirmatrelvir used in the foreign phase I study (Study C4671001) was different from one to be marketed, but nirmatrelvir 250 mg (suspension) and nirmatrelvir 300 mg (to-be-marketed formulation), when administered in combination with RTV 100 mg to non-Japanese participants, resulted in almost similar plasma nirmatrelvir exposure. The information about the safety of nirmatrelvir in this study is therefore considered to be useful in evaluating the safety of nirmatrelvir at the clinical dose in Japanese. For reference, the pharmacokinetic profile of nirmatrelvir is unlikely to differ between ethnic groups because (i) there were no clear ethnic differences in the pharmacokinetic profile of nirmatrelvir between Japanese and non-Japanese populations in the foreign phase I study (Study C4671001) or global phase II/III study (Study C4671005); and (ii) nirmatrelvir co-administered with RTV is mainly excreted into urine.

In light of the above findings, it is considered possible to control the safety risk of Paxlovid (nirmatrelvir/RTV) by including precautions for the following points in the package insert with reference to the FACT SHEET for Paxlovid authorized under the EUA in the US, though reaching a definite conclusion on the safety of Paxlovid is difficult due to very limited experience with the use of Paxlovid in Japanese individuals. In addition, the applicant should collect information about the safety of Paxlovid continuously in the post-marketing setting and communicate new findings to healthcare professionals immediately when they become available.

- In view of the incidences of adverse events and adverse drug reactions in the global phase II/III study (Study C4671005), precautions for dysgeusia, diarrhoea, vomiting, etc. should be included in the package insert.
- RTV-containing products approved in Japan (Kaletra Combination Tablets and Norvir Tablets 100 mg) are different from Paxlovid in terms of the target patient population (patients with HIV infection), dosage, the availability of a fixed-dose combination formulation,[20] and treatment period (long-term). Of events commonly listed as clinically significant adverse reactions among package inserts for the RTV-containing products, toxic epidermal necrolysis, oculomucocutaneous syndrome, and hepatic dysfunction should be referred to as those requiring precautions in the package insert, because (i) the risk of toxic epidermal necrolysis and oculomucocutaneous syndrome cannot be ruled out regardless of target patient population, dosage, and treatment period; and (ii) the FACT SHEET for Paxlovid authorized under the EUA in the US states that hepatic dysfunction is listed in association with RTV.[21] In addition, the other clinically significant adverse reactions commonly listed among package inserts of the RTV-containing products (hyperglycaemia, diabetes mellitus, and tendency of bleeding) are events potentially related to the characteristics of patients with HIV infection, long-term treatment, etc. and thus are unlikely to occur in patients with COVID-19. The applicant, however, should take appropriate actions to address these events, for example, by specifying these events as important potential risks for Paxlovid to monitor these events continuously in the post-marketing setting and by revising the package insert when new information becomes available.
- Since RTV, a component of Paxlovid, inhibits CYP3A, Paxlovid possibly interacts with many drugs. The package insert of Paxlovid, therefore, should include precautions for drugs which are contraindicated for concomitant use or require attention, with reference to labeling of the approved RTV-containing products. In addition, RTV is approved for treatment of HIV infection in Japan and used in limited cases. The approval of Paxlovid for treatment of COVID-19 will result in an increased number of medical institutions where RTV is used. The applicant should thoroughly inform healthcare professionals of the risk of drug interactions during the use of Paxlovid and the importance of confirming concomitant medications. At the same time, the applicant should appropriately provide information to healthcare professionals in order to facilitate understanding of the drug interactions. Furthermore, clinical drug interaction studies with nirmatrelvir/RTV

[20] The maintenance daily adult dose of Kaletra (fixed-dose combination tablets) is 800 mg of lopinavir and 200 mg of RTV, and that of Norvir (100-mg tablets) is 1200 mg of RTV.

