Report on the Deliberation Results

November 6, 2020

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

Brand Name	Xofluza Tablets 20 mg
	Xofluza Granules 2%
Non-proprietary Name	Baloxavir Marboxil (JAN*)
Applicant	Shionogi & Co., Ltd.
Date of Application	October 16, 2019

Results of Deliberation

In its meeting held on October 30, 2020, the Second Committee on New Drugs concluded that the partial change application for the product may be approved and that this result should be presented to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

The re-examination period for the present application is the remainder of the re-examination period for the initial approval of the product (until February 22, 2026).

Approval Condition

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

**Japanese Accepted Name (modified INN)*

Review Report

October 19, 2020
Pharmaceuticals and Medical Devices Agency

The following are the results of the review of the following pharmaceutical product submitted for marketing approval conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Brand Name	Xofluza Tablets 20 mg Xofluza Granules 2%
Non-proprietary Name	Baloxavir Marboxil
Applicant	Shionogi & Co., Ltd.
Date of Application	October 16, 2019
Dosage Form/Strength	Film-coated tablets: Each tablet contains 20 mg of baloxavir marboxil. Granules: Each packet contains 10 mg of baloxavir marboxil (mass percent of the active ingredient, 2%).
Application Classification	Prescription drug, (4) Drugs with a new indication, (6) Drugs with a new dosage
Items Warranting Special Mention	None
Reviewing Office	Office of New Drug IV

Results of Review

On the basis of the data submitted, PMDA has concluded that the product has efficacy in the prophylaxis of influenza A or B virus infection, and that the product has acceptable safety in view of its benefits (see Attachment).

As a result of its review, PMDA has concluded that the product may be approved for the indication and dosage and administration shown below, with the following condition.

Indication

Treatment and prophylaxis of influenza A or B virus infection
(Underline denotes an addition: “prophylaxis of influenza A or B virus infection” is added to the approved indication.)

Dosage and Administration

Treatment

1. The usual dosage for adults and adolescents aged ≥12 years is two 20-mg tablets or four packets of granules (40 mg of baloxavir marboxil) administered orally as a single dose. In patients weighing ≥80 kg, four 20-mg tablets or eight packets of granules (80 mg of baloxavir marboxil) are administered orally as a single dose.

2. The usual dosage for children aged <12 years is the following, administered orally as a single dose.

Body weight	Dose
≥40 kg	Two 20-mg tablets or four packets of granules (40 mg of baloxavir marboxil)
≥20 kg and <40 kg	One 20-mg tablet or two packets of granules (20 mg of baloxavir marboxil)
[≥10 kg and <20 kg	One 10-mg tablet (10 mg of baloxavir marboxil)][1)]

Prophylaxis

1. The usual dosage for adults and adolescents aged ≥12 years is two 20-mg tablets or four packets of granules (40 mg of baloxavir marboxil) administered orally as a single dose. In patients weighing ≥80 kg, four 20-mg tablets or eight packets of granules (80 mg of baloxavir marboxil) are administered orally as a single dose.

2. The usual dosage for children aged <12 years is the following, administered orally as a single dose.

Body weight	Dose
≥40 kg	Two 20-mg tablets or four packets of granules (40 mg of baloxavir marboxil)
≥20 kg and <40 kg	One 20-mg tablet or two packets of granules (20 mg of baloxavir marboxil)

(Underline denotes additions.)

Approval Condition

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

[1)] Although the partial change application of the indications and dosage and administration for the prophylaxis does not involve Xofluza Tablets 10 mg, the dosage and administration for the treatment with Xofluza Tablets 10 mg remain unchanged or valid, and thus it is included for convenience.

Attachment

Review Report (1)

August 26, 2020

The following is an outline of the data submitted by the applicant and content of the review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA).

Product Submitted for Approval

Brand Name	Xofluza Tablets 20 mg Xofluza Granules 2%
Non-proprietary Name	Baloxavir Marboxil
Applicant	Shionogi & Co., Ltd.
Date of Application	October 16, 2019
Dosage Form/Strength	Film-coated tablets: Each tablet contains 20 mg of baloxavir marboxil. Granules: Each packet contains 10 mg of baloxavir marboxil (mass percent of the active ingredient, 2%).
Proposed Indication	Treatment and prophylaxis of influenza A or B virus infection (partial change application to add "prophylaxis of influenza A or B virus infection" to the approved indication)

Proposed Dosage and Administration

Treatment

1. The usual dosage for adults and adolescents aged ≥12 years is two 20-mg tablets or four packets of granules (40 mg of baloxavir marboxil) administered orally as a single dose. In patients weighing ≥80 kg, four 20-mg tablets or eight packets of granules (80 mg of baloxavir marboxil) are administered orally as a single dose.
2. The usual dosage for children aged <12 years is the following, administered orally as a single dose.

Body weight	Dose
≥40 kg	Two 20-mg tablets or four packets of granules (40 mg of baloxavir marboxil)
≥20 kg and <40 kg	One 20-mg tablet or two packets of granules (20 mg of baloxavir marboxil)
≥10 kg and <20 kg	One 10-mg tablet (10 mg of baloxavir marboxil)

Prophylaxis

1. The usual dosage for adults and adolescents aged ≥12 years is two 20-mg tablets or four packets of granules (40 mg of baloxavir marboxil) administered orally as a single dose. In patients weighing ≥80 kg, four 20-mg tablets or eight packets of granules (80 mg of baloxavir marboxil) are administered orally as a single dose.
2. The usual dosage for children aged <12 years is the following, administered orally as a single dose.

Body weight	Dose
≥40 kg	Two 20-mg tablets or four packets of granules (40 mg of baloxavir marboxil)
≥20 kg and <40 kg	One 20-mg tablet or two packets of granules (20 mg of baloxavir marboxil)
≥10 kg and <20 kg	One packet of granules (10 mg of baloxavir marboxil)
<10 kg	Granules at 50 mg/kg (1 mg/kg of baloxavir marboxil)

(Underline denotes additions.)

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List of Abbreviations

See Appendix.

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

Baloxavir marboxil (hereinafter referred to as baloxavir) is an influenza antiviral drug discovered by Shionogi & Co., Ltd. It is rapidly hydrolyzed to S-033447 (the active form of baloxavir marboxil) by arylacetamide deacetylase in the small intestine, blood, liver, etc. S-033447 inhibits the activity of endonuclease, which cleaves the cap structure of host pre-mRNA in cells infected with influenza virus (RNA virus). This results in the inhibition of transcription of influenza virus RNA in the infected cells, leading to suppression of viral replication in host cells.

In Japan, uncoated tablets and film-coated tablets containing baloxavir as an active pharmaceutical ingredient (brand name, Xofluza Tablets 10 mg, Xofluza Tablets 20 mg [baloxavir tablets]) were approved for marketing with the indication of "influenza A or B virus infection" in adults, adolescents aged ≥12 years, and children aged <12 years and weighing ≥10 kg in February 2018. Then, a marketing application for an additional dosage form of granules containing baloxavir at 2% (baloxavir granules) was submitted and approved on September 14, 2018.

The applicant conducted a clinical study of baloxavir 20-mg tablets or baloxavir granules for prophylaxis against influenza A or B virus infection in household contacts (adults and children) of a patient with the infection (index patient) (prophylactic study) (Study T0834). In this study, baloxavir was demonstrated to suppress onset of influenza virus infection with no additional safety concerns. The applicant therefore has filed a marketing application pertinent to a drug with a new indication and a new dosage. As of August 14, 2020, baloxavir has been approved for treatment of influenza virus infection in 21 foreign countries including the US, Hong Kong, and Thailand, but not approved for the prophylaxis in any country or region.

2. Data Relating to Quality and Outline of the Review Conducted by PMDA

In the present application, no data relating to quality have been submitted.

3. Non-clinical Pharmacology and Outline of the Review Conducted by PMDA

The pharmacological action of S-033447 was investigated in primary pharmacodynamics studies. In addition, unless otherwise specified in Section 3.1.1, 0.5% (w/v) methylcellulose solution was used as vehicle.

3.1 Primary pharmacodynamics

3.1.1 *In vivo* antiviral activity

3.1.1.1 Mortality reduction and suppression of body weight decrease by prophylactic use of S-033447 against influenza A or B virus (CTD 4.2.1.1-01, CTD 4.2.1.1-02)

Female BALB/c mice subcutaneously received a vehicle or S-033447 suspension (0.8 or 1.6 mg/kg) as a single dose and then were intranasally inoculated with influenza A virus A/PR/8/34 strain (H1N1) (2.6 $\log_{10}$ [4.00×10^2] 50% tissue culture infectious dose [$TCID_{50}$] [lethal load]) at 48, 72, or 96 hours post-dose. The survival rate was evaluated at 28 days after inoculation. Table 1 shows survival rate in each group. In groups inoculated with the virus at 48, 72, or 96 hours after receiving subcutaneous S-033447 suspension at 0.8 or 1.6 mg/kg, the survival period was longer in a dose-dependent manner than that in the vehicle control group. Changes in body weight were measured until 7 days after inoculation; the

vehicle control group showed a body weight decrease probably associated with viral replication, but the S-033447 groups showed a dose-dependent suppression of body weight decrease.

Table 1. Survival rates in mice at 28 days after inoculation of influenza A virus

S-033447 dose (mg/kg)	Survival rates at 28 days after inoculation		
	Administered 48 hours before inoculation	Administered 72 hours before inoculation	Administered 96 hours before inoculation
0 (vehicle)	0% (0/10)	10% (1/10)	0% (0/10)
0.8	100% (10/10)	20% (2/10)	10% (1/10)
1.6	100% (10/10)	100% (10/10)	100% (10/10)

% (number of survived animals/number of animals tested)

Female BALB/c mice subcutaneously received a vehicle or S-033447 suspension (1.6, 3.2, or 6.4 mg/kg) as a single dose and then were intranasally inoculated with influenza B virus B/Hong Kong/5/72 strain (3.3 $\log_{10}$ [1.80×10^3] $TCID_{50}$ [lethal load]) at 48, 72, or 96 hours post-dose. The survival rate was evaluated at 28 days after inoculation. Table 2 shows survival rates in each group. In groups inoculated with the virus at 72 or 96 hours after receiving subcutaneous S-033447 suspension at 1.6 mg/kg and animals inoculated with the virus at 48, 72, or 96 hours after receiving subcutaneous S-033447 suspension at 3.2 or 6.4 mg/kg, the survival period was longer than that in the vehicle control group. Changes in body weight were measured until 7 days after virus inoculation; the S-033447 groups showed a dose-dependent suppression of body weight decrease associated with viral replication.

Table 2. Survival rates in mice at 28 days after inoculation of influenza B virus

S-033447 dose (mg/kg)	Survival rates at 28 days after inoculation		
	Administered 48 hours before inoculation	Administered 72 hours before inoculation	Administered 96 hours before inoculation
0 (vehicle)	10% (1/10)	10% (1/10)	20% (2/10)
1.6	40% (4/10)	50% (5/10)	50% (5/10)
3.2	80% (8/10)	100% (10/10)	70% (7/10)
6.4	100% (10/10)	100% (10/10)	100% (10/10)

% (number of survived animals/number of animals tested)

In groups[2)] of influenza A and B virus infection mouse models that showed a significantly longer survival period than the vehicle control group, the minimum plasma S-033447 concentration at 24 hours after inoculation was 0.444 ng/mL for influenza A virus (1.6 mg/kg, the group receiving S-033447 96 hours before inoculation) and 2.35 ng/mL for influenza B virus (3.2 mg/kg, the group receiving S-033447 72 hours before inoculation). The applicant therefore explained that S-033447 is expected to have a prophylactic effect against influenza A and B virus infections when administered at doses and timing that achieve the plasma S-033447 concentration of ≥0.444 ng/mL (influenza A) and ≥2.35 ng/mL (influenza B) at 24 hours after inoculation.

2) The applicant's explanation about investigation of effective concentration in prophylaxis of influenza virus infection:
- In all groups classified by timing of administration (48, 72, and 96 before inoculation), 1 or 2 animals receiving 0.8 mg/kg had a S-033447 concentration below the lower limit of quantitation (<0.100 ng/mL). Therefore, the dose of 0.8 mg/kg was excluded from the investigation of effective concentration in prophylaxis of influenza virus infection.
- A group showing significantly longer survival than the vehicle control group was excluded from the investigation if another group had a higher plasma S-033447 concentration at 24 hours after inoculation than the group but showed no significantly longer survival than the vehicle control group.

3.1.1.2 Suppression of intrapulmonary viral replication by prophylactic S-033447 administration against influenza A or B virus (CTD 4.2.1.1-03, CTD 4.2.1.1-04)

Female BALB/c mice subcutaneously received a single dose of (a) vehicle or S-033447 suspension 3.2 mg/kg or (b) S-033447 suspension 1.6 mg/kg and, at (a) 72 hours post-dose or (b) 96 hours post-dose, were intranasally inoculated with influenza A virus A/PR/8/34 strain (H1N1) (2.6 $\log_{10}$ [4.00×10^2] $TCID_{50}$ [lethal load]). Changes in intrapulmonary viral titer until 10 days after inoculation were evaluated. Table 3 shows changes in intrapulmonary viral titer in each group. Intrapulmonary viral titers in the S-033447 groups remained lower than that in the vehicle group from Day 1 of viral inoculation.

Table 3. Intrapulmonary viral titer in mice treated with S-033447 before influenza A virus infection

S-033447 dose (mg/kg)	Time from dosing to inoculation	Intrapulmonary viral titer ($TCID_{50}$/mL)					
		1 day after inoculation	2 days after inoculation	4 days after inoculation	6 days after inoculation	8 days after inoculation	10 days after inoculation
0 (vehicle)	72 hours	4.12 ± 0.37 (10/10)	5.64 ± 0.23 (10/10)	6.02 ± 0.38 (10/10)	5.19 ± 0.30 (10/10)	2.80 ± 1.37 (2/10)	-
1.6	96 hours	3.03 ± 0.50 (9/9)	4.88 ± 0.40 (10/10)	5.07 ± 0.59 (10/10)	5.05 ± 0.40 (10/10)	2.36 ± 1.07 (9/10)	1.50 ± 0.00[a)] (8/10)
3.2	72 hours	1.73 ± 0.41 (10/10)	3.18 ± 0.73 (10/10)	3.51 ± 0.94 (10/10)	3.46 ± 0.66 (10/10)	1.83 ± 0.74 (10/10)	1.50 ± 0.00[a)] (10/10)

Mean ± standard deviation (SD) (number of survived animals/number of animals tested)
-, Not applicable (all animals died)
a) Limit of quantitation

Female BALB/c mice subcutaneously received a single dose of (a) vehicle or S-033447 suspension 3.2 mg/kg or (b) S-033447 suspension 6.4 mg/kg and, at (a) 72 hours post-dose or (b) 48 hours post-dose, were intranasally inoculated with influenza B virus B/Hong Kong/5/72 strain (3.3 $\log_{10}$ [1.80×10^3] $TCID_{50}$ [lethal load]). Intrapulmonary viral titers until 10 days after inoculation were evaluated. Table 4 shows changes in intrapulmonary viral titer in each group. Intrapulmonary viral titers in the S-033447 groups remained lower than that in the vehicle group from 1 day after viral inoculation.

Table 4. Intrapulmonary viral titer in mice treated with S-033447 before influenza B virus infection

S-033447 dose (mg/kg)	Time from dosing to inoculation	Intrapulmonary viral titer ($TCID_{50}$/mL)					
		1 day after inoculation	2 days after inoculation	4 days after inoculation	6 days after inoculation	8 days after inoculation	10 days after inoculation
0 (vehicle)	72 hours	2.92 ± 0.41 (10/10)	5.42 ± 0.30 (10/10)	5.15 ± 0.29 (10/10)	4.32 ± 0.45 (10/10)	3.00 (1/10)	-
3.2	72 hours	1.96 ± 0.44 (10/10)	4.79 ± 0.31 (10/10)	4.77 ± 0.41 (10/10)	4.23 ± 0.41 (10/10)	1.78 ± 0.40 (10/10)	1.50 ± 0.00[a)] (5/10)
6.4	48 hours	1.65 ± 0.15 (10/10)	3.88 ± 0.37 (10/10)	3.97 ± 0.37 (10/10)	3.68 ± 0.25 (10/10)	1.55 ± 0.08 (10/10)	1.50 ± 0.00[a)] (10/10)

Mean ± SD (number of survived animals/number of animals tested)
-, Not applicable (all animals died)
a) Limit of quantitation

3.1.2 Selection of resistant virus

3.1.2.1 Development of S-033447-resistant strains in prophylactic study (Study T0834) (CTD 5.3.5.4-01, 5.3.5.4-03)

A prophylactic study (Study T0834) was conducted in household contacts of patients with influenza A or B virus infection (index patients). Of 749 subjects in the modified intention-to-treat (mITT) population (374 in the baloxavir group, 375 in the placebo group), 186 (63 in the baloxavir group, 123 in the placebo group) tested positive for influenza virus by a reverse transcription polymerase chain

reaction (RT-PCR) either before or after administration. From the 186 positive subjects and their corresponding 114 index patients (limited to patients with Day 1 sequence data), samples were collected and subjected to base sequence analysis on the region coding the polymerase acidic protein (PA)[3)] by Sanger sequencing.

The analysis did not detect any amino acid substitution virus in the index patients or pre-dose subjects at the time of screening (Day 1). After administration of the study drug, substitutions were detected at the residue 38 of isoleucine in the PA protein (PA/I38) in 12 subjects (10 in the baloxavir group, 2 in the placebo group) (subtype A/H1N1pdm, I38T in 3 subjects; subtype A/H3NX, I38T in 8 subjects and I38M in 1 subject) and at the residue 23 of glutamic acid in the PA protein (PA/E23) in 5 subjects (5 in the baloxavir group, 0 in the placebo group) (subtype A/H1N1pdm, E23K in 4 subjects; subtype A/H3NX, E23K in 1 subject).

3.1.2.2 Replication of resistant virus

3.1.2.2.1 Replication of recombinant viruses with amino acid substitution (CTD 4.2.1.1-09, 4.2.1.1-10)

MDCK cells or RPMI2650 cells were infected with recombinant virus strains with PA/I38 or PA/E23K substitution generated by reverse genetics and their parent strains (A/H1N1, rgA/WSN/33-PA; A/H3N2, rgA/Victoria/3/75-PA; type B, rgB/Maryland/1/59-PA), and effects of these amino acid substitutions on viral replication were investigated using the viral titer as an indicator. Table 5 shows the results. Titers of A/H1N1 and A/H3N2 viruses with PA/I38T, PA/I38N, PAI38K, PAI38S, or PA/E23K substitution in culture supernatants of MDCK cells and RPMI2650 cells, tended to be lower than those of wild-type viruses. Titers of A/H1N1 and A/H3N2 viruses with PA/I38V or PA/I38L substitution were similar to those of wild-type viruses. Titers of influenza B virus with PA/I38T, PA/I38N, PAI38S, PA/I38V, or PA/I38L substitution were similar to that of wild-type virus. Titer of influenza B virus with PA/E23K substitution was similar to that of wild-type virus at 24 hours after infection but tended to be lower than that of wild-type virus at 48 and 72 hours.

[3)] The base sequence analysis was performed focusing on 4 amino acid substitutions with reduced sensitivity in the PA region (PA/I38, PA/E23, PA/E199, and PA/A37), which were identified during clinical use of baloxavir.

