Report on the Deliberation Results

March 4, 2014
Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau
Ministry of Health, Labour and Welfare

[Brand name]	Avigan Tablet 200 mg
[Non-proprietary name]	Favipiravir (JAN*)
[Applicant]	Toyama Chemical Co., Ltd.
[Date of application]	March 30, 2011

[Results of deliberation]
In the meeting held on February 3, 2014, the Second Committee on New Drugs concluded that the product may be approved and that this result should be reported to the Pharmaceutical Affairs Department of the Pharmaceutical Affairs and Food Sanitation Council.

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

Some changes to the conditions for approval were decided in the course of the deliberation. The revised conditions for approval are as follows:

[Conditions for approval]
1. The applicant is required to conduct a pharmacokinetic study in accordance with the approved dosage and administration in Japan, and submit the study data and analysis results immediately after the completion of the study and within 1 year after the date of the marketing approval.

2. The applicant is required to conduct a clinical study of the product in patients with seasonal influenza virus infection to verify the efficacy and confirm the safety, and to submit the study data and analysis results immediately after the completion of the study.

3. The applicant must not manufacture the product without the request of the Minister of Health, Labour and Welfare, unless the study data and analysis results specified in the above 1 and 2 are submitted and necessary actions are taken accordingly.

4. The applicant is required to establish a strict distribution management system, and take thorough safety measures in order to ensure that the product is not used in patients with seasonal influenza virus infection, even when the product is to be marketed.

5. The applicant is required to take strict and proper measures in order to ensure that the product is not administered to patients unless each individual patient, who is judged to be eligible for its use, or his/her family member is informed of the efficacy and risk of the product in writing and their written informed consent is obtained prior to the start of treatment.

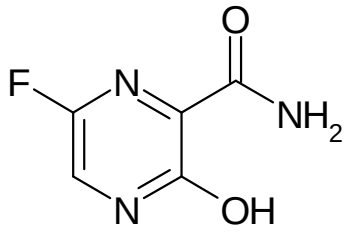
**Japanese Accepted Name (modified INN)*

Review Report

January 23, 2014
Pharmaceuticals and Medical Devices Agency

The results of a regulatory review conducted by the Pharmaceuticals and Medical Devices Agency on the following pharmaceutical product submitted for registration are as follows.

[Brand name]	Avigan Tablet 200 mg
[Non-proprietary name]	Favipiravir
[Applicant]	Toyama Chemical Co., Ltd.
[Date of application]	March 30, 2011
[Dosage form/Strength]	Film-coated tablets: Each tablet contains 200 mg of favipiravir.
[Application classification]	Prescription drug, (1) Drug with a new active ingredient
[Chemical structure]	



Molecular formula:	$C_5H_4FN_3O_2$
Molecular weight:	157.10
Chemical name:	6-Fluoro-3-hydroxypyrazine-2-carboxamide

[Items warranting special mention]
Priority Review (Notification No. 0630-1 from the Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, MHLW, dated June 30, 2011)

[Reviewing office] Office of New Drug IV

Review Results

January 23, 2014

[Brand name]	Avigan Tablet 200 mg
[Non-proprietary name]	Favipiravir
[Applicant]	Toyama Chemical Co., Ltd.
[Date of application]	March 30, 2011

[Results of review]
Based on the submitted data, the Pharmaceuticals and Medical Devices Agency (PMDA) considers that the efficacy of Avigan (favipiravir) in patients with seasonal influenza A or B virus infection has not been confirmed, and only the clinical efficacy has been suggested in the US. Favipiravir, however, has a mechanism of action different from those of the approved influenza antiviral drugs, and is expected to have an antiviral activity against avian influenza A (H5N1) and A (H7N9) viruses, which has only been demonstrated by non-clinical data. In light of the recent outbreaks of influenza infection, therefore, it is of significance to make favipiravir available for patients with novel or re-emerging pandemic influenza virus infection in whom other influenza antiviral drugs are ineffective or not sufficiently effective, and in whom the efficacy of favipiravir can be expected.