[21] Although no definitive signal was detected in the global phase II/III study (Study C4671005), this event has been mentioned in the FACT SHEET of Paxlovid and RTV in light of the US label of VIEKIRA PAK (ombitasvir, paritaprevir, and ritonavir tablets; dasabuvir tablets [not approved in Japan]), whose regimen leads to administration of RTV at 100 mg/day for 12 to 24 weeks. (CDER Scientific Review Documents Supporting Emergency Use Authorizations for Drug and Biological Therapeutic Products: https://www.fda.gov/media/155194/download [last accessed on February 2, 2022])

co-administered with midazolam (substrate of CYP3A) or other drugs are currently ongoing. The applicant should appropriately communicate new findings to healthcare professionals when they become available.

3.3 Indication and clinical positioning

In view of results of the global phase II/III study (Study C4671005), Paxlovid should be indicated for the treatment of disease caused by SARS-CoV-2 infection (COVID-19).

Because the global phase II/III study (Study C4671005) included patients with generally mild to moderate I[22] COVID-19, Paxlovid can serve as a treatment option for such patient population. This study included patients with risk factors for severe COVID-19. Although Paxlovid should be mainly administered to the same patient population, PMDA still considers it useful to make Paxlovid available for patients in whom the use of Paxlovid is considered necessary irrespective of the risk factors, for example, those who present with considerable symptoms, such as high fever and respiratory symptoms, potentially causing severe illness, because (a) there are limited treatment options for patients with mild to moderate disease who have no risk factors for severe COVID-19 in Japan; (b) the above study demonstrated the anti-viral activity of Paxlovid (nirmatrelvir/RTV) in patients with risk factors for severe COVID-19, and similar results can be predicted for patients without the risk factors; and (c) Paxlovid is available as an oral formulation suitable for use in patients with mild to moderate disease. In addition, a randomized, double-blind, placebo-controlled study (global phase II/III study, Study C4671002, NCT05011513) is currently ongoing to investigate the efficacy and safety of nirmatrelvir/RTV 300 mg/100 mg orally administered twice daily for 5 days to patients with COVID-19 at non-high risk for severe COVID-19. The applicant should provide information about the appropriate target patient population of Paxlovid to healthcare professionals immediately when new findings about that become available from this study.

3.4 Dosage and administration

In view of results of the global phase II/III study (Study C4671005), the dosage and administration should be “The usual adult dosage is 300 mg of nirmatrelvir with 100 mg of ritonavir orally taken together twice daily for 5 days.”

In a foreign phase I study (Study C4671011)[23] in participants with renal impairment, AUC_{inf} values of nirmatrelvir (adjusted geometric means) in those with mild (eGFR ≥60 mL/min and <90 mL/min), moderate (eGFR ≥30 mL/min and <60 mL/min), and severe (eGFR <30 mL/min) renal impairment were approximately 24%, 87%, and 204%, respectively, higher than that in participants with normal renal function (eGFR ≥90 mL/min). The dosage and administration for patients with moderate renal impairment, therefore, should be “150 mg of nirmatrelvir with 100 mg of ritonavir orally taken together twice daily” so that their nirmatrelvir exposure will be comparable to that in patients with

[22] Guidelines for Diagnosis and Treatment of COVID 19, ver. 6.2, Ministry of Health, Labour and Welfare

[23] In this study, a single dose of nirmatrelvir 100 mg was administered in combination with RTV 100 mg (administered at −12, 0, 12, and 24 hours relative to the administration of nirmatrelvir) to participants with mild (eGFR ≥60 mL/min and <90 mL/min), moderate (eGFR ≥30 mL/min and <60 mL/min), and severe (eGFR <30 mL/min) renal impairment as well as those with normal renal function (eGFR ≥90 mL/min) to investigate the pharmacokinetics and safety.

normal renal function.[24] Note that the use of Paxlovid is not recommended in patients with severe renal impairment, in whom nirmatrelvir exposure would be further increased, because a recommended clinical dose in this patient population has not been investigated so far. The applicant has claimed that they plan to conduct a clinical study in patients with COVID-19 who have severe renal impairment (including patients on hemodialysis) to investigate the dosage and administration appropriate for this patient population. The results of this study should be used to determine the dosage and administration appropriate for patients with severe renal impairment.