Table 5. Effect of amino acid substitution on replication of influenza A or B virus

Type/ subtype	Strain	Viral titer (log $TCID_{50}$/mL)								
		MDCK cells				RPMI2650 cells				
		After 6 hours	After 24 hours	After 48 hours	After 72 hours	After 6 hours	After 24 hours	After 48 hours	After 72 hours	After 96 hours
A/H1N1	rgA/WSN/33 (wild-type)	1.50 ± 0.00	5.88 ± 0.46	7.44 ± 0.30	6.98 ± 0.23	1.50 ± 0.00	4.48 ± 0.17	7.44 ± 0.10	7.48 ± 0.04	7.42 ± 0.08
	rgA/WSN/33-PA/I38T	1.50 ± 0.00	3.36 ± 0.72	5.31 ± 0.18	5.91 ± 0.62	1.50 ± 0.00	2.68 ± 0.31	5.36 ± 0.18	5.56 ± 0.24	5.13 ± 0.35
	rgA/WSN/33-PA/I38N	1.50 ± 0.00	2.50 ± 0.00	5.23 ± 0.21	5.60 ± 0.77	1.50 ± 0.00	1.70 ± 0.17	5.08 ± 0.52	6.06 ± 0.30	5.67 ± 0.30
	rgA/WSN/33-PA/I38K	1.50 ± 0.00	2.81 ± 0.54	3.88 ± 0.66	4.46 ± 0.83	1.50 ± 0.00	1.50 ± 0.00	3.55 ± 0.13	3.87 ± 0.36	3.81 ± 0.60
	rgA/WSN/33-PA/I38S	1.50 ± 0.00	3.93 ± 0.81	6.83 ± 0.91	7.11 ± 0.10	1.50 ± 0.00	3.48 ± 0.42	6.12 ± 0.40	6.62 ± 0.16	6.72 ± 0.25
	rgA/WSN/33-PA/I38V	1.50 ± 0.00	6.07 ± 0.38	7.26 ± 0.05	7.00 ± 0.00	1.50 ± 0.00	4.90 ± 0.46	7.55 ± 0.13	7.48 ± 0.04	7.19 ± 0.34
	rgA/WSN/33-PA/I38L	1.50 ± 0.00	5.02 ± 0.54	7.40 ± 0.36	6.75 ± 0.16	1.50 ± 0.00	3.83 ± 0.32	7.33 ± 0.00	7.24 ± 0.08	7.04 ± 0.27
	rgA/WSN/33-PA/E23K	1.50 ± 0.00	2.60 ± 0.05	4.49 ± 0.08	4.37 ± 0.19	1.50 ± 0.00	1.92 ± 0.29	4.63 ± 0.23	4.49 ± 0.16	4.00 ± 0.20
A/H3N2	rgA/Victoria/3/75 (wild-type)	1.50 ± 0.00	5.38 ± 0.66	7.11 ± 0.19	7.03 ± 0.15	1.50 ± 0.00	1.71 ± 0.10	3.57 ± 0.23	4.30 ± 0.41	4.43 ± 0.46
	rgA/Victoria/3/75-PA/I38T	1.50 ± 0.00	4.01 ± 0.53	6.64 ± 0.06	6.48 ± 0.04	1.50 ± 0.00	1.52 ± 0.04	2.53 ± 0.24	3.25 ± 0.59	3.41 ± 0.11
	rgA/Victoria/3/75-PA/I38N	1.50 ± 0.00	2.99 ± 0.61	6.43 ± 0.06	6.50 ± 0.21	1.52 ± 0.04	1.50 ± 0.00	2.06 ± 0.65	2.40 ± 0.15	2.90 ± 0.36
	rgA/Victoria/3/75-PA/I38K	1.50 ± 0.00	1.55 ± 0.04	4.43 ± 0.28	5.52 ± 0.25	1.50 ± 0.00	1.50 ± 0.00	1.50 ± 0.00	1.50 ± 0.00	2.10 ± 0.17
	rgA/Victoria/3/75-PA/I38S	1.50 ± 0.00	3.46 ± 0.14	6.16 ± 0.31	6.07 ± 0.23	1.50 ± 0.00	1.50 ± 0.00	2.00 ± 0.20	2.53 ± 0.87	3.57 ± 0.24
	rgA/Victoria/3/75-PA/I38V	1.50 ± 0.00	5.17 ± 0.35	7.26 ± 0.12	6.80 ± 0.40	1.50 ± 0.00	1.55 ± 0.04	3.36 ± 0.32	3.63 ± 0.50	4.31 ± 0.27
	rgA/Victoria/3/75-PA/I38L	1.50 ± 0.00	4.09 ± 0.58	7.07 ± 0.31	6.57 ± 0.14	1.50 ± 0.00	1.52 ± 0.04	2.75 ± 0.32	3.38 ± 0.79	3.57 ± 0.40
	rgA/Victoria/3/75/E23K	1.50 ± 0.00	2.97 ± 0.41	6.14 ± 0.51	6.78 ± 0.21	1.50 ± 0.00	1.50 ± 0.00	2.00 ± 0.00	2.54 ± 0.56	2.75 ± 0.22
B	rgB/Maryland/1/59 (wild-type)	1.50 ± 0.00	3.99 ± 0.53	7.40 ± 0.24	6.65 ± 0.13	1.50 ± 0.00	2.70 ± 0.31	5.22 ± 0.56	6.80 ± 0.35	6.58 ± 0.08
	rgB/Maryland/1/59-PA/I38T	1.50 ± 0.00	4.63 ± 0.14	7.14 ± 0.31	6.48 ± 0.10	1.50 ± 0.00	2.61 ± 0.10	4.67 ± 0.29	6.33 ± 0.10	5.95 ± 0.41
	rgB/Maryland/1/59-PA/I38N	1.50 ± 0.00	4.49 ± 0.25	7.40 ± 0.05	6.72 ± 0.25	1.50 ± 0.00	2.80 ± 0.28	5.48 ± 0.37	6.19 ± 0.54	6.32 ± 0.19
	rgB/Maryland/1/59-PA/I38S	1.50 ± 0.00	4.21 ± 0.35	7.30 ± 0.27	6.56 ± 0.13	1.50 ± 0.00	2.62 ± 0.04	4.69 ± 0.11	5.66 ± 0.54	5.68 ± 0.10
	rgB/Maryland/1/59-PA/I38V	1.50 ± 0.00	4.80 ± 0.35	7.14 ± 0.13	6.97 ± 0.39	1.52 ± 0.04	2.82 ± 0.17	5.44 ± 0.32	6.32 ± 0.19	6.23 ± 0.49
	rgB/Maryland/1/59-PA/I38L	1.50 ± 0.00	4.87 ± 0.12	7.18 ± 0.22	6.70 ± 0.03	1.52 ± 0.04	2.68 ± 0.11	5.00 ± 0.26	6.20 ± 0.62	5.87 ± 0.25
	rgB/Maryland/1/59-PA/E23K	1.50 ± 0.00	3.75 ± 0.23	5.56 ± 0.10	5.26 ± 0.25	1.52 ± 0.04	2.63 ± 0.05	4.78 ± 0.19	5.02 ± 0.48	4.84 ± 0.52

Mean ± SD

Subtype A/H3N2 influenza virus with 2 amino acid substitutions (PA/I38 and PA/I201T) was detected in Studies T0831 and T0833, which are clinical studies of therapeutic administration in patients with influenza virus infection (therapeutic studies). The effect of the 2 substitutions on viral replication was investigated using recombinant virus strain with the 2 substitutions generated by reverse genetics. Table 6 shows the results. Titer of the virus with PA/I201T plus PA/I38T or PA/I38M substitutions was comparable to that of virus with the corresponding PA/I38 substitution alone. The applicant explained that the PA/I201T substitution did not affect replication of virus with PA/I38 substitution.

Table 6. Effect of PA/I38 plus PA/I201T substitutions on replication of influenza A virus

Type/ subtype	Strain	Viral titer (log $TCID_{50}$/mL)								
		MDCK cells				RPMI2650 cells				
		After 6 hours	After 24 hours	After 48 hours	After 72 hours	After 6 hours	After 24 hours	After 48 hours	After 72 hours	After 96 hours
A/H3N2	rgA/Victoria/3/75 (wild-type)	1.50 ± 0.00	5.57 ± 0.21	7.42 ± 0.14	6.76 ± 0.08	1.50 ± 0.00	1.58 ± 0.08	3.99 ± 0.29	6.02 ± 0.24	5.97 ± 0.28
	rgA/Victoria/3/75-PA/I38T	1.50 ± 0.00	4.51 ± 0.09	7.02 ± 0.24	6.65 ± 0.03	1.50 ± 0.00	1.50 ± 0.00	2.33 ± 0.30	4.24 ± 0.58	4.68 ± 0.19
	rgA/Victoria/3/75-PA/I38M	1.50 ± 0.00	5.27 ± 0.21	6.81 ± 0.31	6.54 ± 0.37	1.50 ± 0.00	1.50 ± 0.00	2.96 ± 0.56	4.13 ± 0.43	4.47 ± 0.55
	rgA/Victoria/3/75-PA/I201T	1.52 ± 0.04	5.60 ± 0.17	7.41 ± 0.20	6.85 ± 0.21	1.50 ± 0.00	1.56 ± 0.10	3.78 ± 0.28	5.68 ± 0.11	5.89 ± 0.28
	rgA/Victoria/3/75-PA/ I38T + I201T	1.50 ± 0.00	4.61 ± 0.25	6.64 ± 0.20	6.53 ± 0.10	1.50 ± 0.00	1.55 ± 0.04	2.53 ± 0.09	3.70 ± 0.12	4.77 ± 0.12
	rgA/Victoria/3/75-PA/ I38M + I201T	1.50 ± 0.00	5.01 ± 0.61	6.82 ± 0.17	6.53 ± 0.17	1.50 ± 0.00	1.50 ± 0.00	2.97 ± 0.30	4.23 ± 0.62	5.36 ± 0.39

Mean ± SD

3.1.2.2.2 Competitive replication of recombinant virus with PA/I38 substitution and wild-type virus (CTD 4.2.1.1-05)

MDCK cells were exposed to a mixture of a recombinant virus strain with PA/I38T or PA/I38F substitution generated by reverse genetics and its parent strain (A/H1N1, rgA/WSN/33-PA; A/H3N2, rgA/Victoria/3/75-PA; type B, rgB/Maryland/1/59-PA) at the infectious titer ratio of 1:1. The abundance of the wild-type virus and recombinant virus in the culture supernatant after each passage was investigated by comparing the detection intensity of base sequence with PA/I38T codon as determined by Sanger sequencing. The abundance of all recombinant viruses with PA/I38 substitution decreased with the increasing number of passages, allowing the wild-type virus to become dominant.

3.1.2.2.3 Replication of clinical isolates with PA/I38 substitution and their competitive replication against wild-type virus (CTD 4.2.1.1-06, 4.2.1.1-07)

Specimens were obtained from 3 subjects who were found to be infected with A/H3N2 virus with PA/I38T substitution in a therapeutic study in patients with influenza virus infection (Study T0831). These specimens were used to investigate the effect of PA/I38T substitution on viral replication. Primary culture cells from human nasal epithelium were infected with (a) wild-type virus isolates from specimens collected before administration of baloxavir or (b) recombinant virus isolates with PA/I38 substitution from specimens collected after administration of baloxavir. The effect of PA/I38 substitution on viral replication was investigated using the viral titer as an indicator. Table 7 shows the S-033447 concentration required to reduce the viral titer and number of plaques of each isolate by 50% (50% effective concentration [EC_{50}]). Except for Subject C specimen at 24 hours after infection, no clear differences were observed in replication between wild-type virus and virus with PA/I38T substitution. The S-033447 concentration required to reduce the number of plaques by 50% (EC_{50}) was 0.31 to 0.69 ng/mL for wild-type virus and 36 to 53 ng/mL for virus with PA/I38T substitution, indicating that the virus with PA/I38T substitution was less sensitive to S-033447 than the wild-type virus.

Table 7. Effect of amino acid substitution on replication of influenza A or B virus and EC_{50} of S-033447 against viral replication

Type/ subtype	Subject ID	Strain	Viral titer (log $TCID_{50}$/mL)				EC_{50} (ng/mL)
			0 hours	After 24 hours	After 48 hours	After 72 hours	
A/H3N2	A	T0831_253104_D1 (wild-type)	1.50 ± 0.00	5.33 ± 0.30	8.20 ± 0.00	7.59 ± 0.14	0.69 ± 0.32
		T0831_253104_D9-PA/I38T	1.50 ± 0.00	5.21 ± 0.79	7.81 ± 0.39	7.81 ± 0.34	53[a)]
	B	T0831_339111_D1 (wild-type)	1.50 ± 0.00	4.63 ± 0.05	7.71 ± 0.08	7.60 ± 0.05	0.31 ± 0.12
		T0831_339111_D5-PA/I38T	1.50 ± 0.00	4.47 ± 0.78	7.71 ± 0.08	7.83 ± 0.44	49 ± 22
	C	T0831_344103_D1 (wild-type)	1.50 ± 0.00	5.55 ± 0.15	8.14 ± 0.32	7.55 ± 0.04	0.39 ± 0.06
		T0831_344103_D5-PA/I38T	1.50 ± 0.00	4.41 ± 0.68	7.70 ± 0.29	7.58 ± 0.08	36 ± 11

n = 3, Mean ± SD
a) Result at n = 1

Primary culture cells from human nasal epithelium were exposed to a mixture of a wild-type virus strain and recombinant virus strain with PA/I38 substitution at the infectious titer ratio of 1:1. The abundance of recombinant virus versus the wild-type virus in the culture supernatant after each passage was determined by sequencing PA/I38T codon with next-generation sequencing. Table 8 shows the abundance of recombinant virus with respect to the wild-type virus in each passage culture, indicating that presence of the virus with PA/I38T substitution decreased with the increasing number of passages.

Table 8. Abundance (%) of recombinant virus in each passage culture

Type/ Subtype	Subject ID	Abundance (%) of recombinant virus with PA/I38T			
		P0	P1	P2	P3
A/H3N2	A	35.9 ± 4.79	18.6 ± 11.12	15.6 ± 16.01	1.4 ± 1.95
	B	40.6 ± 0.04	56.2 ± 10.69	25.5 ± 0.88	1.6 ± 2.31
	C	45.1 ± 0.46	11.5 ± 14.57	6.1 ± 8.59	0.8 ± 1.12

Mean ± SD; P, Passage number

3.R Outline of the review conducted by PMDA

3.R.1 Effects of prophylactic S-033447 administration

The applicant's explanation:

Baloxavir is expected be effective in the prophylaxis of influenza A or B virus infection, provided that the person receiving baloxavir maintains a plasma S-033447 concentration enough to inhibit viral replication when exposed to influenza A or B virus, based on the following findings obtained:

(a) Suppression against body weight decrease and resultant extension of survival period [see Section 3.1.1.1], and reduction in intrapulmonary viral titer [see Section 3.1.1.2] observed in influenza A and B virus infection mouse models that received prophylactic S-033447 administration.
(b) Effective concentration in the prophylaxis of influenza A and B virus infection [see Section 3.1.1.1].
(c) *In vitro* suppression of release of influenza A and B viruses ("Review Report of Xofluza Tablets 10 mg and 20 mg" dated January 17, 2018).

On the basis of the data submitted and the applicant's explanation, PMDA has concluded that baloxavir was shown to have pharmacological effects for the prophylaxis of influenza A and B virus infection.

3.R.2 S-033447-resistant virus in prophylactic administration of baloxavir

In the prophylactic study (Study T0834), viruses with reduced sensitivity to S-033447 (virus with PA/I38 or PA/E23 substitution) were detected. The applicant provided explanation about (a) difference in the emergence of the viruses between therapeutic and prophylactic administration of baloxavir and (b) characteristics of the viruses (e.g., sensitivity, replication capacity, and pathogenicity).

The applicant' explanation:

It is difficult to directly compare results between the population receiving prophylactic administration and the population receiving therapeutic administration because of the difference in subject characteristics and in the definition of analysis population. Table 9 shows the frequencies of PA/I38 and PA/E23 substitutions in therapeutic studies (Studies T0821, T0822, T0831, T0832, and T0833) and prophylactic study (Study T0834).

Table 9. Number of subjects with PA/I38 or PA/E23 substitution

	Study No.	ITTI/mITT population[a)]	No. of subjects evaluated by paired sequencing[b)]	No. of subjects with PA/I38 substitution	No. of subjects with PA/E23 substitution	Ratio of subjects with PA/E23 substitution to subjects with PA/I38 substitution
Therapeutic	T0821	300	182	4	1	0.25
	T0822	103	76	18	0	0
	T0831	456	370	36	2	0.06
	T0833	33	26	5	1	0.20
	T0832	388	290	15	1	0.07
Prophylactic	T0834	Baloxavir: 374 Placebo: 375	Baloxavir: 63 Placebo: 123	Baloxavir: 10 Placebo: 2[c)]	Baloxavir: 5 Placebo: 0	Baloxavir: 0.5 Placebo: 0

a) ITTI population was used in Studies T0821, T0822, T0831, T0833, and T0832, while mITT population was used in Study T0834.
b) For Study T0834, the number of subjects testing positive by RT-PCR either before or after administration of baloxavir in the mITT population.
c) In the 2 subjects, initially wild-type virus was detected in specimens collected at 3 days after onset of pyrexia and respiratory symptoms followed by rescue treatment with baloxavir on the same day of collection, and then virus with PA/I38 substitution was detected at 5 days after the onset.

● Characteristics of virus with PA/E23 substitution (sensitivity, replication capacity, and pathogenicity)

In clinical studies conducted so far, PA/E23 substitution has been detected only in influenza A virus.

The effect of PA/E23K substitution on sensitivity to S-033447 was investigated using recombinant virus generated by reverse genetics. The ratio of EC_{50} of S-033447 (recombinant virus A/H1N1pdm with PA/E23K substitution versus wild-type influenza A virus [A/H1N1pdm, rgA/WSN/33]) was 4.74, showing the recombinant virus had reduced sensitivity to S-033447 ("Review Report of Xofluza Tablets 10 mg and 20 mg" dated January 17, 2018). This decrease in sensitivity (a 4.74-fold decrease) exceeded the provisional criterion of the WHO (a 3-fold decrease, which has been used in the antiviral resistance surveillance in Japan[4)] of the National Institute of Infectious Diseases) and the criterion for viruses with reduced sensitivity to cap-dependent endonuclease inhibitors (a 3-fold decrease, which has been adopted in an article[5)] published by the US Centers for Disease Control and Prevention [CDC]). Influenza virus with PA/E23K substitution is therefore considered as a virus with reduced sensitivity to S-033447. In the therapeutic study of Xofluza Tablets 10 mg and 20 mg, on the other hand, baloxavir was effective against wild-type influenza B viruses that were less sensitive (a 3- to 21-fold decrease) than wild-type

4) https://www.niid.go.jp/niid/ja/influ-resist/9293-flu-r20200109.html (last accessed on February 28, 2020)
5) Euro Surveill 2019; 24: 1800666

influenza A viruses ("Review Report of Xofluza Tablets 10 mg and 20 mg" dated January 17, 2018). In view of this finding, baloxavir is expected to be effective against influenza A viruses with PA/E23K substitution as well.

The effect of PA/E23K substitution on replication capacity was investigated using recombinant influenza A virus generated by reverse genetics. The titer of recombinant influenza A virus with PA/E23K substitution was lower than that of wild-type influenza virus [see Section 3.1.2.2.1]. This suggests that influenza virus with PA/E23K substitution has lower replication capacity than wild-type influenza virus. There are no non-clinical reports or literature on the effect of PA/E23K substitution on pathogenicity or transmissibility.

- Characteristics of virus with PA/I38 substitution (replication capacity and transmissibility) (new findings obtained after the initial approval review[6])

As described below, while some reports suggested that virus with PA/I38 substitution had lower replication and competitive replication capacities than the wild-type virus, others suggested that virus with PA/I38 substitution and wild-type virus had a similar replication capacity and transmissibility.

- The applicant evaluated replication of viruses with PA/I38 substitution and their competitive replication in the presence of wild-type virus using MDCK cells and primary culture cells from human nasal epithelium. Both the recombinant virus generated by reverse genetics and the clinical isolate with PA/I38T substitution had a lower replication capacity than the corresponding wild-type viruses [see Sections 3.1.2.2.2 and 3.1.2.2.3].

- The US CDC evaluated replication of viruses with PA/I38 substitution and their competitive replication in the presence of wild-type virus using MDCK cells and the ferret model. The viruses with PA/I38 substitution had a lower replication capacity than wild-type viruses (*J Infect Dis.* 2020;221:367-71).

- The National Institute of Infectious Diseases, the Institute of Medical Science, the University of Tokyo, and Université du Québec in Canada, evaluated replication of viruses with PA/I38 substitution and their competitive replication in the presence of wild-type virus using culture cells, mice, and hamsters. The viruses with PA/I38 substitution had a similar replication capacity to that of wild-type virus (*Euro Surveill.* 2019;24:1900170, *Nat Microbiol.* 2020;5:27-33, *J Infect Dis.* 2020;221:63-70).

- In an *in vivo* transmissibility study in ferrets at the Institute of Medical Science, the University of Tokyo, both virus with PA/I38 substitution and wild-type virus were transmitted through nasal droplets to a similar extent (*Nat Microbiol.* 2020;5:27-33).