PMDA has concluded that it is meaningful to approve Avigan (favipiravir) for the indication of treatment of patients with novel or re-emerging pandemic influenza virus infection on the premise that post-marketing requirements are imposed on the approval as the risk control measures, which include the following conditions: (1) a clinical study should be conducted immediately after the approval in consideration that the efficacy of favipiravir against seasonal influenza virus infection has not been confirmed, that favipiravir has the risk of teratogenicity, etc., and that the proposed dosage and administration are set mainly based on the foreign clinical study data while the dosage regimen has not been studied in Japan; (2) favipiravir must not be administered to patients unless each individual patient, who is judged to be eligible for its use, or his/her family is informed of the efficacy and risk of favipiravir in writing and their written informed consent is obtained prior to treatment with favipiravir; and (3) a strict distribution management system and thorough safety measures should be in place to ensure that favipiravir is not used in patients with seasonal influenza virus infection.

As a result of its regulatory review, PMDA has concluded that, at the current stage, it is meaningful to approve the product for the indication and the dosage and administration as shown below, with the following conditions.

[Indication]
Treatment of novel or re-emerging pandemic influenza virus infections (limited to cases in which other influenza antiviral drugs are ineffective or not sufficiently effective).

[Dosage and administration]
The usual adult dosage is 1600 mg of favipiravir administered orally twice daily on Day 1, followed by 600 mg orally twice daily from Day 2 to Day 5. The total treatment duration should be 5 days.

[Conditions for approval]
1. The applicant is required to conduct a pharmacokinetic study in accordance with the approved dosage and administration in Japan, and submit the study data and analysis results immediately after the completion of the study.

2. The applicant is required to conduct a clinical study of the product in patients with seasonal influenza virus infection to verify the efficacy and confirm the safety, and to submit the study data and analysis results immediately after the completion of the study.

3. The applicant is required to establish a strict distribution management system, and take thorough safety measures in order to ensure that the product is not used in patients with seasonal influenza virus infection.

4. The applicant is required to take strict and proper measures in order to ensure that the product is not adminitered to patients unless each individual patient, who is judged to be eligible for its use, or his/her family member is informed of the efficacy and risk of the product in writing and their written informed consent is obtained prior to the start of treatment.

Review Report (1)

October 6, 2011

I. Product Submitted for Registration

[Brand name]	Avigan Tablet 200 mg
[Non-proprietary name]	Favipiravir
[Applicant]	Toyama Chemical Co., Ltd.
[Date of application]	March 30, 2011
[Dosage form/Strength]	Film-coated tablets: Each tablet contains 200 mg of favipiravir.
[Proposed indication]	Influenza A or B virus infection
[Proposed dosage and administration]	The usual adult dosage is 1200 mg of favipiravir administered orally as the initial dose and 400 mg as the second dose on Day 1, followed by 400 mg orally twice daily from Day 2 to Day 5.

II. Summary of the Submitted Data and Outline of the Review by the Pharmaceuticals and Medical Devices Agency

A summary of the submitted data and the outline of a review by the Pharmaceuticals and Medical Devices Agency (PMDA) are as shown below.

1. Origin or history of discovery and usage conditions in foreign countries etc.

Favipiravir is a new antiviral drug against influenza discovered by Toyama Chemical Co., Ltd. Favipiravir is metabolized into favipiravir ribosyl triphosphate (favipiravir RTP) by an intracellular enzyme, and favipiravir RTP selectively inhibits RNA polymerase (RNA-dependent RNA polymerase) of the influenza virus, preventing replication of the influenza virus.

Influenza virus is classified into the 3 types A, B, and C, and of these, 2 strains of type A (H1N1, H3N2) and type B have epidemically spread in recent years. In addition, animal influenza viruses, especially, avian and swine viruses may become infectious to humans through gene mutation or recombination, leading to a rapid spread of infection from human to human. Such a mutated virus is called a pandemic influenza virus.