In addition, although no clinical studies with nirmatrelvir/RTV have been conducted in children, it would be beneficial to make Paxlovid available for pediatric use in light of need of emergency actions to control the COVID-19 pandemic and an increasing number of pediatric patients with COVID-19.[25] Based on the following points, it is understandable to select the same dosage regimen for children aged ≥12 years and weighing ≥40 kg as that for adults. Furthermore, the EUA in the US also allows children aged ≥12 years and weighing ≥40 kg to receive Paxlovid at the same dosage regimen as that for adults. The applicant, however, should continuously collect information about the efficacy and safety of Paxlovid in children, including data from the planned clinical study in children and post-marketing investigations, and communicate new findings to healthcare professionals immediately when they become available.

- Nirmatrelvir is a SARS-CoV-2 main protease inhibitor; it targets an adventitious agent. The intended nirmatrelvir exposure is unlikely to differ between adults and children.
- Nirmatrelvir, when co-administered with RTV, is mainly excreted into urine. By 1 year of age, the renal function in children is developed to a similar extent to that in adults (N Engl J Med 2003; 349: 1157-67), and thus children aged ≥12 years are deemed to have similar renal function to that in adults.
- In a study using the population pharmacokinetic model,[26] estimated plasma nirmatrelvir exposure in children weighing ≥40 kg after twice-daily administration of nirmatrelvir/RTV 300 mg/100 mg was almost similar to that in adults. In addition, in the global phase II/III study (Study C4671005), adult patients weighing ≥40 and <50 kg received Paxlovid.

4. Overall Evaluation

On the basis of the data submitted, PMDA has concluded that Paxlovid 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 Paxlovid must be evaluated again.

In view of the above, the indication, dosage and administration, and approval conditions for emergency approval of Paxlovid should be specified as shown below. Since Paxlovid is a drug with a

[24] Plasma nirmatrelvir exposure in patients with moderate renal impairment was estimated on the assumption that clearance of nirmatrelvir would be reduced by half in the population pharmacokinetic model, developed using data from clinical studies in healthy adults, in view of the finding that the AUC_{inf} value of nirmatrelvir in participants with moderate (eGFR ≥30 mL/min and <60 mL/min) renal impairment was approximately 87% higher than that in participants with normal renal function (eGFR ≥90 mL/min)

[25] COVID-19 weekly surveillance update (Week 3 of 2022) of the National Institute of Infectious Diseases: https://www.niid.go.jp/niid/images/epi/PDF/COVID-19_2022w3.pdf (last accessed on February 2, 2022). The materials for the 69th meeting of the COVID-19 Advisory Board (January 26, 2022): https://www.mhlw.go.jp/content/10900000/000888030.pdf (last accessed on February 2, 2022).

[26] Plasma nirmatrelvir exposure was estimated with the difference in body weight distribution between adults and children taken into account.

new active ingredient, the re-examination period is 8 years. Paxlovid is not classified as a biological product or a specified biological product. The drug substance, nirmatrelvir, is not classified as a poisonous drug or a powerful drug, and its drug product is classified as a powerful drug.

Indication

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

Dosage and Administration

The usual dosage for adults and children aged ≥12 years and weighing ≥40 kg is 300 mg of nirmatrelvir with 100 mg of ritonavir orally taken together 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 7 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.

List of Abbreviations

3CL	3C-like
AUC_{inf}	Area under plasma concentration-time curve up to infinity
AUC_{tau}	Area under plasma concentration-time curve over the dosing interval
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)
CKD-EPI	Chronic kidney disease-epidemiology collaboration
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
COVID-19	Coronavirus disease or disease caused by SARS-CoV-2 infection
dNHBE	Differentiated normal human bronchial epithelial cells
EC_{50}	Concentration required for 50% effect
EC_{90}	Concentration required for 90% effect
eGFR	estimated glomerular filtration rate
FDA	Food and Drug Administration
HIV	Human immunodeficiency virus
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
Nirmatrelvir	Nirmatrelvir
Paxlovid	Paxlovid PACK
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)
PK	Pharmacokinetics
RTV	Ritonavir
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
TMPRSS	Transmembrane serine protease