6) At the time of the initial approval review, the following characteristics (sensitivity and replication) of virus with PA/I38 substitution were confirmed (Review Report of Xofluza Tablets 10 mg and 20 mg" dated January 17, 2018):
- Sensitivity (EC_{50}): Investigation using recombinant virus generated by reverse genetics showed that influenza A virus with PA/I38 substitution was 27.24-fold and 56.59-fold less sensitive to S-033447 than the wild-type influenza A viruses (A/H1N1pdm [rgA/WSN/33] and subtype H3N2 [rgA/Victoria/3/75], respectively).
- Replication: Using MDCK cells or RPMI2650 cells infected with recombinant virus generated by reverse genetics, viral titer was measured 24 or 48 hours after infection. The results showed that influenza A virus with PA/I38 substitution reduced replication capacity compared with the corresponding wild-type viruses (A/H1N1pdm [rgA/WSN/33] and subtype H3N2 [rgA/Victoria/3/75]).

Virus with PA/I38 substitution was detected even in patients untreated with baloxavir as shown below. In these patients, human-to-human infection of virus with PA/I38 substitution probably occurred.

- According to the 2018/2019 influenza season report from the antiviral resistance surveillance in Japan, issued by the National Institute of Infectious Diseases (https://www.niid.go.jp/niid/ja/influ-resist.html, date of last update December 27, 2019), virus with PA/I38 substitution was detected in 8 patients untreated with baloxavir. According to the 2019/2020 influenza season report (*Antiviral Res*. 2020;180:104828), virus with PA/E23K substitution was detected in 1 patient untreated with baloxavir, but no virus with PA/I38 substitution was detected.

- According to the "specified use-results surveys (sensitivity survey)" conducted by the applicant, virus with PA/I38 substitution was detected in 5 patients untreated with baloxavir during the 2018/2019 influenza season (Periodic safety update report No. 3 submitted on October 30, 2019) and in 1 patient untreated with baloxavir during the 2019/2020 influenza season (Periodic safety update report No. 4 submitted on May 21, 2020).

- According to a report from the Institute of Medical Science, the University of Tokyo, virus with PA/I38 substitution was detected in 2 patients untreated with baloxavir during the 2018/2019 influenza season (*Nat Microbiol.* 2020;5:27-33).

The above findings suggest that virus with PA/I38 substitution transmitted from human to human, although at present the transmission is considered to be sporadic. There are, however, neither reports showing that viruses with reduced sensitivity to S-033447 (PA/I38 and PA/E23K substitution) have a significantly greater replication capacity than wild-type virus nor evidence suggesting that viruses with reduced sensitivity may prevail. Because characteristics of prevailing influenza virus differ from season to season, the applicant considers it necessary to continue to carefully monitor emergence of viruses with reduced sensitivity to S-033447.

PMDA's view:

Emergence of virus with PA/E23K substitution is sporadic at present, and its effect on clinical effectiveness of baloxavir remains unclear, but this substitution was confirmed to contribute to decreased sensitivity to S-033447 ("Review Report of Xofluza Tablets 10 mg and 20 mg" dated January 17, 2018). In addition, the frequency of virus with PA/E23K substitution tended to be higher in the prophylactic study (Study T0834) than in the therapeutic studies (Studies T0821, T0822, T0831, T0832, and T0833). In view of these findings, close attention should be paid continuously to the emergence of virus with PA/E23K substitution.

At present, there are no reports showing that virus with PA/I38 substitution has a significantly greater replication capacity than wild-type virus, but adequate attention should be paid to its clinical effect even in prophylactic use because of the following findings:

(1) Virus with PA/I38 substitution was detected in a certain number of subjects in both therapeutic and prophylactic studies.
(2) Human-to-human transmission of virus with PA/I38 substitution has been observed in some subjects.

(3) Data from therapeutic studies suggest that the clinical efficacy of baloxavir tended to be lower in patients with virus with PA/I38 substitution than in those without [see Section 7.R.1.3.2.1].
(4) Some of the clinical study results show that virus with PA/I38 substitution frequently emerged in children [see Section 7.R.1.3.2.1].

PMDA considers it necessary to carefully investigate (a) the effect of baloxavir-resistant amino acid substitution on the efficacy and (b) the appropriateness of prophylactic administration of baloxavir in children in view of emergence of virus with PA/I38 substitution. These issues are discussed in Section 7.R.1.3.

4. Non-clinical Pharmacokinetics and Outline of the Review Conducted by PMDA

In the present application, no additional study results have been submitted.

5. Toxicity and Outline of the Review Conducted by PMDA

In the present application, no additional study results have been submitted.

6. Summary of Biopharmaceutic Studies and Associated Analytical Methods, Clinical Pharmacology, and Outline of the Review Conducted by PMDA

6.1 Summary of biopharmaceutic studies and associated analytical methods

In the prophylactic study (Study T0834) conducted for the present application, 20-mg tablets and 2% granules, commercial formulations of baloxavir, were used. S-033447 concentrations in human plasma were measured by liquid chromatography/tandem mass spectrometry (lower limit of quantitation, 0.100 ng/mL).

6.2 Clinical pharmacology

The applicant submitted pharmacokinetics (PK) data in a study of prophylactic baloxavir against influenza virus infection (Study T0834) and results from population pharmacokinetics (PPK) analysis.

6.2.1 Study of prophylactic use against influenza virus infection (CTD 5.3.5.1-01, Study T0834, November 2018 to March 2019)

Baloxavir was orally administered to household contacts of patients with influenza A or B virus infection (373 subjects included in the PK analysis) as a single dose (without any rule on a meal) to investigate its PK in terms of plasma S-033447 concentrations. Plasma S-033447 concentrations were measured in subjects on the day of administration of baloxavir (Day 1), Day 5, Day 15, and at discontinuation and in subjects who visited a clinic being suspected of having influenza virus infection between Day 1 and Day 10.

Figure 1 and Figure 2 show plasma S-033447 concentrations in 303 subjects aged ≥12 years and 70 subjects aged <12 years.

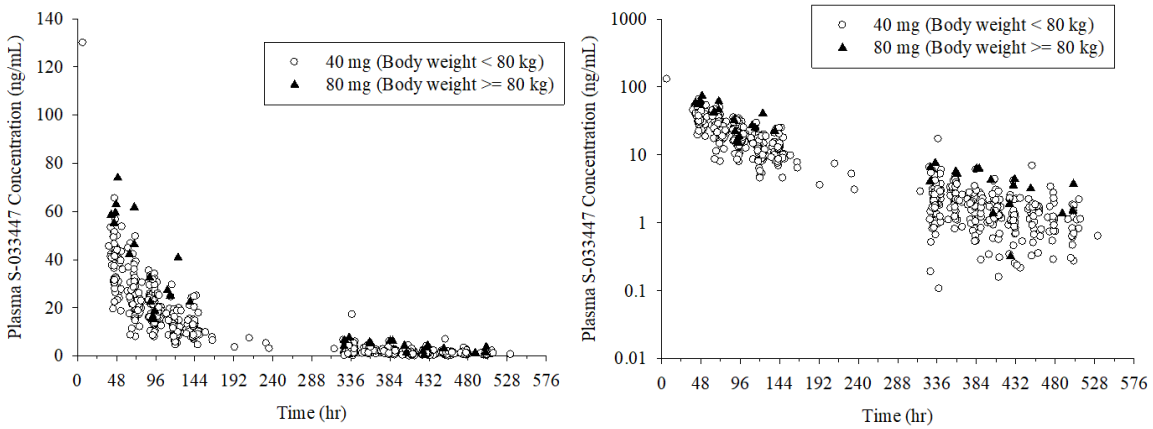

Figure 1. Plasma S-033447 concentrations in subjects aged ≥12 years (left, normal graph; right, semilogarithmic graph)

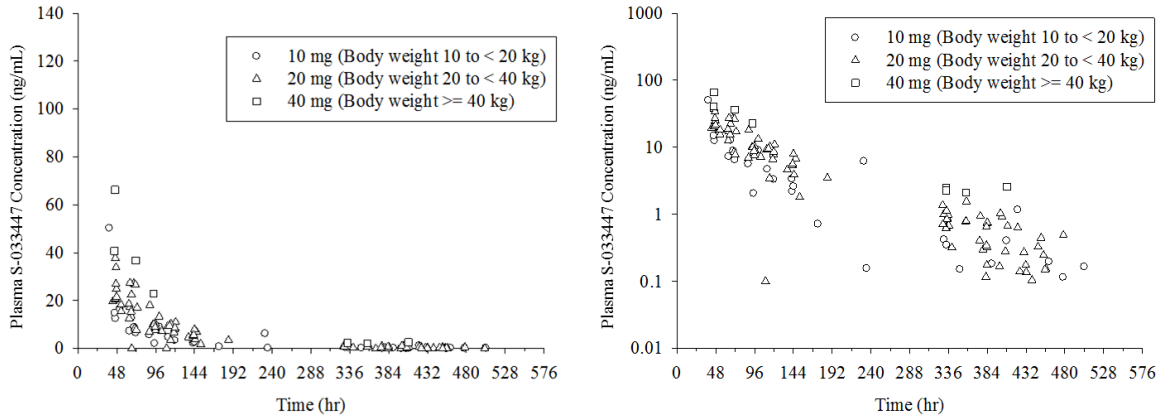

Figure 2. Plasma S-033447 concentrations in subjects aged <12 years (left, normal graph; right, semilogarithmic graph)

6.2.2 PPK analysis

6.2.2.1 PPK analysis in subjects aged ≥12 years (CTD 5.3.3.5-01)

PPK analysis (NONMEM version 7.3) was performed on PK data of S-033447 (11,848 sampling time points in 1,827 subjects) in healthy subjects, subjects with hepatic impairment, or patients with influenza virus infection in 13 Japanese and foreign clinical studies.[7)] The final model was described as a 3-compartment model with first-order absorption and lag time. The following parameters were selected as covariates: Body weight for apparent total body clearance (CL/F), Q1/F, Q2/F, apparent volume of central compartment (V_c/F), V_p1/F, and V_p2/F; ethnicity (Asian, non-Asian) for CL/F and V_c/F; and sex for absorption rate constant (Ka).[8)]

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7) Phase I studies (Studies T0811, T0813, T0815, T0816, T0817, T0818, T081B, T081C, T081F, and T081G), phase II study (Study T0821), and phase III studies (Studies T0831 and T0832)

8) The following candidate covariates were examined: (1) Body weight, age, body mass index (BMI), sex, aspartate aminotransferase (AST), alanine aminotransferase (ALT), estimated glomerular filtration rate (eGFR), creatinine clearance (CL_{cr}), ethnicity (Asian, White, Black, African American), region (Asia, North America/Europe), and health status (healthy subjects, patients with influenza virus infection, patients without infection), risk factors (asthma or chronic lung disease, endocrine system disease, neurodevelopmental disorder, cardiac disease, ≥65 years of age, metabolic disease, BMI ≥40 kg/m^2) for CL/F; (2) body weight, age, BMI, sex, ethnicity, region, and health status for V_c/F; (3) age and sex for K_a; (4) food intake (fasted, fed), ethnicity, and region for bioavailability; and (5) body weight for the other parameters (V_p1/F, V_p2/F, Q1/F, and Q2/F).

6.2.2.2 PPK analysis in subjects aged <12 years (CTD 5.3.3.2-01)

PK data of S-033447 (104 sampling time points in 32 subjects) from a Japanese study (Study T0833) were pooled into the PPK analysis model constructed from PK data (328 sampling time points in 107 subjects) in a Japanese clinical study (Study T0822) in patients with influenza virus infection aged <12 years ("Review Report of Xofluza Tablets 10 mg and 20 mg" dated January 17, 2018), and PPK analysis (NONMEM version 7.3) was performed on the pooled data (432 sampling time points in 139 subjects in total). The final model was described as a 2-compartment model with first-order absorption and lag time. Classification by body weight was selected as a covariate for CL/F, apparent inter-compartmental clearance (Q/F), V_c/F, and apparent volume of peripheral compartment (V_p/F).[9)]

6.2.2.3 Bayesian estimation of PK parameters in prophylactic study (Study T0834) (CTD 5.3.3.1-01)

PK parameters of S-033447 were estimated by Bayesian method in which PK data of S-033447 (754 sampling time points in 370 subjects) in the prophylactic study (Study T0834) in household contacts of patients with influenza A or B virus infection (index patients) were applied to constructed final PPK models for subjects aged ≥12 years and subjects aged <12 years [see Sections 6.2.2.1 and 6.2.2.2]. Table 10 and Table 11 show PK parameters in subjects aged ≥12 years and subjects aged <12 years.

Table 10. PK parameters of S-033447 in subjects aged ≥12 years (Study T0834, Bayesian estimates using the final model)

Dose (body weight)	40 mg (<80 kg)	80 mg (≥80 kg)	Overall
Number of subjects	N = 284	N = 17	N = 301
AUC_{inf}	6107 [3813, 9470]	10560 [5527, 14930]	6168 [3813, 10550]
C_{max}	91.1 [52.5, 147]	121 [45.3, 195]	92.1 [52.5, 148]
$C_{24\ h}$ (Day 1)	52.7 [34.1, 74.6]	77.0 [36.3, 108]	53.1 [34.3, 77.7]
$C_{48\ h}$ (Day 2)	36.2 [24.0, 52.6]	55.8 [29.1, 77.9]	36.6 [24.1, 55.1]
$C_{72\ h}$ (Day 3)	26.4 [16.6, 38.4]	43.7 [23.9, 60.1]	26.7 [17.1, 41.8]
$C_{96\ h}$ (Day 4)	19.8 [11.0, 29.7]	34.8 [18.4, 47.3]	20.0 [11.5, 32.7]
$C_{120\ h}$ (Day 5)	15.2 [7.76, 23.2]	28.0 [12.9, 37.8]	15.3 [8.20, 26.2]
$C_{144\ h}$ (Day 6)	11.7 [5.85, 18.7]	22.8 [9.21, 30.7]	12.0 [5.95, 21.4]
$C_{168\ h}$ (Day 7)	9.32 [4.32, 15.5]	18.7 [6.67, 25.3]	9.40 [4.40, 17.7]
$C_{192\ h}$ (Day 8)	7.51 [3.22, 12.9]	15.4 [4.90, 21.1]	7.61 [3.31, 14.8]
$C_{216\ h}$ (Day 9)	6.14 [2.47, 10.8]	12.9 [3.64, 17.8]	6.19 [2.53, 12.6]
$C_{240\ h}$ (Day 10)	5.02 [1.92, 9.16]	10.8 [2.73, 15.1]	5.11 [1.96, 10.7]
$C_{336\ h}$ (Day 14)	2.38 [0.72, 4.82]	5.78 [0.92, 8.23]	2.43 [0.73, 5.78]

Median [90% prediction interval]

9) The following candidate covariates were examined: (1) Body weight, age, BMI, sex, AST, ALT, total bilirubin, eGFR, CL_{cr}, health status (patients with influenza virus infection, patients without infection) for CL/F; (2) body weight, age, BMI, sex, and health status for V_c/F; (3) age, sex, health status, and food intake (fasted, fed) for K_a; (4) food intake for bioavailability; and (5) body weight for V_p/F and Q/F.

Table 11. PK parameters of S-033447 in subjects aged <12 years (Study T0834, Bayesian estimates using the final model)

Dose (body weight)	10 mg (≥10 kg and <20 kg)	20 mg (≥20 kg and <40 kg)	40 mg (≥40 kg)	Overall
Number of subjects	N = 18	N = 46	N = 4	N = 68
AUC_{inf}	3193 [2221, 5788]	4433 [3548, 5671]	7228 [6591, 7931]	4278 [2807, 6591]
C_{max}	83.8 [63.9, 126]	93.1 [76.5, 121]	118 [85.7, 124]	90.6 [72.2, 123]
$C_{24\ h}$ (Day 1)	41.9 [30.2, 59.4]	54.6 [44.6, 69.0]	77.1 [62.9, 83.1]	52.3 [36.7, 71.3]
$C_{48\ h}$ (Day 2)	19.4 [12.9, 35.4]	28.1 [22.6, 35.6]	44.7 [41.4, 50.0]	27.0 [17.0, 41.4]
$C_{72\ h}$ (Day 3)	10.3 [6.61, 23.5]	16.3 [11.9, 21.4]	29.3 [26.2, 32.4]	15.6 [8.83, 26.2]
$C_{96\ h}$ (Day 4)	6.37 [4.01, 17.0]	10.6 [7.26, 14.5]	20.8 [17.7, 22.6]	9.93 [5.40, 17.7]
$C_{120\ h}$ (Day 5)	4.38 [2.73, 12.9]	7.50 [4.96, 10.4]	15.5 [12.7, 16.7]	6.91 [3.63, 12.9]
$C_{144\ h}$ (Day 6)	3.21 [1.97, 10.2]	5.57 [3.63, 8.05]	12.1 [9.68, 12.9]	5.13 [2.63, 10.2]
$C_{168\ h}$ (Day 7)	2.41 [1.47, 8.12]	4.23 [2.75, 6.42]	9.66 [7.61, 10.5]	3.93 [1.94, 8.12]
$C_{192\ h}$ (Day 8)	1.79 [1.11, 6.55]	3.27 [2.13, 5.21]	7.81 [6.11, 8.73]	3.04 [1.43, 6.55]
$C_{216\ h}$ (Day 9)	1.32 [0.84, 5.31]	2.56 [1.63, 4.27]	6.40 [4.97, 7.36]	2.37 [1.06, 5.31]
$C_{240\ h}$ (Day 10)	0.99 [0.64, 4.31]	2.03 [1.25, 3.52]	5.29 [4.08, 6.26]	1.86 [0.79, 4.31]
$C_{336\ h}$ (Day 14)	0.34 [0.21, 1.89]	0.81 [0.46, 1.60]	2.52 [1.90, 3.39]	0.74 [0.24, 1.90]

Median [90% prediction interval]

6.R Outline of the review conducted by PMDA

6.R.1 Dosage regimen in prophylactic study (Study T0834)

The applicant's explanation about the dosage regimen in a prophylactic study (Study T0834):

A pharmacology study in influenza virus infection mouse model showed that survival periods were prolonged in animals with a plasma S-033447 concentration ≥0.444 ng/mL for influenza A virus and ≥2.35 ng/mL for influenza B virus at 24 hours after influenza infection [see Section 3.1.1.1]. For a prophylactic study (Study T0834), the target exposure was defined based on these non-clinical study results (0.444 ng/mL for influenza A virus, 2.35 ng/mL for influenza B virus). The applicant considered that baloxavir would be effective in the prophylaxis of influenza in humans who achieve a plasma S-033447 concentration above the target exposure, and therefore selected doses by age and weight as follows:

- Changes in plasma S-033447 concentration over time in adults and adolescents aged ≥12 years receiving a single dose of baloxavir were estimated using the PPK model constructed from the PK data of S-033447 in 13 Japanese and foreign clinical studies[7)] [see Section 6.2.2.1]. When a single dose of baloxavir 40 mg is administered to a population weighing <80 kg and baloxavir 80 mg to a population weighing ≥80 kg, plasma S-033447 concentrations (mean) are predicted to be kept above the target value (0.444 ng/mL for influenza A virus, 2.35 ng/mL for influenza B virus) until Days 22 to 25 ($C_{528\ h}$ to $C_{600\ h}$) for influenza A virus and until Days 14 to 17 ($C_{336\ h}$ to $C_{408\ h}$) for influenza B virus.

- Changes in plasma S-033447 concentration over time in children aged <12 years receiving a single dose of baloxavir were estimated using the PPK model constructed from the PK data of S-033447 in Japanese phase III studies (Studies T0822[10] and T0833[11]) in patients with influenza virus infection [see Section 6.2.2.2]. When a single dose of baloxavir is administered (10 mg to children weighing

10) An uncontrolled, open-label study conducted in patients with influenza virus infection aged <12 years (target sample size, 100 subjects) to investigate the efficacy and safety of baloxavir 10- and 20-mg tablets. In this study, a single dose of baloxavir was orally administered at 5 mg to patients weighing ≥5 and <10 kg; at 10 mg to patients weighing ≥10 and <20 kg; at 20 mg to patients weighing ≥20 and <40 kg; or at 40 mg to patients weighing ≥40 kg.

11) An uncontrolled, open-label study conducted in patients with influenza virus infection aged <12 years and weighing <20 kg (target sample size, 30 subjects) to investigate the efficacy and safety of granules containing baloxavir at 2%. In this study, a single dose of baloxavir was orally administered at 10 mg to patients weighing ≥10 kg and <20 kg or at 1 mg/kg to patients weighing <10 kg.