Outbreaks of pandemic influenza virus infection occur once every decade to several decades. The circumstances surrounding influenza are changing every moment; in 2009, the outbreak of pandemic H1N1 influenza virus infection was confirmed in the American Continent, and human infection cases of highly pathogenic avian influenza A (H5N1) virus have been reported worldwide since 2003. Since influenza antiviral drugs are the only measures against the pandemics at the early stage, such drugs are increasingly needed not only medically but also socially. It is thus important to add new therapeutic options for pandemic influenza virus infection.

Influenza antiviral drugs currently available in Japan include amantadine hydrochloride (M2 protein inhibitor), oseltamivir phosphate, zanamivir hydrate, peramivir hydrate, and laninamivir octanoate hydrate (neuraminidase inhibitor).

Favipiravir 200 mg tablet is a drug with a mechanism of action different from that of the existing influenza antiviral drugs and effective against all types and sub-types of human influenza A, B, and C viruses *in vitro*, showing a wide range of anti-viral activity against various influenza virus

strains including avian and swine viruses. Favipiravir also has shown anti-viral activity even against amantadine-, oseltamivir- and zanamivir-resistant influenza viruses *in vitro*.

Based on the above, the applicant explained that favipiravir may possibly serve as a new antiviral drug against influenza, and thus its development was carried out to evaluate the efficacy and safety of favipiravir in patients with seasonal influenza virus infection, of which epidemics occur annually.

As of September 2011, favipiravir has not been approved overseas.

2. Data relating to quality

2.A Summary of the submitted data

2.A.(1) Drug substance

2.A.(1).1) Characterization

(a) General properties

The determined physicochemical properties of the drug substance include description, X-ray powder diffraction, solubility, hygroscopicity, melting point and thermal analysis, dissociation constant, partition coefficient, and crystalline polymorphism.

The drug substance is a white to light yellow powder. It is sparingly soluble in acetonitrile and in methanol, and slightly soluble in water and in ethanol (99.5). It is slightly soluble at pH 2.0 to 5.5 and sparingly soluble at pH 5.5 to 6.1.

The drug substance is not hygroscopic at 25°C/51% to 93%RH. The melting point is 187°C to 193°C, and the dissociation constant (pKa) is 5.1 due to the hydroxyl group of favipiravir. Measurement results on the partition ratio of favipiravir in water/octanol at 25°C indicate that favipiravir tends to be distributed in the 1-octanol phase at pH 2 to 4 and in the water phase at pH 5 to 13.

(b) Structure determination

The structure of the drug substance is supported by elemental analysis, ultraviolet-visible spectrophotometry, infrared spectrophotometry, nuclear magnetic resonance spectroscopy (^{1}H-NMR, ^{13}C-NMR), mass spectrometry, and single crystal crystallography.

(c) Crystalline polymorphism

[redacted].

[redacted]. Any batch manufactured by the current manufacturing process is in Form A. The stability study does not show any change in crystal form over time; and a change from Form A to Form B is unlikely.

2.A.(1).2) Manufacturing process

The drug substance, favipiravir, is manufactured in the following 2 steps using Substance A[1] as the starting material.

[redacted][2][redacted]. Since Process [redacted] can also control the production volume of Substance C[3] ([redacted]–[redacted] kg) on the planned production scale, Process [redacted] is planned to be adopted in the future. A certain amount of the drug substance manufactured by Process [redacted] is, however, already available and is planned to be used for manufacturing of the commercial formulation. The application form, therefore, includes both manufacturing processes. An application for manufacturing change will be submitted to delete Process [redacted] from the section for manufacturing process after the drug substance manufactured by Process [redacted] is run out.

Step 1: Synthesis of Substance D[4]

[redacted][5][redacted].

[redacted][6][redacted].

[redacted].

[redacted].

Step 2: Synthesis of favipiravir

[redacted].

(a) Controls of critical process steps and intermediates

In the manufacturing process of favipiravir, steps that significantly affect the quality of the drug substance are Step 1 and Step 2, and the critical intermediate is Substance D.

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1 Substance A: [redacted]
2. Substance B: [redacted]
3 Substance C: [redacted]
4 Substance D: [redacted]
5 Substance E: [redacted]
6 Substance F: [redacted]

(b) Manufacturing process development

Step [redacted] of the manufacturing process of favipiravir at the development stage is classified according to the synthetic route into [redacted] processes: Processes [redacted] and [redacted], and Process [redacted] is further divided into Processes [redacted] and [redacted] due to a difference in some of reaction reagents used.

[redacted]. In Process [redacted] that is not a synthetic route via Substance G[7], Substance D is derived from Substance A to manufacture favipiravir. The change from Process [redacted] to Process [redacted] is expected to improve the quality of the drug substance, because Substance I,[8] the most abundant impurity in the drug substance manufactured by Process [redacted], is no longer present in the drug substance after the change while the impurity profile except for Substance I will remain unchanged.

[redacted].

2.A.(1).3) Control of drug substance

The specifications of the drug substance were established in accordance with "Specifications: Test Procedures and Acceptance Criteria for New Drug Substances and New Drug Products: Chemical Substances" (PMSB/ELD Notification No. 568 dated May 1, 2001, ICH Q6A guideline). The specifications for the related substances were established in accordance with "Impurities in New Drug Substances" (PMSB/ELD Notification No. 1216001 dated December 16, 2002, ICH Q3A guideline), and those for the residual solvents were established in accordance with "Impurities: Guideline for Residual Solvents" (PMSB/ELD Notification No. 307 dated March 30, 1998).

[redacted].

(a) Reference standard

The proposed specifications for the reference material include description, identification (ultraviolet-visible spectrophotometry, infrared spectrophotometry, nuclear magnetic resonance spectroscopy), melting point, purity (related substances), water content, and assay.

2.A.(1).4) Container closure system

The container closure system for the drug substance is as follows: the drug substance is placed in a polyethylene bag, which is tied up with a plastic band, and then the closed bag is placed in another polyethylene bag, which is tied up with a plastic band. The closed double-layered bag is placed in a fiber drum, which is sealed tightly.

2.A.(1).5) Stability of drug substance

The long-term and accelerated studies and stress studies (heat, humidity, light) of the drug substance were conducted each using 3 batches manufactured on a commercial scale.

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[7] Substance G: [redacted]

[8] Substance I: [redacted]

Long-term and accelerated studies

Study	Temperature	Humidity	Storage form	Measurement time points
Long-term	30°C	65%RH	Polyethylene bag[a] double-layered/Fiber drum[b]	0, 3, 6, 9, 12, 18, 24, 36 (at submission), 48, and 60 months
Accelerated	40°C	75%RH	Polyethylene bag[a] double-layered/Fiber drum[b]	0, 1, 3, and 6 months

a) The sample was placed in a low-density polyethylene bag, which was tied up with a plastic band. This bag is placed in another low-density polyethylene bag, which was tied up with a plastic band.
b) The low-density polyethylene bag (double-layered) containing the sample was placed in a fiber drum, which was sealed tightly.

Stress studies

Study	Temperature	Humidity	Light	Storage form	Measurement time points
Heat	60°C	–	–	Glass container (sealed)[a]	0, 1, and 3 months
Humidity	25°C	85%RH	–	Glass Petri dish (open)[b]	0, 1, and 3 months
Light	25°C	60%RH	D_{65} lamp (2000 lx)	Colorless glass Petri dish[c] (covered with polyvinylidene chloride film)	0, 1.2 million (≥200 W·h/m^2), 2.4 million lx·hr
				(Colorless glass Petri dish[c] [covered with a polyvinylidene chloride film]) covered with aluminum foil (control)	

a) The specimen was placed in a glass sample bottle, which was lightly closed.
b) The specimen was placed in a colorless glass Petri dish, which was covered with a piece of gauze.
c) The specimen was thoroughly spread to the thickness of ≤3 mm on a colorless glass Petri dish

(a) Long-term and accelerated studies

During the storage period of 36 months in the long-term study, the content was changed from [redacted]% to [redacted]%, and the total amount of the related substances was changed from [redacted]% to [redacted]%. There were no changes over time in other test parameters after 36 months of storage compared to the baseline.

In the accelerated study, there were no changes over time in any test parameters after 6 months of storage compared to the baseline.

(b) Stress studies

In the stress studies (heat, humidity), there were no changes in any test parameters after the specified storage period compared to the baseline.