≥10 kg and <20 kg, 20 mg to children weighing ≥20 kg and <40 kg, and 40 mg to children ≥40 kg), plasma S-033447 concentrations (mean) are predicted to be kept above the target value (0.444 ng/mL for influenza A virus, 2.35 ng/mL for influenza B virus) until Days 15 to 22 ($C_{360\ h}$ to $C_{580\ h}$) for influenza A virus and until Days 9 to 13 ($C_{216\ h}$ to $C_{312\ h}$) for influenza B virus. In addition, when a single dose of baloxavir 1 mg/kg is administered to children weighing <10 kg, plasma S-033447 concentrations are predicted to be kept above the target value until Days 13 to 14 ($C_{312\ h}$ to $C_{336\ h}$) for influenza A virus and until Days 8 to 9 ($C_{192\ h}$ to $C_{216\ h}$) for influenza B virus.[12)]

Table 10 and Table 11 show Bayesian estimates of plasma S-033447 concentrations in subjects treated with baloxavir at the above dosage regimen in the prophylactic study (Study T0834) based on the final PPK model [see Section 6.2.2.3].[13)] In adults and adolescents aged ≥12 years, the median plasma S-033447 concentrations were predicted to remain above the target exposures for both influenza A and B viruses (0.444 ng/mL for influenza A virus, 2.35 ng/mL for influenza B virus) for ≥10 days after administration of baloxavir. In children aged <12 years, the plasma S-033447 concentrations were predicted to be kept above the target exposure for influenza A virus for ≥10 days after administration of baloxavir at any dose determined by either age or body weight. For influenza B virus, on the other hand, the median plasma S-033447 concentrations were predicted to be kept above the target exposure for 7 days in children weighing ≥10 kg and <20 kg and 9 days in children weighing ≥20 kg and <40 kg based on the predicted medium plasma S-033447 concentration.

PMDA's view:
The plasma S-033447 concentrations estimated with Bayesian approach using PK data from the prophylactic study (Study T0834) show that the proposed dosage and administration of baloxavir will ensure the target exposure for prophylaxis against influenza A and B virus infection for a certain period, and the measured exposure in individuals treated with baloxavir was not largely different from the exposure estimated by the applicant at the time of planning Study T0834.

For the following reasons, however, appropriateness of the dosage regimen of baloxavir for prophylaxis against influenza A and B virus infection should be discussed continuously in view of the efficacy and safety of baloxavir in the prophylactic study (Study T0834) [see Sections 7.R.1, 7.R.2, and 7.R.6]:

- The target exposures (i.e., plasma S-033447 concentrations) to achieve a prophylactic effect of baloxavir against influenza A and B (0.444 ng/mL for influenza A and 2.35 ng/mL for influenza B) were established based on the survival extension effect in mice infected with influenza A or B virus at the lethal load, and whether this finding in mice is relevant to humans remains unclear. Therefore, the finding that plasma S-033447 concentrations in humans exceeded the target exposures for a certain period, does not necessarily lead to the conclusion that the prophylactic effect against influenza A and B virus can be attained for a sufficient period.

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12) Because PK parameters in children aged <2 years (approximately weighing <10 kg) cannot be explained only by body weight (*Paediatr Anaesth*. 2011;21:222-37), plasma S-033447 concentrations were estimated using a PPK model with the following maturation factor incorporated in CL/F.
Maturation factor = (postconceptional weeks)$^{\gamma}$/ ([postconceptional weeks]$^{\gamma}$ + [postconceptional weeks up to 50% maturation])$^{\gamma}$; γ, Hill coefficient
Postconceptional weeks up to 50% maturation and Hill coefficient of morphine (54.2 weeks and 3.92) were used because among compounds with published parameter values, morphine undergoes metabolic and elimination processes closest to those of S-033447.

13) Because the prophylactic study (Study T0834) did not provide results in children weighing <10 kg who received baloxavir, the proposed dosage and administration for children weighing <10 kg was withdrawn [see Section 7.R.1.2].

- Because S-033447 is eliminated from plasma faster in children of lower age or weight, the plasma S-033447 concentration in such children tends to become lower with increasing time after administration of baloxavir at the proposed dosage [see Table 10 and Table 11].

7. Clinical Efficacy and Safety and Outline of the Review Conducted by PMDA

The applicant submitted results from 1 study (Study T0834) as pivotal efficacy and safety data on baloxavir for prophylactic use against influenza virus infection and also results from 2 studies (Studies T0832 and T0833) as reference data. Table 12 shows an outline of major clinical studies.

Table 12. Outline of major clinical studies for efficacy and safety of baloxavir

Data category	Region	Study	Phase	Subjects	Number of enrollments	Dosage regimen	Main endpoints
Prophylaxis							
Evaluation	Japan	Study T0834	III	Household contacts of patients with influenza A or B virus infection (index patients) (without any age restriction on study subjects)	N = 752	(a) Baloxavir, single dose as follows: *≥12 years:* 80 mg for body weight ≥80 kg 40 mg for body weight <80 kg *<12 years:* 40 mg for body weight ≥40 kg 20 mg for body weight ≥20 kg and <40 kg 10 mg for body weight ≥10 kg and <20 kg 1 mg/kg for body weight<10 kg (b) Placebo, single dose	Efficacy Safety PK
Treatment							
Reference	Global	Study T0832	III	Patients with influenza virus infection having high-risk factors aged ≥12 years	N = 2,182	(a) Baloxavir at 40 mg (body weight<80 kg) or 80 mg (body weight ≥80 kg), single dose (b) Placebo, single dose or twice daily for 5 days (c) Oseltamivir at 75 mg twice daily for 5 days	Efficacy Safety PK
Reference	Japan	Study T0833	III	Patients with influenza virus infection aged <12 years and weighing <20 kg	N = 33	Baloxavir at 1 mg/kg (<10 kg) or 10 mg (≥10 kg and <20 kg), single dose	Efficacy Safety PK

7.1 Prophylactic study

7.1.1 Japanese phase III study (CTD 5.3.5.1-01, Study T0834, November 2018 to March 2019)

A randomized, placebo-controlled, double-blind, parallel-group study was conducted to evaluate prophylaxis of influenza virus infection and safety of baloxavir in household contacts (target sample size, 750 subjects) of patients with influenza A or B virus infection (index patients) at 52 study sites in Japan.

Subjects received a single dose of oral baloxavir at the following doses:

Age ≥12 years: 40 mg for body weight <80 kg or 80 mg for body weight ≥80 kg;

Age <12 years: 1 mg/kg for body weight <10 kg, 10 mg for body weight ≥10 kg and <20 kg, 20 mg for body weight ≥20 kg and <40 kg, or 40 mg for body weight ≥40 kg.

Of randomized subjects, 749 subjects (374 in the baloxavir group, 375 in the placebo group) who had received at least 1 dose of the study drug were included in the safety analysis population and mITT population. The mITT population was mainly subjected to efficacy analysis.

Of these, 2 subjects in the baloxavir group (request from subjects for both) and 2 subjects in the placebo group (request from subject for one, adverse events for the other) discontinued the study.

Table 13 shows results of the primary endpoint, the proportion of subjects with RT-PCR-confirmed symptomatic influenza involving both pyrexia and respiratory symptoms[14)] occurring between Day 1 (the day of administration of study drug) and Day 10. Baloxavir suppressed the onset of influenza compared with placebo in a statistically significant manner. Figure 3 shows Kaplan-Meier plots of time to documentation of RT-PCR-confirmed symptomatic influenza involving both pyrexia and respiratory symptoms.[14)]

Table 13. Proportion of subjects with RT-PCR-confirmed symptomatic influenza involving both pyrexia and respiratory symptoms (mITT population)

Treatment	Incidence[a)]	Adjusted risk ratio (95% CI)[b)]	*P* value[b), c)]
Baloxavir	7/374 (1.9)	0.14 [0.06, 0.30]	<0.0001
Placebo	51/375 (13.6)	-	-

a) n/N (%)
b) A modified Poisson regression approach (*Am J Epidemiol.* 2004;159:702-6) was taken using "RT-PCR-confirmed symptomatic influenza involving both pyrexia and respiratory symptoms (yes, no)" as the response, and "time from onset in the index patient to subject's informed consent (<24 hours, ≥24 hours)," "influenza antiviral drug used in the index patient (baloxavir, other)," and "age of the subject" as covariates.
c) Two-sided significance level of 5%

[14)] Subjects testing positive for influenza virus by RT-PCR who had axillary temperature ≥37.5°C and "2, moderate" or "3, severe" respiratory symptoms (cough or runny nose/nasal congestion) recorded in a subject diary entry

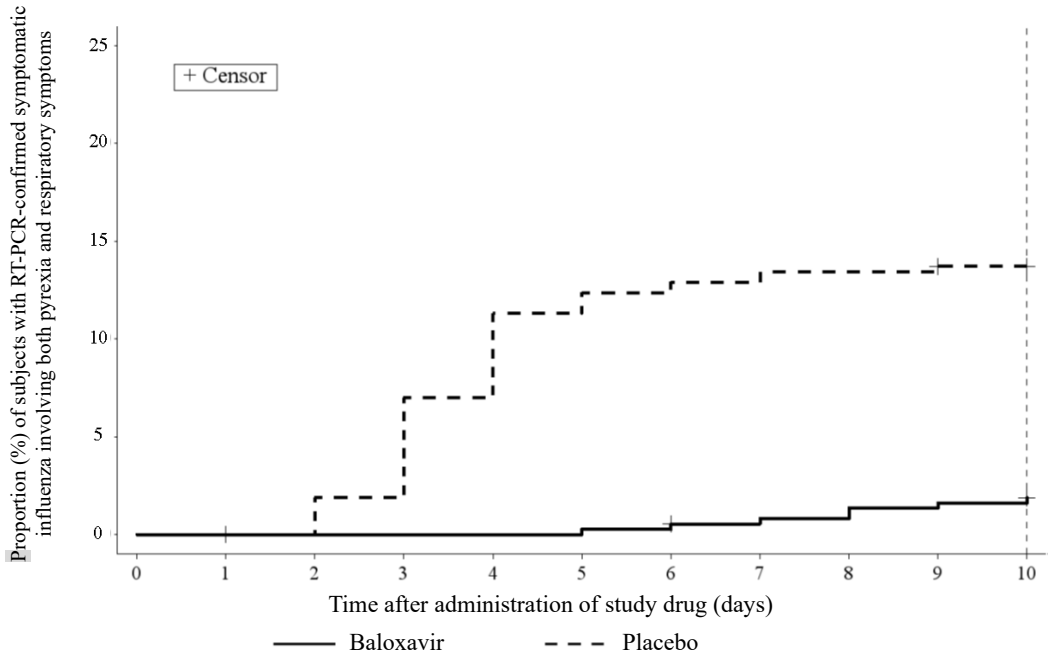

Figure 3. Kaplan-Meier plots on time to documentation of RT-PCR-confirmed symptomatic influenza[14] involving both pyrexia and respiratory symptoms (mITT population) (cited from CTD 2.7.6 Figure 2.7.6.1-2)

Adverse events (including abnormal changes in laboratory tests) occurred in 22.2% (83 of 374) of subjects in the baloxavir group and 20.5% (77 of 375) of subjects in the placebo group. Adverse drug reactions[15] occurred in 1.9% (7 of 374) of subjects in the baloxavir group and 1.6% (6 of 375) of subjects in the placebo group. Table 14 shows adverse events and adverse drug reactions reported by ≥1% of subjects in any group.

A serious adverse event or adverse event leading to discontinuation occurred in 1 subject (psychotic disorder) in the placebo group. There were no adverse events leading to death.

Table 14. Adverse events and adverse drug reactions reported by ≥1% of subjects in any group (safety analysis population)

Events	Adverse events		Adverse drug reactions	
	Baloxavir (N = 374)	Placebo (N = 375)	Baloxavir (N = 374)	Placebo (N = 375)
Overall	83 (22.2)	77 (20.5)	7 (1.9)	6 (1.6)
Nasopharyngitis	24 (6.4)	25 (6.7)	0	0
Headache	8 (2.1)	6 (1.6)	0	1 (0.3)
Blood urine present	6 (1.6)	1 (0.3)	1 (0.3)	0
Pharyngitis	4 (1.1)	1 (0.3)	0	0
ALT increased	4 (1.1)	1 (0.3)	0	1 (0.3)

n (%)

[15] Adverse events for which a causal relationship to the study drug could not be ruled out.

7.2 Therapeutic clinical studies

7.2.1 Global study in patients with influenza virus infection having high-risk factors (CTD 5.3.5.4-04, Study T0832, January 2017 to April 2018)

A randomized, double-blind, parallel-group study was conducted to evaluate the efficacy and safety of baloxavir versus placebo or oseltamivir phosphate in ≥12-year-old patients[16)] with influenza virus infection having high-risk factors (target sample size, 1,185 subjects [395 per group]) at 551 study sites in 14 countries including the US, Japan, Australia, Belgium, and South Africa.

A single oral dose of baloxavir 40 mg was administered to patients weighing <80 kg or baloxavir 80 mg to patients weighing ≥80 kg. Oral oseltamivir was administered at 75 mg twice daily for 5 days; and placebo was orally administered.

Of 2,184 randomized patients, 2,178 who had received at least 1 dose of the study drug were included in the safety analysis population. Of these, 1,163 patients (388 in the baloxavir group, 389 in the oseltamivir group, 386 in the placebo group) were included in the intention-to-treat infected (ITTI) population. The remaining patients were excluded because their influenza infection status was unconfirmed by RT-PCR or they had been enrolled at non-GCP-compliant centers. The ITTI population was subjected to efficacy analysis.

The median duration[17)] of influenza illness [95% confidence interval (CI)[18)]], the primary endpoint, was 73.2 [67.2, 85.1] hours in the baloxavir group, 102.3 [92.7, 113.1] hours in the placebo group, and 81.0 [69.4, 91.5] hours in the oseltamivir group. Figure 4 shows the Kaplan-Meier plots.

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16) High-risk factors were specified according to definition of high-risk patients by the US Centers for Disease Control and Prevention (CDC) (http://www.cdc.gov/flu/about/disease/high_risk.htm, accessed on August 7, 2020). More specifically, patients meeting at least one of the following criteria were deemed as patients having high-risk factors [high-risk patients]:
- Patients with asthma or chronic lung disease (chronic obstructive pulmonary disease, cystic fibrosis, etc.)
- Patients with endocrine disease (including diabetes mellitus)
- Patients staying at a long-term care facility (nursing facility, etc.)
- Immunosuppressed patients (including patients receiving prednisolone at ≤20 mg or corticosteroid at an equivalent dose and human immunodeficiency virus (HIV) carriers who are currently receiving treatment with a $CD4^+$ lymphocyte count of >350 cells/mm^3 within the past 6 months)
- Patients with neurological disease and neurodevelopmental disorder (including brain disease, spinal cord disease, peripheral nerve disease, and muscular disease such as cerebral palsy, epilepsy [epileptic seizure], stroke, muscular dystrophy, and spinal cord injury)
- Patients with heart disease (congenital heart disease, congestive heart failure, coronary artery disease, etc. except for those only with hypertension)
- Patients aged ≥65 years
- American Indians and Alaska Natives
- Patients with hematologic disease (sickle cell disease, etc.)
- Patients with metabolic abnormality (inborn error of metabolism, mitochondrial disease, etc.)
- Patients with BMI ≥40
- Patients ≤2 weeks postpartum but not nursing

17) Duration until all the influenza symptoms are judged to be resolving, be ongoing, or have disappeared as described below.
Resolving: Of symptoms (cough, fatigue, and muscle or joint pain) existing before onset of influenza virus infection, those reported by the patient to have been exacerbated at pre-dose examination have changed in severity (a) from "moderate" to "mild or none" or (b) from "severe" to "moderate, mild, or none."
Ongoing: Of symptoms (cough, fatigue, and muscle or joint pain) existing before onset of influenza, those reported by the patient to have not been exacerbated at pre-dose examination remain unchanged in severity (from "moderate" to "moderate," or from "severe" to "severe").
Disappeared: New symptoms reported at pre-dose examination have changed in severity to "mild or none."

18) Calculated according to Brookmeyer and Crowley's method (*Biometrics.* 1982;38(1):29–41).

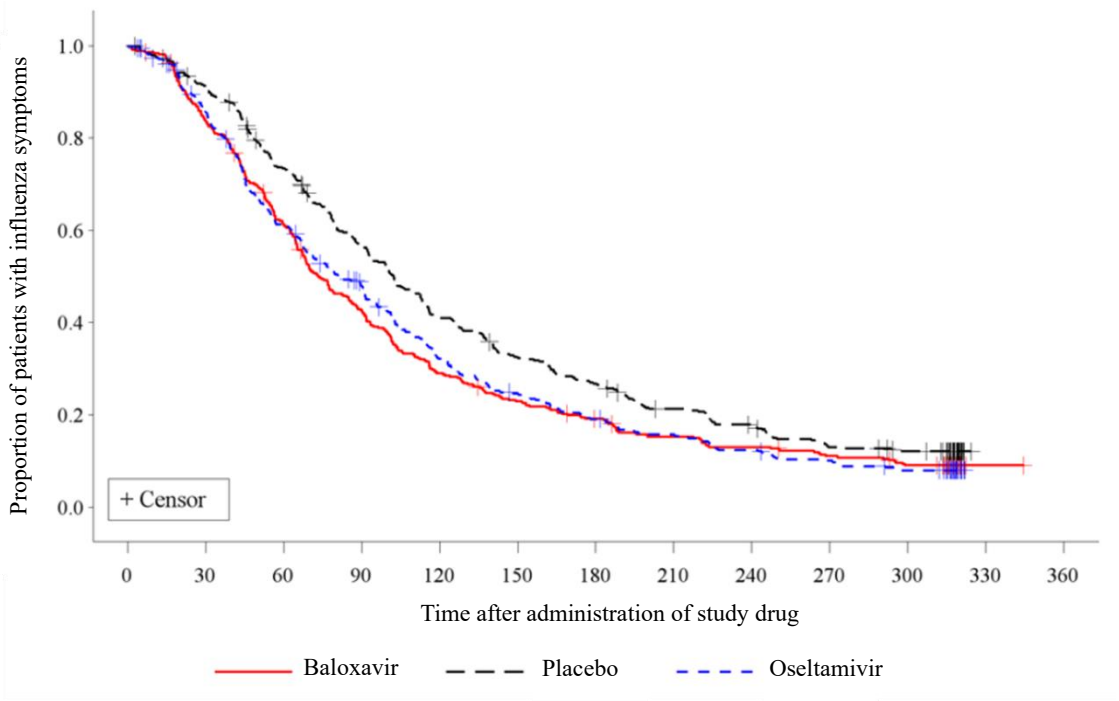

Figure 4. Kaplan-Meier plots of duration of influenza illness (ITTI population) (cited from CTD 2.7.6 Figure 2.7.6.2-2)

Adverse events (including abnormal changes in laboratory tests) occurred in 25.1% (183 of 730) of patients in the baloxavir group, 29.7% (216 of 727) of patients in the placebo group, and 28.0% (202 of 721) of patients in the oseltamivir group. Adverse drug reactions occurred in 5.6% (41 of 730) of patients in the baloxavir group, 8.3% (60 of 727) of patients in the placebo group, and 7.9% (57 of 721) of patients in the oseltamivir group. Table 15 shows adverse events and adverse drug reactions reported by ≥1% of patients in any group. There were no deaths, serious adverse events, or adverse events leading to discontinuation.

Table 15. Adverse events and adverse drug reactions reported by ≥1% of subjects in any group (safety analysis population)

Events	Adverse events			Adverse drug reactions		
	Baloxavir (N = 730)	Placebo (N = 727)	Oseltamivir (N = 721)	Baloxavir (N = 730)	Placebo (N = 727)	Oseltamivir (N = 721)
Overall	183 (25.1)	216 (29.7)	202 (28.0)	41 (5.6)	60 (8.3)	57 (7.9)
Bronchitis	21 (2.9)	33 (4.5)	30 (4.2)	0	2 (0.3)	1 (0.1)
Diarrhoea	20 (2.7)	21 (2.9)	23 (3.2)	9 (1.2)	6 (0.8)	8 (1.1)
Nausea	20 (2.7)	29 (4.0)	34 (4.7)	16 (2.2)	20 (2.8)	23 (3.2)
Sinusitis	14 (1.9)	21 (2.9)	22 (3.1)	0	3 (0.4)	0
Vomiting	8 (1.1)	6 (0.8)	14 (1.9)	2 (0.3)	3 (0.4)	8 (1.1)
ALT increased	7 (1.0)	5 (0.7)	2 (0.3)	5 (0.7)	4 (0.6)	1 (0.1)
Headache	6 (0.8)	7 (1.0)	9 (1.2)	1 (0.1)	2 (0.3)	2 (0.3)
Abdominal pain	5 (0.7)	12 (1.7)	3 (0.4)	3 (0.4)	10 (1.4)	1 (0.1)
Pneumonia	5 (0.7)	4 (0.6)	8 (1.1)	0	0	0
Dizziness	4 (0.5)	6 (0.8)	7 (1.0)	0	1 (0.1)	2 (0.3)
Acute sinusitis	2 (0.3)	7 (1.0)	2 (0.3)	0	0	0

n (%)

7.2.2 Japanese study in patients with influenza virus infection aged <12 years and weighing <20 kg (CTD 5.3.5.4-05, Study T0833, December 2017 to February 2018)

An uncontrolled, open-label study was conducted to investigate the efficacy and safety of granules containing baloxavir at 2% in patients with influenza virus infection aged <12 years and weighing <20 kg (target sample size, 30 subjects) at 20 study sites in Japan. In this study, a single dose of baloxavir was orally administered at 10 mg to patients weighing ≥10 kg and <20 kg or at 1 mg/kg to patients weighing <10 kg.