In the stress study (light), the content decreased by [redacted]% following illumination at 1.2 million lx·hr, and the amount of the related substances increased by [redacted]%, but the changed values fell within their specification ranges. In the sample of the drug substance protected from light with aluminum foil, the amount of the related substances did not increase.

When the drug substance was stored under the accelerated condition for 6 months, the quality remained unchanged over time, and furthermore when it was stored under the long-term storage condition for 36 months, the quality remained unchanged over time as well. Based on these results, a re-test period of 4 years has been proposed for the drug substance when stored at room temperature in accordance with the "Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003).

The re-test period is planned to be extended depending on the results of the currently ongoing long-term studies.

2.A.(2) Drug product

2.A.(2).1) Description and composition of the drug product

The drug product is a round film-coated tablet containing 200 mg of favipiravir, and the diameter is about 8.7 mm. The composition of the drug product is as shown below.

Composition of the drug product (in 1 tablet)

Function	Specification	Components	Amount (mg)
Active ingredient	[redacted]	Favipiravir	200
[redacted]	[redacted]	Light anhydrous silicic acid	[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Low substituted hydroxypropylcellulose	[redacted]
[redacted]	[redacted]	Crospovidone	[redacted]
[redacted]	[redacted]	Sodium stearyl fumarate	[redacted]
Sub-total			[redacted]
[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	Titanium oxide	[redacted]
[redacted]	[redacted]	Talc	[redacted]
[redacted]	[redacted]	Yellow ferric oxide	[redacted]
Sub-total			[redacted]
Total			[redacted]
Container closure system			PTP/aluminum bag[a)]

a) [redacted]

(a) Pharmaceutical development

In Japanese clinical studies, 4 types of the formulations were used, including T-705a capsule [30] (one capsule containing 30 mg of favipiravir), T-705a capsule [100] (one capsule containing 100 mg of favipiravir), T-705a tablet [100] (one tablet containing 100 mg of favipiravir), and the drug product (one tablet containing 200 mg of favipiravir). In foreign clinical studies, 3 types of the formulations were used, including T-705a capsule [30], T-705a capsule [100], and the drug product (200 mg tablet).

[redacted]. The use of different formulations in clinical studies was considered to have no effects on the bioavailability.

In addition, the dissolution test was performed to compare dissolution profiles between 2 tablets of T-705a [100] and 1 tablet of the drug product (200 mg tablet) in accordance with "Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms" (PFSB/ELD Notification No. 1124004, Annex 2 dated November 24, 2006). [redacted]. The dissolution profile of T-705a tablet [100] was determined to be similar to that of the drug product (200 mg tablet). The bioequivalence study data demonstrated that they were biologically equivalent.

The specifications for the drug product (200 mg tablet) have only been proposed in this application.

2.A.(2).2 Manufacturing process

The drug product is produced by the manufacturing process consisting of the following 7 steps.

[redacted].

(a) Controls of critical process steps and intermediates

[redacted].

2.A.(2).3) Control of drug product

The proposed specifications for the drug product consist of description (color, shape), identification (ultraviolet-visible spectrophotometry), uniformity of dosage units, dissolution, and assay.

2.A.(2).4) Container closure system

The container and closure system for the drug product employs a push-through pack (PTP) as the primary packaging and an alminium bag as the secondary packaging. [redacted].

2.A.(2).5) Stability of drug product

Pivotal stability studies submitted were conducted using 3 batches manufactured on a pilot scale and 3 batches manufactured on a commercial scale. The main storage conditions and storage period in the stability studies are as shown below.

Long-term and accelerated studies

Study	Temperature	Humidity	Storage form	Storage period
Long-term	30°C	65%RH	PTP/aluminum bag (10 tablets × 10 sheets)	0, 3, 6, 9, 12, 18, 24 (at submission), 36, 48, 60, 72, 84, 96, 108, and 120 months
			PTP/aluminum bag ([redacted])	0, 3, 6 (at submission), 9, 12[a)], 18, 24, 36, 48, 60, 72, 84, 96, 108, and 120 months
Accelerated	40°C	75%RH	PTP/aluminum bag (10 tablets × 10 sheets, [redacted])	0, 1, 3, and 6 months

a) Study data at Month 12 were additionally submitted during the review.

Stress studies

Study	Temperature	Humidity	Light	Storage form	Storage period
Heat	60°C	–	–	Glass Petri dish open	0, 1, 3 months
Humidity	25°C	85%RH	–	PTP/aluminum bag, PTP, glass Petri dish open	0, 3, 6 months
Humidity	40°C	75%RH	–	PTP, glass Petri dish open	0, 1, 2, 3, 6 months
Light	25°C	60%RH	D_{65} lamp (2000 lx)	PTP/aluminum bag,[b)] Colorless glass Petri dish,[a)] colorless glass Petri dish + aluminum foil cover[a)]	0, 1.2 million lx·hr (≥200 W·h/m^2), 2.4 million lx·hr

a) Samples were evenly spread in a single layer.
b) [redacted]

(a) Long-term and accelerated studies

In the study with packs of 10 tablets × 10 sheets under the long-term storage condition, there were no changes over time in any test parameter after 24 months of storage compared to the baseline.

In the accelerated study, there were no changes over time in any test parameter after 6 months of storage compared to the baseline.

[redacted].

In the accelerated study, there were no changes over time in any test parameter after 6 months of storage compared to the baseline.

In any packaging form, the long-term testing is planned to be continued up to Month 120.

(b) Stress studies

In the stress study (heat), there were no changes in any test parameter compared to the baseline.

In the stress study (humidity) with the sample in the storage form of a PTP/aluminum bag, there were no changes in any test parameter compared to the baseline. In the packaging form of PTP only, when compared to the baseline, the water content increased by about [redacted]%, and the hardness decreased by about [redacted] N, but values of the other test parameters remained unchanged. In the packaging form of the open Petri dish, the water content increased by about [redacted]%, and the hardness decreased by about [redacted] N, but values of the other test parameters remained unchanged. These results suggested that humidity does not affect the quality.

[redacted]. The water content increased by about [redacted]%, and the hardness decreased by about [redacted] N. The dissolution rate, however, did not decrease, and no changes were found in the other test parameters. These changes were thus considered not to affect the quality.

[redacted]. Based on the data of long-term and accelerated studies with 10 tablets × 10 sheets, a shelf life of 3 years has been proposed for the drug product when stored at room temperature in accordance with the "Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003).

The shelf life is planned to be extended using data obtained from the ongoing long-term studies.

2.B Outline of the review by PMDA

2.B.(1) Appropriateness of the starting material

PMDA considered that impurities contained in Substance A, the starting material of the drug substance, should be more strictly controlled because (1) many of the impurities contained in the drug substance are potentially process-related impurities derived from the synthesis of Substance A; (2) in some lots, Substance A at the acceptance test contained impurities at a level above the acceptance criteria; and (3) the GMP inspection revealed that rework process had taken place to remove the impurities after the acceptance test. PMDA therefore asked the applicant to explain whether or not the appropriateness of the starting material and reworking process should be specified in the application as one of the controls.

The applicant responded as follows:

Substance A was selected as the starting material of the drug substance since it is well characterized in terms of its chemical properties and structure, and is chemically stable. The previous investigation has shown that most of the impurities contained in the drug substance are derived from the process to obtain the Substance D, and the process-related impurity derived from the synthesis of Substance A is only Substance J. Furthermore, impurities contained in Substance A at >[redacted]% and those potentially contained in Substance A have all been identified, and appropriate acceptance criteria and specifications have been set based on the results from impurity-spiking studies and behavior research. The impurities of the drug substance can be controlled without any safety concern as long as Substance A meeting the pre-defined acceptance criteria and process parameters is used as the starting material to manufacture the drug substance in the controlled manufacturing process. Therefore, it is appropriate to select Substance A as the starting material.

The rework process has been applied to Substance A that does not meet the pre-defined acceptance criteria and process parameters to manufacture the drug substance. This rework process was applied to [redacted] lots of Substance A, and the results demonstrate that the impurities are appropriately removed. Since rework may possibly take place again in the future, the rework process is also to be specified as one of the controls in the application.