All of the 33 patients (21 weighing ≥10 kg and <20 kg, 12 weighing <10 kg) who had received the study drug were included in the safety analysis population and ITTI population.[19)] ITTI population was mainly subjected to efficacy analysis.

The duration of influenza illness, the primary endpoint, was defined as the period between the start of study treatment and the resolution of influenza symptoms (i.e., "0, none" or "1, mild" for both "cough" and "runny nose/nasal congestion" and axillary temperature <37.5°C, based on patient diary entries[20)]). The median [95% CI[18)]] of duration of influenza illness was 45.3 [28.5, 64.1] hours. Figure 5 shows the Kaplan-Meier plots.

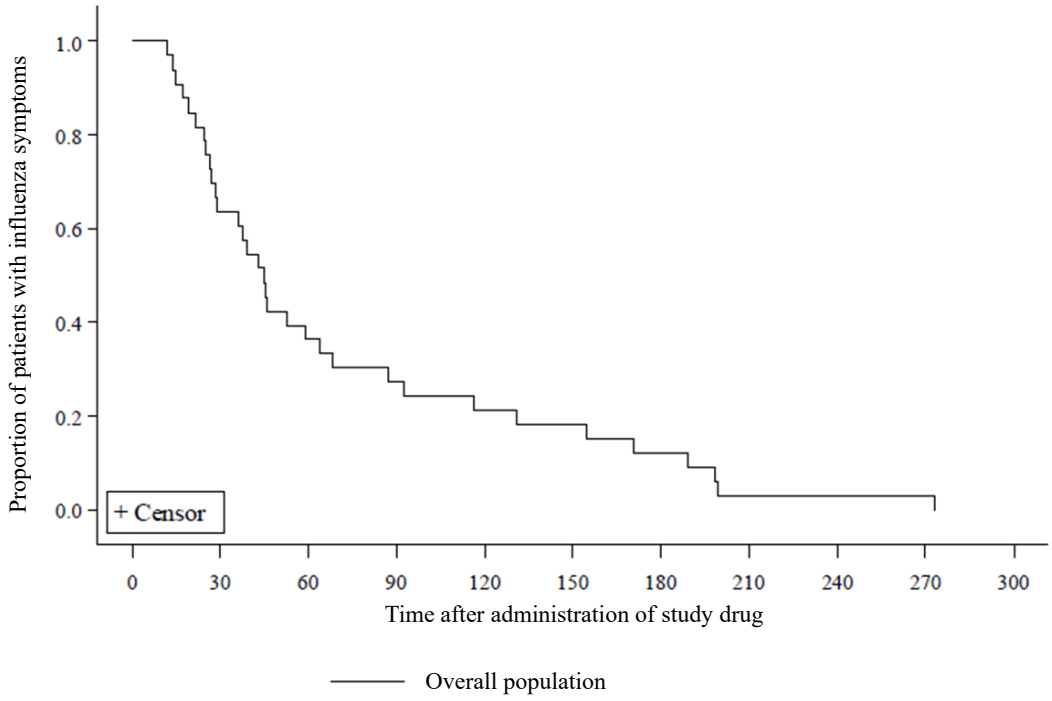

Figure 5. Kaplan-Meier plots of duration of influenza illness (ITTI population) (cited from CTD 2.7.6 Figure 2.7.6.3-1)

Adverse events (including abnormal changes in laboratory tests) occurred in 54.5% (18 of 33) of patients and adverse drug reactions in 3.0% (1 of 33) of patients. Table 16 shows adverse events and adverse

19) Population of patients who received at least 1 dose of the study drug and tested positive for influenza by RT-PCR
20) Influenza symptoms were judged to have resolved when both of the following (a) and (b) are maintained for at least 21.5 hours:
(a) The severity of all influenza symptoms (cough and runny nose/nasal congestion) is "0, none" or "1, mild." (The symptoms are rated on a 4-point scale [0, none; 1, mild; 2, moderate; and 3, severe] and recorded in the patient diary entries.)
(b) Axillary temperature <37.5°C.

drug reactions reported by ≥2 patients. There were no deaths, serious adverse events, or adverse events leading to discontinuation.

Table 16. Adverse events and adverse drug reactions reported by ≥2 patients (safety analysis population)

Events	Adverse events (N = 33)	Adverse drug reactions (N = 33)
Overall	18 (54.5)	1 (3.0)
Vomiting	6 (18.2)	0
Upper respiratory tract infection	2 (6.1)	0
Otitis media	2 (6.1)	0
Nasopharyngitis	2 (6.1)	0

n (%)

7.R Outline of the review conducted by PMDA

7.R.1 Efficacy

7.R.1.1 Efficacy by type/subtype of influenza virus in index patients

The applicant's explanation about efficacy by type/subtype of influenza virus in index patients:

Table 17 shows proportions of subjects with PR-PCR-confirmed symptomatic influenza with both pyrexia and respiratory symptoms[14)] by type/subtype of influenza virus in index patients, the primary endpoint in the prophylactic study (Study T0834). In the subgroups in which the index patients were infected with influenza A/H1N1pdm or A/H3NX,[21)] the proportion of subjects with RT-PCR-confirmed symptomatic influenza involving both pyrexia and respiratory symptoms was smaller in the baloxavir group than in the placebo group, as observed in the mITT population. In the subgroup in which the index patients were infected with influenza B, on the other hand, no subjects developed RT-PCR-confirmed symptomatic influenza with pyrexia and respiratory symptoms, although both baloxavir and placebo groups had only a limited number of subjects.

Table 17. Primary endpoint by type/subtype of influenza virus in index patients (mITT population)

Virus type/subtype	Baloxavir[a)]	Placebo[a)]	Adjusted risk ratio[b)] [95% CI]
A/H1N1pdm	2/176 (1.1)	19/180 (10.6)	0.11 [0.03, 0.45]
A/H3NX[c)]	5/181 (2.8)	32/183 (17.5)	0.15 [0.06, 0.39]
Type B	0/2 (0)	0/3 (0)	-

a) n/N (%)

b) A modified Poisson regression approach (*Am J Epidemiol.* 2004;159:702-6) was taken using RT-PCR-confirmed symptomatic influenza involving both pyrexia and respiratory symptoms (yes, no) as the response, and time from onset in the index patient to subject's informed consent (<24 hours, ≥24 hours), influenza antiviral drug used in the index patient (baloxavir, other), and age of the subject as covariates.

c) A/H3NX means that the subtype of NA has not been determined.

Table 18 shows results of the secondary endpoints: (a) proportions of subjects with RT-PCR-confirmed influenza with pyrexia or influenza symptoms (respiratory symptoms or general symptoms),[22)] (b) proportions of subjects with RT-PCR-confirmed influenza,[23)] and (c) proportions of subjects with RT-PCR-confirmed non-symptomatic influenza.[24)] Both baloxavir and placebo groups included only a limited number of subjects whose index patients were infected with influenza B; therefore the results of

21) A/H3NX means that the subtype of NA has not been determined.

22) Proportion of subjects who meet all of the following criteria: (a) axillary temperature ≥37.5°C; (b) either of the influenza symptoms (i.e., respiratory symptoms or general symptoms) recorded in a subject diary entry is classified as "2, moderate" or "3, severe"; (c) positive for influenza virus by RT-PCR.

23) Proportion of subjects testing positive for influenza virus by RT-PCR regardless of pyrexia and influenza symptoms

24) Proportion of subjects who meet all of the following criteria: (a) positive for influenza virus by RT-PCR; (b) axillary temperature <37.5°C; (c) all influenza symptoms recorded in a subject diary entry are classified as "0, none" or "1, mild."

the secondary endpoints, as with the primary endpoint, were insufficient for discussing the efficacy in those subjects.

Table 18. Secondary endpoints by type/subtype of influenza virus in index patients (mITT population)

Secondary endpoint	Virus type/subtype	Baloxavir[a)]	Placebo[a)]	Adjusted risk ratio[b)] [95% CI]
Proportions of subjects with RT-PCR-confirmed influenza with pyrexia or influenza symptoms (respiratory symptoms or general symptoms)	A/H1N1pdm	6/176 (3.4)	32/180 (17.8)	0.19 [0.08, 0.44]
	A/H3NX[c)]	14/181 (7.7)	51/183 (27.9)	0.28 [0.16, 0.48]
	Type B	0/2 (0)	0/3 (0)	-
Proportions of subjects with RT-PCR-confirmed influenza	A/H1N1pdm	17/176 (9.7)	45/180 (25.0)	0.39 [0.23, 0.65]
	A/H3NX[c)]	31/181 (17.1)	67/183 (36.6)	0.47 [0.32, 0.68]
	Type B	1/2 (50.0)	1/3 (33.3)	-
Proportions of subjects with RT-PCR-confirmed non-symptomatic influenza	A/H1N1pdm	11/176 (6.3)	12/180 (6.7)	0.95 [0.42, 2.16]
	A/H3NX[c)]	17/181 (9.4)	16/183 (8.7)	1.08 [0.57, 2.07]
	Type B	1/2 (50.0)	1/3 (33.3)	-

a) n/N (%)
b) A modified Poisson regression approach (*Am J Epidemiol.* 2004;159:702-6) was taken using "RT-PCR-confirmed symptomatic influenza involving both pyrexia and respiratory symptoms (yes, no)" as the response, and "time from onset in the index patient to subject's informed consent (<24 hours, ≥24 hours)," "influenza antiviral drug used in the index patient (baloxavir, other)," and "age of the subject" as covariates.
c) A/H3NX means that the subtype of NA has not been determined.

In the prophylactic study (Study T0834), the baloxavir group included 2 household contacts whose index patients were co-infected with influenza A and B viruses and the placebo group included 3 such household contacts. None of them had RT-PCR-confirmed symptomatic influenza involving both pyrexia and respiratory symptoms, or tested positive for influenza B virus by RT-PCR after administration.

The applicant's explanation:
In the prophylactic study (Study T0834), both the baloxavir and placebo groups included a limited number of subjects whose index patients were infected with influenza B, but baloxavir is be expected to be effective in the prophylaxis of influenza B virus infection for the reasons presented below. However, results of the prophylactic effect of baloxavir against influenza B virus infection are limited, and thus the applicant will continue collecting relevant information after the market launch.

- Non-clinical studies showed that baloxavir suppressed the replication of influenza B virus and improve d the mortality associated with virus infection ("Review Report of Xofluza Tablets 10 mg and 20 mg" dated January 17, 2018).

- In therapeutic studies in patients with influenza virus infection (Studies T0821 and T0831), viral titer of influenza B tended to decrease in patients receiving baloxavir ("Review Report of Xofluza Tablets 10 mg and 20 mg" dated January 17, 2018).

- In the therapeutic study (Study T0832) in high-risk patients with influenza virus infection aged ≥12 years, the population primarily eligible for prophylactic administration of baloxavir, the median duration of influenza illness (primary endpoint) in patients with influenza B virus infection was 74.6, 100.6, and 101.6 hours in the baloxavir (n = 166), placebo (n = 167), and oseltamivir (n = 148) groups, respectively, showing a significant reduction in duration of influenza illness in the baloxavir group compared with the placebo and oseltamivir groups (vs. placebo, P = 0.0138; vs. oseltamivir, P =

0.0251). In addition, on Days 2 and 3, viral titers of influenza B were lower in the baloxavir group than in the placebo and oseltamivir groups.

- In the therapeutic study (Study T0833) in children with influenza virus infection aged <12 years and weighing <20 kg, the median duration of influenza illness [95% CI], the primary endpoint, was 41.7 [19.3, 86.9] hours in patients with influenza B virus infection (n = 12) and 45.3 [28.5, 64.1] hours in the overall population (n = 33), showing no clear difference. Changes in viral titer of influenza B from baseline to Days 2, 4, and 6 (mean ± standard deviation [SD]) were −4.30 ± 1.43, −1.61 ± 1.72, and −3.63 ± 1.97 $\log_{10}$ ($TCID_{50}$/mL), respectively, showing a decrease in viral titer similar to that observed in the overall population[25] on Day 6, although a temporal re-increase[26] was observed on Day 4. The median body temperature (range) in patients with influenza B virus infection on Days 4, 5, and 6 was 36.60°C [36.20°C, 37.10°C], 37.20°C [35.70°C, 39.20°C], and 36.75°C [36.40°C, 37.70°C], respectively, showing a re-increasing trend in temperature on Day 5, which was small in extent, followed by recovery on Day 6, and the subsequent temperature changes were similar to those in the overall population.

- A single dose of baloxavir is considered to allow the plasma S-033447 concentration (median) to be kept at the target plasma exposure against influenza B virus (2.35 ng/mL) for ≥10 days in adults and adolescents aged ≥12 years, 9 days in children weighing ≥20 kg and <40 kg, and 6 days in children weighing ≥10 kg and <20 kg[27] [see Section 6.R.1].

PMDA's view:
The results from the prophylactic study (Study T0834) show that baloxavir has a prophylactic effect against influenza A virus infection.

The applicant explained that baloxavir was expected to have a prophylactic effect against influenza B virus infection in the population aged ≥12 years; this explanation is understandable to a certain extent.

For the reasons presented below, however, it is difficult to conclude that baloxavir is effective in the prophylaxis of influenza B virus infection. The applicant should therefore continue collecting information about the prophylactic effect of baloxavir against influenza B virus infection and appropriately provide the obtained findings to healthcare professionals. The indication of baloxavir is discussed in Section 7.R.5.

- Laboratory strains or clinical isolates of influenza B virus tended to be less sensitive to S-033447 than those of influenza A virus ("Review Report of Xofluza Tablets 10 mg and 20 mg" dated January 17, 2018). In non-clinical pharmacology studies that evaluated the effects of prophylactic administration of S-033447, the plasma S-033447 concentration required to attain the prophylactic effect against influenza B virus infection was higher than that against influenza A virus infection [see Section 3.1.1.1].

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[25] In the overall population, changes in influenza virus titer from baseline to Days 2, 4, and 6 (mean ± SD) were −4.62 ± 1.61, −3.05 ± 2.39, and −3.94 ± 2.11 $\log_{10}$ ($TCID_{50}$/mL), respectively.
[26] Patients with influenza A virus infection showed no re-increase in viral titer.
[27] The applicant explained that because the prophylactic study (Study T0834) did not provide results in children weighing <10 kg who received baloxavir, the proposed dosage and administration for children weighing <10 kg was withdrawn [see Section 7.R.1.2].

- In general, the exposure required to attain the expected efficacy and the required duration of the exposure differ between treatment of and prophylaxis against influenza virus infection. That is, it is unclear whether the dosage regimen found to achieve the therapeutic effect on influenza virus infection can provide the prophylactic effect against influenza virus infection for an adequate period.

- The target exposure for a prophylactic effect against influenza B virus (plasma S-033447 concentration ≥2.35 ng/mL) was established based on the survival extension effect in mice infected with influenza B virus at the lethal load [see Section 3.1.1.1], and whether this finding in mice is relevant to humans remains unclear. The dosage regimen in the prophylactic study (Study T0834) was determined based on the target exposure; this was acceptable. However, just because the estimated plasma concentrations exceeded the target exposure (2.35 ng/mL) does not necessarily mean that baloxavir can provide the prophylactic effect against influenza B virus for a sufficient period in clinical settings, in the context where specific clinical results of prophylactic baloxavir against influenza B are limited [see Section 6.R.1].

The applicant explained that baloxavir was expected to be effective in the prophylaxis of influenza virus B infection in children aged <12 years (especially low-weight children). PMDA finds limitations in this applicant's view for the following reasons:

- The prophylactic study (Study T0834) has not provided results from subjects aged <12 years whose index patient was infected with influenza B virus.

- In general, the duration of drug exposure required to attain the expected efficacy should be longer for prophylactic use against influenza than for therapeutic use. For baloxavir, S-033447 is eliminated faster from plasma in children of lower age or weight than in adolescents aged ≥12 years or adults. The plasma S-033447 concentration in such children thus tends to become lower with increasing time after administration of baloxavir [see Tables 10 and 11].

- As for the therapeutic study (Study T0833) in children with influenza virus infection weighing <20 kg, the applicant provided the following explanation:

  > Viral titer and body temperature temporarily re-increased in patients with influenza B virus infection, but these parameters returned to similar levels to those in the overall population from Day 6, raising no clinically relevant problems.

  In therapeutic studies in patients aged ≥12 years (Studies T0831 and T0832), however, no re-increase in viral titer or body temperature was observed in patients with influenza B virus infection. These findings raise a concern that baloxavir may be less effective in children weighing <20 kg than in the population aged ≥12 years.

In Section 7.R.1.3, PMDA discusses whether the prophylactic use of baloxavir should be allowed in children aged <12 years in view of the above discussion and the emergence of virus with amino acid substitution with reduced sensitivity to S-033447.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.1.2 Efficacy by age and by body weight

The applicant's explanation about the efficacy of baloxavir by age (≥12 years or <12 years) and by body weight (dose) (<10 kg, ≥10 kg and <20 kg, ≥20 kg and <40 kg, ≥40 kg and <80 kg, ≥80 kg):

Table 19 shows incidences of subjects with RT-PCR-confirmed symptomatic influenza involving both pyrexia and respiratory symptoms[14)] by age (≥12 years or <12 years) and by body weight (dose) (<10 kg, ≥10 kg and <20 kg, ≥20 kg and <40 kg, ≥40 kg and <80 kg, ≥80 kg) in the prophylactic study (Study T0834). In all the age subgroups and body-weight subgroups (except for the subgroup of body weight <10 kg), the proportion of subjects with RT-PCR-confirmed symptomatic influenza involving both pyrexia and respiratory symptoms[14)] was lower in the baloxavir group than in the placebo group, and thus baloxavir is expected to be effective in the prophylaxis of influenza.

Because the prophylactic study did not provide results of baloxavir administered to children weighing <10 kg, the proposed dosage and administration for children weighing <10 kg is withdrawn.

Table 19. Proportion of subjects with RT-PCR-confirmed symptomatic influenza involving both pyrexia and respiratory symptoms by age and by body weight

	Baloxavir[a)]	Placebo[a)]	Adjusted risk ratio[b)] [95% CI]
Age			
<12 years	3/71 (4.2)	11/71 (15.5)	0.27 [0.08, 0.90]
≥12 years	4/303 (1.3)	40/304 (13.2)	0.10 [0.04, 0.28]
Body weight			
<10 kg (baloxavir 1 mg/kg)	0/0	1/1 (100)	-
≥10 kg and <20 kg (baloxavir 10 mg)	1/19 (5.3)	5/30 (16.7)	0.31 [0.04, 2.39]
≥20 kg and <40 kg (baloxavir 20 mg)	2/57 (3.5)	5/43 (11.6)	0.29 [0.06, 1.43]
≥40 kg and <80 kg (baloxavir 40 mg)	4/280 (1.4)	35/283 (12.4)	0.12 [0.04, 0.32]
≥80 kg (baloxavir 80 mg)	0/18 (0)	5/18 (27.8)	-

a) n/N (%)
b) Modified Poisson regression approach (*Am J Epidemiol*. 2004;159:702-6) using RT-PCR-confirmed symptomatic influenza involving both pyrexia and respiratory symptoms (yes, no) as the response.
The following covariates were used for modified Poisson regression approach:
The age subgroups: Time from onset in the index patient to subject's informed consent (<24 hours, ≥24 hours) and influenza antiviral drug of the index patient (baloxavir, other).
The body-weight subgroups: Time from onset in the index patient to subject's informed consent (<24 hours, ≥24 hours), influenza antiviral drug of the index patient (baloxavir, others), and age of the subject.