Confirming the appropriateness of the starting material and considering that the impurities contained in the starting material are controlled appropriately, PMDA accepted the applicant's response.

3. Non-clinical data

3.(i) Summary of pharmacology studies

3.(i).A Summary of the submitted data

The results from 21 primary pharmacodynamic studies, 3 secondary pharmacodynamic studies, and 6 safety pharmacology studies were submitted in the application as the evaluation data. The results from 14 primary pharmacodynamic studies and 1 secondary pharmacodynamic study were submitted as the reference data.

3.(i).A.(1) Primary pharmacodynamics

3.(i).A.(1).1) *In vitro* influenza antiviral activity

(a) Antiviral activity against influenza A, B, and C virus laboratory strains (4.2.1.1.1, 4.2.1.1.2)

The antiviral activity of favipiravir against influenza A, B, and C virus laboratory strains was measured by the plaque reduction assay[9] (Woods, et al.). Madin-Darby Canine Kidney (MDCK) cells were inoculated with the virus solution, and 1 hour later the inoculation medium was replaced with a measurement medium containing the test drug followed by incubation for several days.[10] After staining with amido black, etc., the plaque forming inhibitory effect of each test drug (EC_{50}, concentration of the test drug required to reduce the number of plaques to 50%, where the number of plaques formed in the absence of the test drug is taken as 100%) was measured using the number of the formed plaques as an indicator. Oseltamivir carboxylate[11] and amantadine were used for the comparators. The results are as shown in the table below.

[9] *Antimicrob Agents Chemother*. 1993;37:1473-1479.

[10] Influenza A and B virus strains were inoculated at 5% CO_2, 35°C for 2 or 3 days; and type C virus was inoculated at 5% CO_2, 34°C for 6 days.

[11] Active form of oseltamivir phosphate

Antiviral activity against influenza A, B, and C virus laboratory strains

Type	Strain	EC_{50} value (μg/mL)		
		Favipiravir	Oseltamivir carboxylate	Amantadine
A (H1N1)	A/PR/8/34	0.11	0.0060	36
	A/FM/1/47	0.14	0.0032	0.34
	A/NWS/33	0.10	0.0013	48
	A/Yamagata/120/86	0.050	0.029	2.3
	A/Suita/1/89	0.022	0.0018	29
A (H2N2)	A/Kaizuka/2/65	0.014	2.0	0.25
	A/Okuda/57	0.016	0.00029	0.28
	A/Japan/305/57	0.24	0.00043	0.068
	A/Takatsuki/4/65	0.029	0.00014	0.16
A (H3N2)	A/Port Chalmers/1/73	0.55	0.00037	0.32
	A/Aichi/2/68	0.12	0.0065	0.20
	A/Ibaraki/1/90	0.34	0.00033	0.63
	A/Kitakyushu/159/93	0.35	0.00034	>100
B	B/Nagasaki/1/87	0.042	0.0050	>100
	B/Guandong/5/94	0.053	0.031	>100
	B/Mie/1/93	0.039	0.015	35
C	C/Taylor/1233/47	0.13	>100	19

(b) Antiviral activity against various influenza virus clinical isolates (4.2.1.1.3; Reference data, 4.2.1.1.4)

The antiviral activity of favipiravir against influenza virus clinical isolates obtained between 1992 and 2009 was measured by the plaque reduction assay. The results are as shown in the table below. "R" stands for "resistant" and indicates that this clinical isolate was found to have mutations in the gene involved in the drug susceptibility, and "S" stands for "sensitive" and indicates that it was found to have no such mutations.[12]

Antiviral activity against influenza A virus strain

Type	Strain	EC_{50} value (μg/mL)		
		Favipiravir	Oseltamivir carboxylate	Amantadine
A (H1N1)	A/Osaka/681/98	0.096	>100	>30
	A/Osaka/103/2000	0.078	0.014	>30
	A/Osaka/124/2000	0.080	0.0077	>30
	A/Osaka/12/92	0.067	0.0092	>30
A (H3N2)	A/Osaka/981/99	0.21	0.017	0.16
	A/Osaka/1480/96	0.27	0.0042	0.63
	A/Osaka/179/2000	0.31	1.8	0.22
	A/Osaka/169/2000	0.28	1.3	0.22

[12] *J infect Dis.* 2003;188:57-61, *Antimicrob Agents Chemother.* 2008;52:3284-3292.