PMDA accepts withdrawal of the proposed dosage and administration for children weighing <10 kg but discusses the appropriateness of the dosage regimen for prophylactic administration of baloxavir in Section 7.R.6.

7.R.1.3 Virus with amino acid substitution with reduced sensitivity to S-033447

7.R.1.3.1 Virus with amino acid substitution with reduced sensitivity to S-033447 in prophylactic study (Study T0834)

The applicant explained emergence of resistance (including viruses with reduced sensitivity) in subjects receiving prophylactic administration of baloxavir in the prophylactic study (Study T0834) and its effect on the efficacy (prophylactic effect).

The applicant's explanation:

Table 9 shows the number of subjects who had virus with PA/I38 or PA/E23 substitution with reduced sensitivity in the prophylactic study (Study T0834) [see Section 3.R.2]. Table 20 shows the number and

proportion of subjects with virus with amino acid substitution by body weight and by age. In subjects receiving baloxavir, the frequency of virus with PA/I38 or PA/E23 substitution tended to be higher in subjects of lower weight. However, among subjects receiving baloxavir who weighed <20 kg and tested negative by RT-PCR before administration, none experienced emergence of amino acid substitution, indicating no clear trend for a relationship between body weight and frequency of virus with amino acid substitutions. The frequency of virus with PA/I38 or PA/E23 substitution tended to be higher in the subgroup aged <12 years than in the subgroup aged ≥12 years in terms of numerical values, but the difference is considered insignificant.[28)] In the prophylactic study (Study T0834), virus with PA/I38 substitution was detected in 2 subjects who received placebo [see Section 3.R.2, Table 9]. In these subjects, wild-type virus was detected in specimens collected 3 days after onset of pyrexia and respiratory symptoms, followed by rescue treatment with baloxavir on the same day of collection, and then virus with PA/I38 substitution was detected at 5 days after the onset. This means that the virus with PA/I38 substitution was not transmitted to these subjects from respective index patients.

Table 20. Number and proportion of subjects in which virus with amino acid substitution was detected after administration of baloxavir by body weight and by age

Subgroup	mITT population			Pre-dose RT-PCR negative in mITT population		
	Number of subjects with PA/I38 substitution	Number of subjects with PA/E23 substitution	Frequency of virus with PA/I38 or PA/E23 substitution[a)]	Number of subjects with PA/I38 substitution	Number of subjects with PA/E23 substitution	Frequency of virus with PA/I38 or PA/E23 substitution[a)]
Overall population	10	5	15/374 (4.0)	7	4	11/348 (3.2)
Body weight						
<10 kg	0	0	-	0	0	-
≥10 kg and <20 kg	1	1	2/19 (10.5)	0	0	0/17 (0)
≥20 kg and <40 kg	2	1	3/57 (5.3)	2	1	3/54 (5.6)
≥40 kg and <80 kg	7	3	10/280 (3.6)	5	3	8/260 (3.1)
≥80 kg	0	0	0/18 (0)	0	0	0/17 (0)
Age						
<12 years	3	2	5/71 (7.0)	-	-	-
≥12 years	7	3	10/303 (3.3)	-	-	-

Number of subjects; -, Not tested
a) n/N (%)

In the baloxavir group, virus with PA/I38 substitution was detected in 10 subjects (including 3 children aged ≤12 years). Eight of the 10 subjects experienced pyrexia or influenza symptoms (respiratory symptoms or general symptoms) during the observation period (Days 1 to 10). Of 5 subjects (including 2 children aged ≤12 years) who had virus with PA/E23 substitution, 3 experienced pyrexia or influenza symptoms (respiratory symptoms or general symptoms) during the observation period (Days 1 to 10).

7.R.1.3.2 Virus with amino acid substitution with reduced sensitivity to S-033447 in therapeutic studies

7.R.1.3.2.1 Emergence of virus with PA/I38 substitution and effects on clinical symptoms

The applicant's explanation about emergence of virus with PA/I38 substitution in therapeutic studies and effects on clinical symptoms:

28) The applicant's explanation:
Viruses with amino acid substitutions occur only in individuals infected with influenza either before or after administration. In this study, virus-positive status was found in 23.9% (17 of 71) of subjects aged <12 years and 15.2% (46 of 303) of subjects aged ≥12 years either before or after administration. This difference in incidence of virus-positive status might be related to the difference in frequency of virus with PA/I38 or PA/E23 substitution between the age subgroups.

In the completed therapeutic studies for influenza virus infection, I38 substitution was the major amino acid substitution in the PA region with reduced sensitivity in subjects treated with baloxavir [see Section 3.R.2].

Table 21 shows emergence of PA/I38 substitution in subjects treated with baloxavir in the pooled population, which included subjects from therapeutic studies using the same dosage regimen as the proposed dosage, by study, by virus type/subtype, and by body weight. The frequency of PA/I38 substitution tended to be higher in children of low weight (<20 kg) and subjects infected with A/H3 virus.

Table 21. Emergence of PA/I38 substitution in subjects treated with baloxavir by study, by virus type/subtype, and by body weight (ITTI population)

	Population of subjects treated with baloxavir who provided specimens available for base sequencing before and after administration				Efficacy analysis population[a)]			
	Overall population[b)]	A/H1N1 pdm[c)]	A/H3[c)]	B[c)]	Overall population[b)]	A/H1N1 pdm[c)]	A/H3[c)]	B[c)]
Global study in patients aged ≥12 years (Study T0831)								
Body weight ≥40 kg	36/370 (9.7)	0/4 (0)	36/330 (10.9)	1/37 (2.7)[d)]	36/456 (7.9)	0/7 (0)	36/397 (9.1)	1/44 (2.3)[d)]
Global study in patients aged ≥12 years having high-risk factors (Study T0832)								
Body weight ≥40 kg	15/290 (5.2)	1/18 (5.6)	13/141 (9.2)	1/131 (0.8)	15/388 (3.9)	1/29 (3.4)	13/183 (7.1)	1/170 (0.6)
Japanese study in children aged <12 years (Study T0822)								
Overall[e)]	18/76 (23.7)	0/2 (0)	18/70 (25.7)	0/5 (0)	18/103 (17.5)	0/3 (0)	18/90 (20.0)	0/9 (0)
Body weight ≥40 kg	1/6 (16.7)	-	1/6 (16.7)	-	1/8 (12.5)	0/1 (0)	1/7 (14.3)	-
Body weight ≥20 kg and <40 kg	9/49 (18.4)	0/2 (0)	9/45 (20.0)	0/3 (0)	9/66 (13.6)	0/2 (0)	9/59 (15.3)	0/5 (0)
Body weight ≥10 kg and <20 kg	8/21 (38.1)	-	8/19 (42.1)	0/2 (0)	8/29 (27.6)	-	8/24 (33.3)	0/4 (0)
Japanese study in children aged <12 years (Study T0833)								
Overall	5/26 (19.2)	1/6 (16.7)	4/9 (44.4)	0/11 (0)	5/33 (15.2)	1/12 (8.3)	4/9 (44.4)	0/12 (0)
Body weight ≥10 kg and <20 kg	3/15 (20.0)	0/4 (0)	3/5 (60.0)	0/6 (0)	3/21 (14.3)	0/9 (0)	3/5 (60.0)	0/7 (0)
Body weight <10 kg	2/11 (18.2)	1/2 (50.0)	1/4 (25.0)	0/5 (0)	2/12 (16.7)	1/3 (33.3)	1/4 (25.0)	0/5 (0)

n/N (%); -, Not applicable

a) If base sequence data were not available or virus RNA enough to analyze base sequence was not obtained after administration, the subject was handled as one without amino acid substations, assuming that the virus had disappeared.
b) In the overall population, any subject with multiple infections were counted as "1 subject."
c) In the population classified by virus type/subtype, any subject infected with more than 1 influenza type/subtype was counted as "1 subject" for each type/subtype determined by base sequencing before and after administration.
d) One subject was infected with both influenza A and B viruses, and I38 substitution was found in both influenza types.
e) One subject weighing <10 kg who received a 5-mg tablet (which was not the approved dosage) was excluded.

In the global phase III study (Study T0831) in adults and ≥12-year old adolescents with influenza virus infection, viral titers increased again from Day 3 after administration of baloxavir in patients who had virus with PA/I38 substitution. However, clinical symptoms (duration of influenza illness, influenza symptoms, and pyrexia) did not differ between patients with and without PA/I38 substitution ("Review Report of Xofluza Tablets 10 mg and 20 mg" dated January 17, 2018).

In the Japanese study (Study T0833) in children with influenza virus infection weighing <20 kg, a re-increase in viral titer was found on Day 6 in patients who had virus with PA/I38 amino acid substitution (see Figure 6). The proportion of patients having influenza symptoms from Day 6 onward tended to be

higher in the subgroup with PA/I38 substitution (80.0% [4 of 5 patients]) than in the subgroup without substitution (10.3% [3 of 28 patients]), but the number of patients having pyrexia from Day 6 onward was very limited (0% [0 of 28 patients with substitution], 20.0% [1 of 5 patients without substitution]).

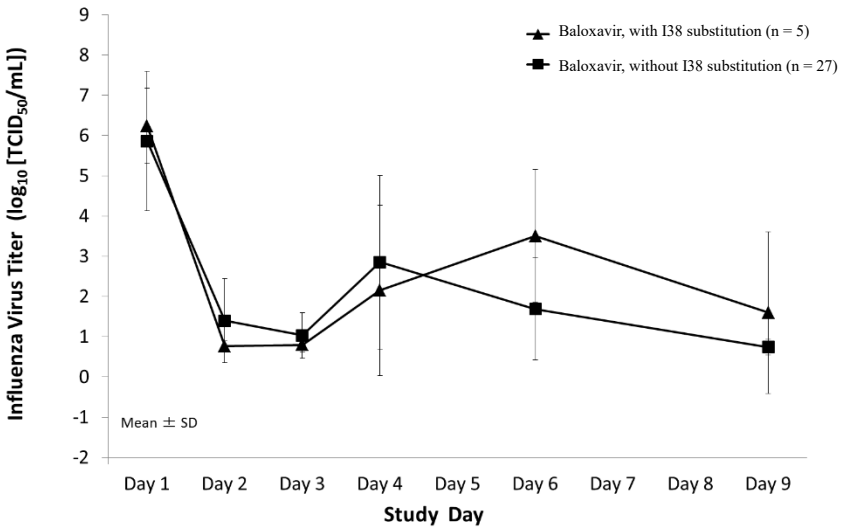

Figure 6. Changes in viral titer in patients with and without PA/I38 substitution (mean ± SD) (Study T0833)

In the following completed therapeutic studies, dosage different from the proposed one was used:

- A Japanese study (Study T0835),[29)] in which a single dose of baloxavir was orally administered to children with influenza virus infection weighing <20 kg.
- A global study (Study CP40617),[30)] in which baloxavir and a neuraminidase (NA) inhibitor were concomitantly administered to patients with severe influenza virus infection requiring hospitalization aged ≥12 years and weighing ≥40 kg.

Table 22 shows the frequency of PA/I38 substitution in these studies. Compared with the other therapeutic studies in children (Studies T0822 and T0833), Study T0835 showed a tendency toward a slightly higher frequency of PA/I38 substitution in patients with A/HIN1pdm or A/H3 influenza virus.[31)] Study CP40617 had a lower frequency of PA/I38 substitution than the other clinical studies.

29) Outline of Study T0835 is as follows:
Objective and design: A multi-center, uncontrolled, open-label study in children with influenza virus infection weighing <20 kg to evaluate the safety, tolerability, PK, and efficacy of a single dose of baloxavir 2% granules.
Dosage regimen:
- Body weight <10 kg and age <3 months: A single oral dose of baloxavir 1 mg/kg
- Body weight <10 kg and age ≥3 months: A single oral dose of baloxavir 2 mg/kg
- Body weight 10 to 20 kg: A single oral dose of baloxavir 20 mg

30) Outline of Study CP40617 is as follows:
Objective and design: A randomized, double-blind, multi-center, global, parallel-group study in hospitalized patients with influenza virus infection to evaluate the efficacy, safety, and PK of baloxavir + an NA inhibitor (oseltamivir, zanamivir, or peramivir) versus placebo + an NA inhibitor (oseltamivir, zanamivir, or peramivir).
Dosage regimen of baloxavir: Baloxavir was administered at 40 mg to patients weighing ≥40 kg and <80 kg or 80 mg to patients weighing ≥80 kg once daily on Days 1 and 4. Patients with symptoms persisting on Day 5 (continuous use of respirator, persistent pyrexia, severe immunodeficient status, influenza-related complication, or pneumonia) received an additional dose on Day 7.
Dosage regimen of NA inhibitors (oseltamivir, zanamivir, or peramivir): Dosage regimen, treatment extension, and dose changes were selected in accordance with clinical practices at the study site. Wherever possible, however, treatment for at least 5 days from Days 1 to 5 was recommended.

31) The frequency of virus with PA/I38 substitution tended to be slightly higher in Study T0835 than in the other studies, but the reason for such a trend remains to be clarified.

Table 22. Emergence of PA/I38 substitution in therapeutic studies using different dosage regimens from the proposed dosage by months of age, body weight, and type/subtype (ITTI population)

	Population of subjects treated with baloxavir who provided specimens available for base sequencing before and after administration				Efficacy analysis population[a)]			
	Overall population[b)]	A/H1N1 pdm[c)]	A/H3[c)]	B[c)]	Overall population[b)]	A/H1N1 pdm[c)]	A/H3[c)]	B[c)]
Japanese study in children weighing <20 kg[d)] (Study T0835) (granules)								
Overall	16/39 (41.0)	2/9 (22.2)	14/20 (70.0)	0/10 (0)	16/43 (37.2)	2/11 (18.2)	14/23 (60.9)	0/10 (0)
Age <3 months	0	0	0	0	0	0	0	0
Body weight <10 kg and age ≥3 months	3/7 (42.9)	0/1 (0)	3/6 (50)	0	3/8 (37.5)	0/2 (0)	3/7 (42.9)	0
Body weight 10-20 kg	13/32 (40.6)	2/8 (25.0)	11/14 (78.6)	0/10 (0)	13/35 (37.1)	2/9 (22.2)	11/16 (68.8)	0/10 (0)
Global study in patients with severe illness requiring hospitalization aged ≥12 years and weighing ≥40 kg[e)] (Study CP40617)								
≥12 years and body weight ≥40 kg	3/134 (2.2)	3/64 (4.7)	0/58 (0)	0/12 (0)	-	-	-	-

n/N (%); -, Not tested

a) If base sequence data were not available or virus RNA enough to analyze base sequence was not obtained after administration, the subject was handled as one without amino acid substations, assuming that the virus had disappeared.

b) In the overall population, any subject with multiple infection was counted as "1 subject."

c) In the population classified by virus type/subtype, any subject with more than 1 influenza type/subtype was counted as "1 subject" for each type/subtype.

d) In Study T0835, a single dose of baloxavir was orally administered at 1 mg/kg to patients weighing <10 kg and aged <3 months, at 2 mg/kg to patients weighing <10 kg and aged ≥3 months, and at 20 mg to patients weighing 10 to 20 kg.

e) In Study CP40617, baloxavir and an NA inhibitor (oseltamivir, zanamivir, or peramivir) were concomitantly administered according to the following regimens:
   - Baloxavir was administered at 40 mg to patients weighing ≥40 kg and <80 kg or 80 mg to patients weighing ≥80 kg once daily on Days 1 and 4. Patients whose symptoms were persisting on Day 5 (continuous use of respirator, persistent pyrexia, severe immunodeficient status, influenza-related complication, or pneumonia) received an additional on Day 7.
   - Dosage, treatment extension, and dose change of NA inhibitors (oseltamivir, zanamivir, or peramivir) were selected in accordance with clinical practices at the study site. Wherever possible, however, treatment for at least 5 days from Days 1 to 5 was recommended.

Table 23 shows the median duration of influenza illness [95% CI] in Study T0835 and the other therapeutic studies in children (Study T0822 and Study T0833) by subtype of influenza A virus and by status of PA/I38 substitution. No clear differences were observed between Study T0835 and the other therapeutic studies in children (Study T0822 and Study T0833). The proportion of patients with influenza symptoms[32)] from Day 6 onward was 37.5% (6 of 16) of patients with PA/I38 substitution and 14.8% (4 of 27) of patients without PA/I38 substitution. The proportion of patients with pyrexia[33)] from Day 6 onward was 18.8% (3 of 16) of patients with PA/I38 substitution and 3.7% (1 of 27) of patients without PA/I38 substitution. The incidence of persisting symptoms tended to be higher in patients with PA/I38 substitution than in those without.

Table 23. Median duration of influenza illness by study, by subtype of influenza A virus, or by status of PA/I38 substitution

Study No.	A/H1N1pdm		A/H3		With PA/I38 substitution		Without PA/I38 substitution	
	N	Duration of influenza illness (hours)	N	Duration of influenza illness (hours)	N	Duration of influenza illness (hours)	N	Duration of influenza illness (hours)
T0835	10	40.0 [12.0, 46.7]	22	42.0 [20.0, 74.7]	16	42.0 [20.0, 92.6]	23	29.1 [23.8, 51.6]
T0822	2	164.2 [151.4, 177.1]	86	45.2 [38.2, 62.5]	17	79.6 [39.8, 116.9]	59	42.8 [28.6, 61.0]
T0833	11	58.9 [17.5, 154.3]	9	26.8 [12.3, 199.3]	5	189.3 [25.0, 272.8]	21	38.9 [26.4, 86.9]

Median [95% CI[a)]]

a) Calculated according to Brookmeyer and Crowley's method (*Biometrics.* 1982;38(1):29–41).

7.R.1.3.2.2 Emergence of virus with PA/E23 substitution and effects on clinical symptoms

The applicant's explanation about emergence of virus with PA/E23 substitution in therapeutic studies and effects on clinical symptoms:

32) Influenza symptoms were defined as moderate or severe cough or runny nose/nasal congestion lasting for ≥21.5 hours.

33) Pyrexia was defined as body temperature ≥37.5°C lasting for ≥12 hours.

In the completed therapeutic studies for influenza virus infection (Studies T0821, T0822, T0831, T0833, and T0832), the frequency of PA/E23 substitution was limited compared with that of PA/I38 substitution, and a total of 5 patients with influenza virus infection had virus with PA/E23 substitution [see Section 3.R.2]. Table 24 shows virus type/subtype and duration of influenza illness, the primary endpoint, in these patients. As for virus type/subtype, A/H3 type was dominant, and the duration of influenza illness was similar to that in the ITTI population, except for 1 patient in Study T0833.

Table 24. Clinical symptoms in patients with virus with PA/E23 substitution

Study No.	Dose	Virus type/ subtype	Amino acid substitution	Duration of influenza illness (hours)	
				Each patient	ITTI population (median)
T0821	20 mg	A/H1N1	PA/E23K	52.93	51.0
T0832	40 mg	A/H3	PA/E23E/K	64.5	73.2
T0831	40 mg	A/H3	PA/E23E/G	36.5	53.7
T0831	40 mg	A/H3	PA/E23K	80.8	
T0833	10 mg	A/H3	PA/E23K/R/E/G	198.1	45.3

7.R.1.3.3 Prophylactic administration of baloxavir to children in view of emergence of virus with amino acid substitution with reduced sensitivity to S-033447

The applicant's explanation in view of Sections 7.R.1.3.1, 7.R.1.3.2.1, and 7.R.1.3.2.2:
Providing baloxavir to children aged <12 years as an option for prophylaxis of influenza is meaningful for the following reasons:

- For the efficacy in the prophylactic study (Study T0834), the number of subjects with RT-PCR-confirmed symptomatic influenza involving both pyrexia and respiratory symptoms in the population of children aged <12 years tended to be smaller in the baloxavir group than in the placebo group, as observed in the population of adults and adolescents aged ≥12 years [see Section 7.R.1.2]. For the safety, the incidence of adverse events in children aged <12 years did not differ between the baloxavir and placebo groups, and no adverse drug reactions occurred in the baloxavir group [see Section 7.R.2].

- In the prophylactic study (Study T0834), the frequency of virus with PA/I38 or PA/E23 substitution did not clearly differ between subjects aged <12 years and subjects aged ≥12 years [see Section 7.R.1.3.1]. There is no clear evidence indicating an increased risk of viruses with amino acid substitution in children aged <12 years who received prophylactic administration of baloxavir.

- All the anti-influenza drugs indicated for prophylaxis against influenza virus infection in Japan must be administered as multiple doses or by inhalation. Drugs requiring multiple doses may raise a concern about treatment incompliance, and patients using the inhalant drug (dry powder inhaler of laninamivir octanoate hydrate) have difficulty inhaling a sufficient amount of the drug (*J Pharm Health Care Sci*. 2017;3:26). Baloxavir, on the other hand, is orally administered as a single dose, ensuring treatment compliance. Unlike the other drugs in the same class, it may not raise any concern about treatment adherence.

- In Japan, all the anti-influenza drugs indicated for prophylaxis against influenza are NA inhibitors. Baloxavir acts through a new mechanism of action (cap-dependent endonuclease inhibition) different from that of NA inhibitors. Baloxavir is thus expected to be effective in the prophylaxis of influenza even in emergency situations such as an epidemic of influenza virus resistant to NA inhibitors.

PMDA's view:

Whether to approve the dosage for prophylactic administration of baloxavir in children aged <12 years should be carefully discussed for the following reasons. At present, prophylactic administration of baloxavir should be limited to adults and adolescents aged ≥12 years in principle.

- In the therapeutic studies (Studies T0822, T0833, and T0835[29]), viruses with amino acid substitution with reduced sensitivity to S-033447 were detected more frequently in children aged <12 years (especially children of low body weight) than in the other populations [see Section 7.R.1.3.2.1]. Related academic societies (the Japanese Association for Infectious Diseases and the Japan Pediatric Society) state[34] that positive use of baloxavir is not recommended (administration of baloxavir should be carefully considered) in view of the high frequency of strains with reduced sensitivity in children with influenza virus infection aged <12 years.

- Viruses with amino acid substitutions occur only in individuals infected with influenza either before or after administration. Therefore, emergence of viruses with PA/I38 or PA/E23 substitution was investigated only in children testing positive for virus either before or after administration,[35] although only limited data are available from children aged <12 years in the prophylactic study (Study T0834). The frequency of such viruses was 29.4% (5 of 17) of subjects aged <12 years and 21.7% (10 of 46) of subjects aged ≥12 years,[36] suggesting that even prophylactic use would lead to emergence of viruses with amino acid substitutions at a certain frequency. In addition, the frequency of such viruses tended to increase with decreasing body weight in the prophylactic study (Study T0834) as observed in the therapeutic studies [see Section 7.R.1.3.1].

- There are limitations in the applicant's discussion that baloxavir is expected to be effective in the prophylaxis of influenza B virus infection in children aged <12 years (especially low-weight children) [see Section 7.R.1.1].

- In view of the above, the approval of the dosage for prophylactic baloxavir in children aged <12 years would raise a public health concern (risk) of spreading viruses with amino acid substitutions with reduced sensitivity. This risk outweighs medical benefits from making baloxavir available as a prophylactic drug against influenza in clinical practice.

Despite the above, PMDA considers that baloxavir, which acts through a new mechanism of action different from that of the other drugs for prophylaxis against influenza virus infection (NA inhibitors), will meet potential medical needs in children aged <12 years. The applicant should thus investigate new dosage that is unlikely to cause viruses with amino acid substitutions with reduced sensitivity, and should continue to develop the drug to make prophylactic baloxavir available for children aged <12 years without any safety concern in the future.

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[34] "Use of anti-influenza drugs" (suggestion by The Japanese Association for Infectious Diseases dated October 19, 2019) and "Clinical Practice Guideline for influenza in 2019/2020 influenza season" (issued in October 2019, Emerging/re-emerging infectious disease measure sub-committee, Vaccination/infectious disease measure committee, Japan Pediatric Society)

[35] Virus-positive status was found in 23.9% (17 of 71) of subjects aged <12 years and 15.2% (46 of 303) of subjects aged ≥12 years either before or after administration.

[36] PA/I38 substitution was found in 3 subjects aged <12 years and 7 subjects aged ≥12 years, and PA/E23 substitution was found in 2 subjects aged <12 years and 3 subjects aged ≥12 years.

On the other hand, the dosage for prophylactic administration of baloxavir in adults and adolescents aged ≥12 years may be approved, because viruses with amino acid substitution with reduced sensitivity are considered less likely to occur in this population than in children aged <12 years [see Sections 7.R.1.3.1 and 7.R.1.3.2.1]. For the reasons presented below, however, the emergence trend of PA/I38 substitution and its pathogenicity should be monitored carefully. Whether to use baloxavir as a prophylactic drug against influenza should be considered carefully, taking into account of (a) other drugs and (b) the balance between benefits from using baloxavir and the risk of causing viruses with amino acid substitution with reduced sensitivity.

- In some subjects, human-to-human transmission of virus with PA/I38 substitution was observed [see Section 3.R.2].

- In the global phase III study (Study T0831) in adults and ≥12-year old adolescents with influenza virus infection, patients with PA/I38 substitution showed a re-increase in viral titers from Day 3 after administration of baloxavir ("Review Report of Xofluza Tablets 10 mg and 20 mg" dated January 17, 2018). In the therapeutic studies (Studies T0833 and T0835[29)]) in children weighing <20 kg, patients with virus with PA/I38 substitution tended to more frequently experience a re-increase in viral titer and pyrexia or influenza symptoms around Day 6 than those without such virus [see Section 7.R.1.3.2.1].

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.2 Safety

The applicant's explanation about the safety of baloxavir administered for prophylaxis against influenza virus infection:

In the prophylactic study (Study T0834), adverse events (including abnormal changes in laboratory tests) occurred in 22.2% (83 of 374) of subjects in the baloxavir group and 20.5% (77 of 375) of subjects in the placebo group. Adverse drug reactions occurred in 1.9% (7 of 374) of subjects in the baloxavir group and 1.6% (6 of 375) of subjects in the placebo group. The incidences in the baloxavir group were similar to those in the placebo group. In addition, adverse events or adverse drug reactions with an incidence of ≥1% in the baloxavir or placebo group did not clearly differ between the baloxavir and placebo groups [see Table 14 in Section 7.1.1].

The most frequently reported adverse drug reaction in the baloxavir group was nausea, which occurred in 0.5% (2 of 374) of subjects. No serious adverse events occurred in the baloxavir group [see Section 7.1].

Table 25 shows incidences of adverse events and adverse drug reactions in the age-based subgroups (<12 years or ≥12 years) and of adverse events (nasopharyngitis and headache) with an incidence of ≥2% in the baloxavir or placebo group. In the baloxavir group, the incidences of all adverse events and nasopharyngitis were slightly higher in subjects aged <12 years than in those aged ≥12 years, but a similar trend was also observed in the placebo group.

Table 25. Adverse events and adverse drug reactions reported by ≥2% of subjects in either age-based subgroup (safety analysis population)

Events	<12 years				≥12 years			
	Adverse events		Adverse drug reactions		Adverse events		Adverse drug reactions	
	Baloxavir (N = 71)	Placebo (N = 71)	Baloxavir (N = 71)	Placebo (N = 71)	Baloxavir (N = 303)	Placebo (N = 304)	Baloxavir (N = 303)	Placebo (N = 304)
Overall	18 (25.4)	18 (25.4)	0	2 (2.8)	65 (21.5)	59 (19.4)	7 (2.3)	4 (1.3)
Nasopharyngitis	6 (8.5)	6 (8.5)	0	0	18 (5.9)	19 (6.3)	0	0
Headache	2 (2.8)	0	0	0	6 (2.0)	6 (2.0)	0	1 (0.3)

n (%)

In the risk management plan, (a) shock, anaphylaxis,[37] colitis ischaemic,[38] and haemorrhage[39] were defined as the important identified risks and (b) neuropsychiatric symptoms[40] and hepatic dysfunction[41] as important potential risks, based on non-clinical and clinical study results and post-marketing case reports collected in Japan. The incidences of these events in the prophylactic study (Study T0834) were investigated as follows:

- Adverse events related to shock, anaphylaxis, or colitis ischaemic did not occur in either the baloxavir or placebo group.

- Adverse events related to haemorrhage

  Blood urine present and contusion occurred in the baloxavir group. For incidences in the baloxavir group (374 subjects) and placebo group (375 subjects), blood urine present occurred in 6 subjects (1.6%) and 1 subject (0.3%), respectively, and contusion occurred in 1 subject (0.3%) and 1 subject (0.3%), respectively. Seven subjects who experienced blood urine present in the baloxavir or placebo group, had no abnormal changes in platelet count with no symptoms or findings suggesting bleeding at the other site.

- Adverse events related to neuropsychiatric symptoms

  Headache and dizziness occurred in the baloxavir group. For incidence in the baloxavir group (374 subjects) and placebo group (375 subjects), headache occurred in 8 subjects (2.1%) and 6 subjects (1.6%), respectively, and dizziness occurred in 2 subjects (0.5%) and 0 subjects (0%), respectively, showing no clear differences between the baloxavir and placebo groups. A causal relationship to baloxavir was ruled out for all events.

- Adverse events related to hepatic dysfunction

  There were alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, γ-glutamyl transferase (γ-GTP) increased, and hepatic function abnormal. For incidences in the baloxavir group (374 subjects) and placebo group (375 subjects), ALT increased occurred in 4 subjects (1.1%) and 1 subject (0.3%), respectively; AST increased occurred in 1 subject (0.3%) and 1 subject (0.3%), respectively; γ-GTP increased occurred in 1 subject (0.3%) and 0 subjects (0%),

[37] Adverse events categorized under "Anaphylactic/anaphylactoid shock conditions (SMQ narrow scope)" or "Anaphylactic reaction (SMQ narrow scope)" in SMQ in MedDRA
[38] Adverse events categorized under "Ischaemic colitis (SMQ narrow scope)" in SMQ in MedDRA
[39] Adverse events categorized under "Haemorrhages" in SMQ in MedDRA
[40] Adverse events categorized under "Psychiatric disorders" or "Nervous system disorders" in SOC in MedDRA
[41] Adverse events categorized under "Drug related hepatic disorders - comprehensive search" in SMQ in MedDRA

respectively; and hepatic function abnormal occurred in 1 subject (0.3%) and 1 subject (0.3%), respectively. The event in the baloxavir group for which a causal relationship could not be ruled out was hepatic function abnormal in 1 subject only. Distribution of maximum liver function test values (maximum of all values at all the sampling points) showed that none of the subjects in the baloxavir group had a maximum liver function test value classified as Grade 3 in severity; an AST or ALT value exceeding 3-fold the upper limit of the reference value; or a total bilirubin value exceeding 1.5-fold the upper limit of the reference value.

According to results from a post-marketing use-results survey (survey period, March 2018 to March 2019; 3,094 patients included in the safety analysis), 345 of 3,094 patients (11.2%) in the safety analysis population experienced adverse drug reactions. Frequently reported events included diarrhoea in 189 patients, headache in 46 patients, nausea in 34 patients, vomiting in 23 patients, abdominal pain in 22 patients, abnormal behaviour in 13 patients, faeces soft in 12 patients, dizziness in 10 patients, rash in 8 patients, urticaria in 7 patients, and hypoaesthesia in 6 patients. The safety profile of baloxavir tablets was similar to that at the time of approval. Of 455 adverse drug reactions reported, 5 (1.1%) were serious, including 3 events of delirium, 1 event of abnormal behaviour, and 1 event of febrile convulsion, but all of the serious adverse drug reactions resolved within 3 days after onset.

As described above, no additional safety concern was raised for baloxavir in the prophylactic study (Study T0834). The applicant therefore considers it unnecessary to provide additional cautions because the safety of baloxavir used for prophylaxis against influenza virus infection has no problems, and the post-marketing surveillance of baloxavir indicated for treatment has not raised any safety concern. The safety information of baloxavir, however, will be continuously collected through regular pharmacovigilance activities.

PMDA's view:
As described in Section 7.R.1.3, prophylactic use of baloxavir against influenza virus infection should be indicated in adults and adolescents aged ≥12 years in principle. No additional cautions for prophylactic use against influenza virus infection are necessary, because the dosage of baloxavir for prophylaxis against influenza in adults and adolescents aged ≥12 years is the same as that for treatment of influenza, and because adverse events reported in the prophylactic study (Study T0834) were mostly known events with therapeutic use and consequently resolved or were resolving.

According to the post-marketing safety information based on case reports in Japan (collected between February 23, 2018 and February 22, 2020; estimated number of patients treated, 7,898,165), however, a certain number of serious adverse drug reactions (560 events) were reported, and thus the safety information of baloxavir should be continuously collected.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.3 Efficacy and safety of baloxavir in high-risk populations

The applicant explained the efficacy and safety of baloxavir in prophylaxis of influenza virus infection in high-risk populations (elderly ≥65 years, patients with chronic respiratory disease or chronic heart

disease, patients with metabolic disease [e.g., diabetes mellitus], etc.[42]), because these populations are expected to use baloxavir for prophylaxis against influenza virus infection.

The applicant's explanation:
In the prophylactic study (Study T0834), 46 of 374 subjects (12.3%) in the baloxavir group and 52 of 375 subjects (13.9%) in the placebo group had high-risk factors. In this high-risk population, RT-PCR-confirmed symptomatic influenza involving both pyrexia and respiratory symptoms developed in 1 of 46 subjects (2.2%) in the baloxavir group and 8 of 52 subjects (15.4%) in the placebo group. In the high-risk population (46 subjects in the baloxavir group, 52 subjects in the placebo group) in the prophylactic study (Study T0834), major high-risk factors were children aged <5 years (14 [3.7%] in the baloxavir group, 20 [5.3%] in the placebo group), asthma (12 [3.2%], 12 [3.2%]), and elderly ≥65 years (8 [2.1%], 15 [4.0%]).

The safety of baloxavir in the high-risk population was evaluated not only in the prophylactic study (Study T0834) but also in the therapeutic study (Study T0832), which enrolled high-risk patients with influenza virus infection. Table 26 shows adverse events and adverse drug reactions in the high-risk populations in these clinical studies. No large differences were observed in incidence of adverse events or adverse drug reactions between the therapeutic and prophylactic studies or between the baloxavir and placebo groups. In the high-risk population (730 subjects in the baloxavir group, 727 subjects in the placebo group) in Study T0832, major high-risk factors were asthma or chronic lung disease (151 [38.9%] in the baloxavir group, 157 [40.7%] in the placebo group), endocrine disease (123 [31.7%], 131 [33.9%]), ≥65 years (113 [29.1%], 103 [26.7%]), metabolic disease (51 [13.1%], 50 [13.0%]), and heart disease (46 [11.9%], 49 [12.7%]).

Table 26. Adverse events and adverse drug reactions in high-risk populations

	Adverse events		Adverse drug reactions	
	Baloxavir	Placebo	Baloxavir	Placebo
Study T0832 (treatment)	183/730 (25.1)	216/727 (29.7)	41/730 (5.6)	60/727 (8.3)
Study T0834 (prophylaxis)	13/46 (28.3)	16/52 (30.8)	1/46 (2.2)	4/52 (7.7)

n/N (%)

In the results from post-marketing surveillance of baloxavir in patients with influenza virus infection in clinical use (surveillance period, March 2018 to March 2019; 3,094 patients included in the safety analysis), 388 patients (12.5%) had high-risk factors. The proportion of patients with adverse drug reactions did not differ between the populations with and without high-risk factors (44 patients with high-risk factors [11.3%], 301 patients without high-risk factors [11.1%]), and thus no safety concern specific to patients with high-risk factors was raised.

As described above, baloxavir orally administered to the high-risk population as a single dose is expected to be effective without posing particular safety concern.

[42] High-risk factors were specified according to definition of high-risk patients by the US Centers for Disease Control and Prevention (CDC) (http://www.cdc.gov/flu/about/disease/high_risk.htm, accessed on August 7, 2020).

PMDA's view:
Data regarding the efficacy and safety of a single oral administration of baloxavir to the high-risk population are limited. The applicant nevertheless explained that a single oral administration of baloxavir to the high-risk population is expected to be effective without posing particular safety concern, based on results from clinical studies of treatment and prophylaxis of influenza virus infection conducted so far; this explanation is acceptable. Among the high-risk population, however, individuals with particular high-risk factors (e.g., immunosuppressed patients, patients with particular underlying diseases such as hematologic diseases) have little experience with baloxavir therapy, and therefore the efficacy and safety data of baloxavir in such individuals are limited. Information in these individuals should be continuously collected after the market launch.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.4 Clinical positioning

The applicant's explanation about clinical positioning of baloxavir:
The primary standard prophylaxis against influenza virus infection is vaccination. Vaccination, however, potentially involves the following problems, and a prophylactic measure against influenza virus infection other than vaccine is needed:

- Vaccination in the elderly has a limited effect in prophylaxis of severe influenza virus infection.
- Antibody-production capacity differs from vaccine recipient to vaccine recipient.
- It takes a certain period of approximately 2 weeks from vaccination to antibody production in the body.
- Vaccination is contraindicated in some individuals.
- Manufacture of a new influenza virus vaccine takes time, and the vaccine may not be available at the early phase of a pandemic.

Because influenza virus infection is easily transmitted and spread, it is important to prophylactically administer an influenza antiviral drug to the population of individuals at a high risk of severe infection and their caregivers. A related academic society recommends that an influenza antiviral drug be administered prophylactically to hospitalized patients or residents who have been in contact with patients with influenza to prevent the disease from spreading in the hospital or nursing home (Principles for Measures Against Nosocomial Influenza Infection in Hospitals [including Nursing Homes] by the Japanese Association for Infectious Diseases in 2012).

In Japan, 3 NA inhibitors, oseltamivir phosphate (oral), zanamivir hydrate (inhaler), and laninamivir octanoate hydrate (inhaler), are approved for prophylaxis against influenza virus infection. Baloxavir, however, has a new mechanism of action different from that of the NA inhibitors and is orally administered as a single dose unlike the other drugs. The applicant therefore considers it clinically meaningful to make baloxavir available not only for treatment of influenza virus infection but also for its prophylaxis as a new option in clinical settings.

The package inserts for all the approved prophylactic drugs against influenza include a caution statement to the effect that in principle the drugs should be administered only to household contacts of patients

with influenza virus infection who have high-risk factors such as age ≥65 years, chronic respiratory disease, chronic heart disease, metabolic disease such as diabetes mellitus, and renal impairment. Prophylactic administration of baloxavir also should be made available with a caution against inappropriately broad use. The "Precautions Concerning Indication" section of the draft package insert includes a caution statement that in principle prophylactic baloxavir should be administered only to individuals who are likely to experience severe illness if infected with influenza virus, based on definition of high-risk patients provided by the US CDC.

PMDA's view:
Fundamentals in prophylaxis of influenza virus infection are appropriate prophylactic measures against infection and influenza virus vaccination, and prophylaxis with baloxavir would not replace the vaccination, but can supplement it. The US CDC also considers that the major target population of influenza prophylaxis is the high-risk individuals who are likely to experience severe influenza illness, and thus particularly recommends influenza vaccination in such high-risk population.[43)] In addition, careless broad use of an influenza antiviral drug for prophylaxis of influenza in individuals who have been in contact with patients infected with influenza without limiting the target population, would increase a risk of emerging viruses with amino acid substitution with reduced sensitivity. Therefore, the target population of prophylactic baloxavir should be carefully selected. In principle, prophylactic baloxavir should be administered only to high-risk individuals who are likely to experience serious complications if affected by influenza, as explained by the applicant.

According to clinical study results and other data of baloxavir, viruses with amino acid substitution with reduced sensitivity was found at a certain frequency [see Sections 3.R.2 and 7.R.1.3]. Baloxavir acts through a new mechanism of action different from that of the other drugs indicated for prophylaxis against influenza (NA inhibitors), and thus is positioned as an important drug in public health, especially in emergency situations such as an epidemic of influenza virus resistant to NA inhibitors. Therefore, in order to prevent the spread of viruses with amino acid substitution with reduced sensitivity to S-033447, whether to use prophylactic baloxavir against influenza should be considered carefully, taking into account of (a) other drugs and (b) the balance between benefits from using baloxavir and the risk of causing viruses with amino acid substitution with reduced sensitivity.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.5 Indication

PMDA's view:
Based on the following review, the proposed additional indication, "prophylaxis of influenza A or B virus infection," is acceptable:

- There are limitations in the applicant's discussion that baloxavir is expected to be effective in the prophylaxis of influenza B virus infection in children aged <12 years (especially low-weight children) [see Section 7.R.1.1]. Based on the review in Section 7.R.1.3, prophylactic use of baloxavir against influenza virus infection should target adults and adolescents aged ≥12 years in principle at present.

43) https://www.cdc.gov/flu/prevent/prevention.htm (last accessed on August 7, 2020)

- As for the efficacy in adults and adolescents aged ≥12 years, the prophylactic effect of baloxavir against influenza A virus infection has been confirmed, and the applicant's explanation that baloxavir is expected to be effective in the prophylaxis against influenza B virus infection is understandable to a certain extent [see Section 7.R.1.1].

- As for the safety, the dosage of prophylactic baloxavir against influenza in adults and adolescents aged ≥12 years is the same as that of therapeutic baloxavir, and no additional safety concerns have been raised regarding prophylactic use of baloxavir against influenza [see Section 7.R.2].

However, there are limitations in concluding that baloxavir was shown to have efficacy in the prophylaxis of influenza B virus infection, for reasons including the following: (a) Results of the prophylactic effect of baloxavir against influenza B virus infection are limited, as described in Section 7.R.1.1.; and (b) Non-clinical pharmacology studies showed that influenza B virus tended to be less sensitive to S-033447 than influenza A virus.

Based on the above, the applicant should appropriately provide study results of baloxavir related to influenza B virus infection available at present to healthcare professionals, furthermore continue collecting the information even after the market launch, and immediately provide the obtained findings to healthcare professionals.

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.6 Dosage and administration

PMDA's view:

The proposed dosage and administration regarding prophylaxis against influenza include doses not only for adults and adolescents aged ≥12 years but also for children aged <12 years (including children of low weight such as <10 kg[13)] and ≥10 kg and <20 kg). In light of the review in Section 7.R.1.3, prophylactic baloxavir against influenza should target adults and adolescents aged ≥12 years in principle at present, and thus the dosage for prophylactic use should be as follows (see the table below).

Baloxavir acts through a new mechanism of action different from that of the other prophylactic drugs against influenza (NA inhibitors), and will meet potential medical needs in children aged <12 years. The applicant should therefore investigate new dosage that is unlikely to cause viruses with amino acid substitutions with reduced sensitivity, and should continue to develop the drug to make prophylactic baloxavir available for children aged <12 years in the future.

Adults and adolescents aged ≥12 years	<80 kg	Two 20-mg tablets or four packets of granules (40 mg of baloxavir marboxil)
	≥80 kg	Four 20-mg tablets or eight packets of granules (80 mg of baloxavir marboxil)

The above conclusion of PMDA will be discussed at the Expert Discussion.

7.R.7 Post-marketing investigations

Clinical results of the prophylactic effect of baloxavir against influenza B virus infection are limited [see Section 7.R.1.1], and experience with baloxavir in individuals with particular high-risk factors (e.g., immunosuppressed patients, patients with a particular underlying disease such as hematologic disease) is limited [see Section 7.R.3]. Therefore, the applicant plans to conduct post-marketing surveillance of baloxavir as shown below.

Specified use-results survey

It is intended to collect the following information:

- Efficacy of baloxavir administered for prophylaxis against influenza B virus infection in clinical use

- Safety and efficacy of baloxavir administered for prophylaxis against influenza virus infection to individuals having risk-factors (immunosuppression, hematologic disease, hepatic disorder, and renal disorder) in whom clinical use of baloxavir is limited.

PMDA's conclusion:

The applicant should continue to collect information about emergence of virus with amino acid substitution with reduced sensitivity to S-033447 and its pathogenicity and transmissibility trends in a careful manner, and should immediately provide new findings obtained, if any, to healthcare professionals.

The above conclusion of PMDA will be discussed at the Expert Discussion.

8. Results of Compliance Assessment Concerning the New Drug Application Data and Conclusion Reached by PMDA

8.1 PMDA's conclusion concerning the results of document-based GLP/GCP inspections and data integrity assessment

The new drug application data were subjected to a document-based compliance inspection and a data integrity assessment in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. On the basis of the inspection and assessment, PMDA concluded that there were no obstacles to conducting its review based on the application documents submitted.

8.2 PMDA's conclusion concerning the results of the on-site GCP inspection

The new drug application data (CTD 5.3.5.1-01) were subjected to an on-site GCP inspection, in accordance with the provisions of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices. As a result, PMDA concluded that the clinical studies as a whole were conducted in accordance with GCP and that there were no obstacles to conducting its review based on the application documents submitted. The inspection revealed the following finding requiring corrective action at a study site although it did not significantly affect the overall evaluation of the study. PMDA notified the head of the site of the finding.

Finding requiring corrective action

Study site

- Deviation from the protocol (incompliance with rules for dosage regimens of the study drug)

9. Overall Evaluation during Preparation of the Review Report (1)

On the basis of the data submitted, PMDA has considered that the product is expected to have efficacy in the prophylaxis of influenza A or B virus infection, and that the product has acceptable safety in view of its expected benefits. The product is clinically meaningful because it offers a new option for prophylaxis of influenza A or B virus infection in adults and adolescents aged ≥12 years. Prophylactic administration of baloxavir to children aged <12 years, however, may lead to the spread of viruses with amino acid substitutions with reduced sensitivity. This public health concern should considered seriously, and the emergence of such viruses should be avoided. Therefore whether to approve the dosage for prophylactic administration of baloxavir in children aged <12 years should be discussed carefully. At present, prophylactic administration of baloxavir should be limited to adults and adolescents aged ≥12 years in principle.

The above conclusion of PMDA will be further discussed at the Expert Discussion on the basis of the Review Report (1).

Review Report (2)

October 19, 2020

Product Submitted for Approval

Brand Name	Xofluza Tablets 20 mg
	Xofluza Granules 2%
Non-proprietary Name	Baloxavir Marboxil
Applicant	Shionogi & Co., Ltd.
Date of Application	October 16, 2019

List of Abbreviations
See Appendix.

1. Content of the Review

Comments made during the Expert Discussion and the subsequent review conducted by the Pharmaceuticals and Medical Devices Agency (PMDA) are summarized below. The expert advisors present during the Expert Discussion were nominated based on their declarations etc. concerning the product submitted for marketing approval, in accordance with the provisions of the Rules for Convening Expert Discussions etc. by Pharmaceuticals and Medical Devices Agency (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

At the Expert Discussion, the expert advisors largely supported PMDA's conclusion on issues presented in the Review Report (1) (Sections "7.R.1.1 Efficacy by type/subtype of influenza virus in index patients," "7.R.2 Safety," "7.R.4 Clinical positioning," and "7.R.7 Post-marketing investigations").

The expert advisors made the following comments regarding Sections "7.R.1.3.3 Prophylactic administration of baloxavir to children in view of emergence of virus with amino acid substitution with reduced sensitivity to S-033447," "7.R.5 Indication," and "7.R.6 Dosage and administration." PMDA additionally discussed these issues and took actions as necessary.

1.1 Prophylactic administration of baloxavir to children aged <12 years in view of emergence of viruses with amino acid substitution with reduced sensitivity

PMDA presented the following conclusion in Section 7.R.1.3 of the Review Report (1):

> Prophylactic administration of baloxavir to children aged <12 years, however, may lead to the spread of viruses with amino acid substitutions with reduced sensitivity. This public health concern should considered seriously, and the emergence of such viruses should be avoided. Therefore whether to approve the dosage for prophylactic administration of baloxavir in children aged <12 years should be discussed carefully. Prophylactic administration of baloxavir should be limited to adults and adolescents aged ≥12 years in principle.

During the Expert Discussion, the expert advisors basically supported PMDA's conclusion. They also presented the following comments at the discussion:

- Broad use of baloxavir in children should be avoided, particularly to prevent the emergence of viruses with amino acid substitution. However, in emergency situations such as an epidemic of influenza virus resistant to NA inhibitors, baloxavir should be made available for children aged <12 years with the target population strictly restricted, because it acts through a mechanism of action different from that of the existing drugs indicated for prophylaxis against influenza virus infection (NA inhibitors). Use of baloxavir in such a restricted population is unlikely to increase the frequency of viruses with amino acid substitution.

- Viruses with amino acid substitution with reduced sensitivity tend to occur more frequently in children weighing <20 kg than in children weighing ≥20 kg and adults. This finding suggests that dosage regimens of baloxavir may have not been fully investigated.

In response to the above comments from the expert advisors, PMDA re-reviewed issues regarding prophylactic administration in children aged <12 years. The agency proposed that children aged <12 years and weighing ≥20 kg be allowed to use prophylactic baloxavir when needed, with the following actions taken. The PMDA's proposal was supported by the expert advisors.

- The following information should be included in the package insert:
  - The following statement should be added under "Common to all indications" in the "Precautions Concerning Indication" section:

    Use in children should be carefully considered by consulting the latest guidelines issued by academic societies because the frequency of low-sensitive strain tended to be higher at lower age.
  - The following statement should be added under "Prophylaxis" in the "Precautions Concerning Indication" section:

    Use in children should be carefully considered by paying attention to information about drug-resistant isolates of epidemic virus and taking into account of using the other influenza antiviral drugs.
  - Results of the frequency of PA/I38 substitution in completed clinical studies including Japanese subjects (therapeutic and prophylactic studies) should be provided by virus type/subtype and by body weight.

- In addition to the above precautions in the package insert, proper use of baloxavir should be promoted in cooperation with related academic societies.

Based on the above, PMDA instructed the applicant to include the dosage of baloxavir for prophylaxis in children aged <12 years and weighing ≥20 kg and modify the dosage for adults and adolescents aged ≥12 years reviewed in the Review Report (1) [see Section 7.R.6], as shown below. The applicant responded appropriately.

Dosage and Administration

Adults and adolescents aged ≥12 years	Body weight ≥80 kg	Four 20-mg tablets or eight packets of granules (80 mg of baloxavir marboxil)
	Body weight <80 kg	Two 20-mg tablets or four packets of granules (40 mg of baloxavir marboxil)
Children aged <12 years	Body weight ≥40 kg	Two 20-mg tablets or four packets of granules (40 mg of baloxavir marboxil)
	Body weight ≥20 kg and <40 kg	One 20-mg tablet or two packets of granules (20 mg of baloxavir marboxil)

1.2 Indication

The expert advisors discussed the indication of baloxavir at the Expert Discussion, based on (a) discussion about appropriateness of approval for use in children weighing ≥20 kg in Section "1.1 Prophylactic administration of baloxavir to children aged <12 years in view of emergence of viruses with amino acid substitution with reduced sensitivity" of the Review Report (2) and (b) PMDA's view in Section "7.R.5 Indication" of the Review Report (1). Expert Discussion has concluded that the proposed indication of "prophylaxis of influenza A or B virus infection" is acceptable even if the target population for baloxavir includes children aged <12 years and weighing ≥20 kg, for the following shown below, provided that the actions listed below are taken by the applicant:

- The applicant's explanation that baloxavir is expected to be effective in the prophylaxis of influenza B virus infection in adults and adolescents aged ≥12 years is understandable to a certain extent [see Section 7.R.1.1].

- There are limitations in the applicant's discussion that baloxavir is expected to be effective in the prophylaxis of influenza B virus infection in children aged <12 years (especially low-weight children) [see Section 7.R.1.1]. However, in light of the following viewpoints and discussion in Section "1.1 Prophylactic administration of baloxavir to children aged <12 years in view of emergence of viruses with amino acid substitution with reduced sensitivity" of the Review Report (2), PMDA considers it clinically meaningful to make baloxavir available for children aged <12 years and weighing ≥20 kg in circumstances where use of baloxavir is needed as a result of weighing it against use of the other influenza antiviral drugs (NA inhibitors) for prophylaxis against not only influenza A but also influenza B.
  - The efficacy of prophylactic use against influenza B virus infection should be evaluated based on results from a randomized, double-blind study. However, it is difficult to conduct an additional clinical study at a scale that can evaluate the efficacy of prophylactic use against influenza B virus infection, because the type/subtype of epidemic virus differs from season to season, and because influenza B season usually comes after influenza A season.
  - If prophylactic baloxavir is approved against influenza A alone, baloxavir should be prescribed to household contacts of a patient only after identifying the influenza virus affecting the patient as influenza A. In clinical settings, however, the virus type of an affected patient is not necessarily identified before prophylactic use of a drug, and thus such a type-specific indication is not consistent with the reality of medical practices.
  - In the therapeutic study (Study T0822), although the number of subjects was limited, the median duration of influenza illness [95% CI] in 4 children aged <12 years and weighing ≥20 kg who received baloxavir for treatment of influenza B virus infection was 44.7 [18.3, 81.7] hours. This duration of influenza illness shows a similar tendency to that in the overall

population (44.6 [38.9, 62.5] hours). Moreover, the 4 children showed no re-increase in either influenza B viral titer or body temperature, unlike a clinical study in children weighing <20 kg (Study T0833) that showed such re-increases.

- The following actions should be taken on the package insert:
  - The following statement should be added under "Prophylaxis" in the "Precautions Concerning Indication" section:

    Use of baloxavir should be carefully considered by taking into account that data indicating the efficacy of prophylactic use against influenza B virus infection are limited.
  - Results of the efficacy by type/subtype of influenza virus in each clinical study (therapeutic and prophylactic studies) should be included in the "Clinical Studies" section, to disseminate information.

- The applicant should continue collecting information on the prophylactic effect of baloxavir against influenza B virus infection even after the market launch and immediately provide findings obtained to healthcare professionals.

Based on the above, PMDA directed the applicant to take the above actions, and the applicant appropriately took actions.

1.3 Risk management plan (draft)

The expert advisors supported PMDA's conclusion in Section "7.R.7 Post-marketing investigations" of the Review Report (1). PMDA has concluded that the risk management plan (draft) for baloxavir should include the safety and efficacy specifications presented in Table 27, and that the applicant should conduct additional pharmacovigilance activities, surveillance and studies on the efficacy, and risk minimization activities presented in Table 28, Table 29, and Table 30.

Table 27. Safety and efficacy specifications in the risk management plan (draft)

Safety specification		
Important identified risks	Important potential risks	Important missing information
• Shock, anaphylaxis • Colitis ischaemic • Haemorrhage	• Neuropsychiatric symptoms • Hepatic dysfunction	• Safety of prophylactic administration to individuals with particular high-risk factors[a)]
Efficacy specification		
• Change in drug sensitivity • Efficacy of prophylactic use against influenza B virus infection		

a), Immunosuppression, hematologic disease, hepatic disorder, and renal disorder

Table 28. Summary of additional pharmacovigilance activities, surveillance and studies on the efficacy, and risk minimization activities included under the risk management plan (draft)

Additional pharmacovigilance activities	Surveillance and studies on the efficacy	Additional risk minimization activities
• Early post-marketing phase vigilance • Specified use-results survey (survey of the safety of prophylactic administration to individuals with particular high-risk factors[a)])	• Specified use-results survey (sensitivity survey) • Specified use-results survey (survey of the efficacy of prophylactic use against influenza B virus infection)	• Organize and disseminate the following information for patients and their guardians *Information for guardians of patients prescribed Xofluza* • Organize and disseminate the following information for healthcare professionals *Information for healthcare professionals (cautions for patients with influenza infection)* • Disseminate data gathered during early post-marketing phase vigilance (prophylaxis)

a), Immunosuppression, hematologic disease, hepatic disorder, and renal disorder

Table 29. Outline of specified use-results survey (draft)
(survey of safety of prophylactic administration to individuals with particular high-risk factors)

Objective	To collect information on the safety and efficacy of prophylactic baloxavir against influenza virus infection in individuals with particular risk-factors (immunosuppression, hematologic disease, hepatic disorder, and renal disorder) in clinical use
Survey method	Central registry system
Population	Individuals with particular risk-factors (immunosuppression, hematologic disease, hepatic disorder, and renal disorder) specified in the important missing information of the risk management plan
Observation period	10 days after the administration of baloxavir
Planned sample size	120 individuals (30 each for each high-risk factor: immunosuppression, hematologic disease, hepatic disorder, and renal disorder)
Main survey items	Characteristics of index patient, characteristics of individuals treated with prophylactic baloxavir and their clinical course (body temperature, respiratory symptoms, post-dose visit [yes, no], onset of influenza at visit, virus test [yes, no], and virus type), and adverse events

Table 30. Outline of specified use-results survey (draft)
(survey of the efficacy of prophylactic use against influenza B virus infection)

Objective	To collect information on the safety and efficacy of prophylactic baloxavir against influenza A and B virus infection in clinical use
Survey method	Central registry system
Population	Household contacts of patients with influenza A or B virus infection
Observation period	10 days after the administration of baloxavir
Planned sample size	480 individuals (240 for influenza A virus, 240 for influenza B virus [120 individuals treated with baloxavir and 120 not treated with baloxavir])
Main survey items	Incidence of pyrexia and respiratory symptoms in individuals receiving prophylactic baloxavir, proportion of individuals testing positive for influenza virus, and incidences of adverse drug reactions, infections, and adverse events

The survey planned at the initial approval of Xofluza Tablets 20 mg is currently ongoing as a specified use-results survey (sensitivity survey) (Table 31).

Table 31. Outline of specified use-results survey (draft) (sensitivity survey)

Objective	To collect information on the effects of baloxavir on clinical isolates (reduced sensitivity and potential trend of resistance development)
Target number of clinical isolates	100 strains per year
Planned duration of survey	January 2019 to May 2025

2. Overall Evaluation

As a result of the above review, PMDA concludes that the product may be approved after modifying the proposed indication and the dosage and administration as shown below, with the following approval condition.

Although the present application has been filed for a marketing approval pertinent to a drug with a new indication, the re-examination period for the present application should be the remainder of the ongoing re-examination period for the initial approval (until February 22, 2026) because ≥4 years are left before the completion date.

Indication

Treatment and prophylaxis of influenza A or B virus infection

Dosage and Administration

Treatment

1. The usual dosage for adults and adolescents aged ≥12 years is two 20-mg tablets or four packets of granules (40 mg of baloxavir marboxil) administered orally as a single dose. In patients weighing ≥80 kg, four 20-mg tablets or eight packets of granules (80 mg of baloxavir marboxil) are administered orally as a single dose.
2. The usual dosage for children aged <12 years is the following, administered orally as a single dose.

Body weight	Dose
≥40 kg	Two 20-mg tablets or four packets of granules (40 mg of baloxavir marboxil)
≥20 kg and <40 kg	One 20-mg tablet or two packets of granules (20 mg of baloxavir marboxil)
[≥10 kg and <20 kg	One 10-mg tablet (10 mg of baloxavir marboxil)][44)]

Prophylaxis

1. The usual dosage for adults and adolescents aged ≥12 years is two 20-mg tablets or four packets of granules (40 mg of baloxavir marboxil) administered orally as a single dose. In patients weighing ≥80 kg, four 20-mg tablets or eight packets of granules (80 mg of baloxavir marboxil) are administered orally as a single dose.
2. The usual dosage for children aged <12 years is the following, administered orally as a single dose.

Body weight	Dose
≥40 kg	Two 20-mg tablets or four packets of granules (40 mg of baloxavir marboxil)
≥20 kg and <40 kg	One 20-mg tablet or two packets of granules (20 mg of baloxavir marboxil)
~~≥10 kg and <20 kg~~	~~One packet of granules~~

44) Although the partial change application of the indications and dosage and administration for the prophylaxis does not involve Xofluza Tablets 10 mg, the dosage and administration for the treatment with Xofluza Tablets 10 mg remain unchanged or valid, and thus it is included for convenience.

	~~(10 mg of baloxavir marboxil)~~
~~<10 kg~~	~~Granules at 50 mg/kg~~ ~~(1 mg/kg of baloxavir marboxil)~~

(Strikethrough denotes deletions.)

Approval Condition

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

Appendix

List of Abbreviations

ALT	Alanine aminotransferase
AST	Aspartate aminotransferase
AUC	Area under the concentration versus time curve
AUC_{inf}	Area under the concentration versus time curve extrapolated to infinite time
Baloxavir	Baloxavir marboxil
BMI	Body mass index
CDC	Centers for Disease Control and Prevention
CL/F	Apparent total body clearance
CL_{cr}	Creatinine clearance
C_{max}	Maximum plasma concentration
$C_{X\,h}$	Plasma concentration at X hours post dose
C_{τ}	Plasma concentration at the end of dosing interval after the first dose
EC_{50}	50% effective concentration
eGFR	Estimated glomerular filtration rate
ITTI	Intention-to-treat infected
Ka	Absorption rate constant
mITT	Modified intention-to-treat
NA	Neuraminidase
PA	Polymerase acidic protein
PCR	Polymerase Chain Reaction
PK	Pharmacokinetics
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	Population pharmacokinetics
Q/F	Apparent inter-compartmental clearance
RT-PCR	Reverse Transcription Polymerase Chain Reaction
S-033447	Active form of baloxavir marboxil
$TCID_{50}$	50% tissue culture infectious dose
V_c/F	Apparent volume of central compartment
V_p/F	Apparent volume of peripheral compartment
Xofluza	S-033188 tablets 20 mg, packet of S-033188 granules 2%
γ-GTP	γ-glutamyl transferase