Antiviral activity of favipiravir against influenza A (H1N1), A (H3N2), and B virus strains

Type	Strain	Sensitivity			M2 Mutation	NA Mutation[a)]	EC_{50} value (μg/mL)
		Amantadine and rimantadine	Oseltamivir	Zanamivir			
A (H1N1)	A/Georgia/17/2006	S	S	S	-[b)]	-	0.23
	A/Georgia/20/2006	S	R	S	-	H274Y	0.40
	A/California/27/2007	S	S	S	-	-	0.57
	A/New Jersey/15/2007	S	R	S	-	H274Y	0.77
	A/Ecuador/5179/2008	S	S	S	-	-	0.39
	A/Santiago/5248/2008	S	R	R	-	D198E	0.74
	A/Brazil/1067/2008	S	S	S	-	-	0.29
	A/Brazil/1633/2008	S	R	R	-	Q136K	0.13
	A/Luhansk/18/2008	R	R	S	G34E	H274Y	0.46
	A/New York/34/2008	S	S	S	L26I	-	0.03
	A/Washington/10/2008	R	S	S	S31N	-	0.51
	A/Florida/21/2008	S	R	S	-	H274Y	0.25
	A/Wisconsin/16/2008	S	R	S	-	H274Y	0.45
	A/North Carolina/02/2009	R	S	S	S31N	-	0.79
	A/Idaho/01/2009	S	R	S	-	H274Y	0.46
A (H3N2)	A/Wuhan/395/1995-like	S	S	S	-	-	0.94
	A/Wuhan/395/1995-like	S	R	S	-	E119V	0.85
	A/Bethesda/956/2006	R	R	R	S31N	R292K	0.19
	A/Washington/01/2007	R	S	S	S31N	-	0.70
	A/Texas/12/2007 (clone)	R	R	S	S31N	E119I	0.62
	A/Texas/12/2007 (clone)	R	R	S	S31N	E119V	0.82
	A/Florida/01/2009	R	S	S	S31N	-	0.07
	A/New Hampshire/01/2009	R	S	S	S31N	-	0.64
	A/Massachusetts/03/2009	R	S	S	S31N	-	0.66
B	B/Memphis/20/1996	R	S	S	N/A[c)]	-	0.19
	B/Memphis/20/1996	R	R	R	N/A	R152K	0.09
	B/Rochester/01/2001	R	S	S	N/A	-	0.22
	B/Rochester/01/2001	R	R	S	N/A	D198N	0.27
	B/New York/22/2008	R	S	S	N/A	-	0.83
	B/Illinois/03/2008	R	R	R	N/A	E119A	0.47
	B/Illinois/47/2005	R	S	S	N/A	-	0.63
	B/Michigan/20/2005	R	R	S	N/A	H274Y	0.79

a) Neuraminidase mutation, b) -: Not detected, c) N/A: Not applicable

In addition, investigation was made on the antiviral activity of favipiravir against the pandemic influenza A (H1N1) virus which emerged in the American Continent in April 2009 (hereinafter referred to as "pandemic influenza A [H1N1] virus" and expressed as "A [H1N1] 2009" in the table) as well as against swine and avian influenza virus clinical isolates (and isolates from birds). The results are as shown in the table below.

Antiviral activity of favipiravir against influenza A virus strains including pandemic influenza A (H1N1) and A (H5N1) virus strains

Type	Strain	Sensitivity			M2 Mutation	NA Mutation[a)]	EC_{50} value (μg/mL)
		Amantadine and rimantadine	Oseltamivir	Zanamivir			
A (H1N1) (2009)	A/Mexico/4604/2009	R	S	S	V28I, S31N	-[b)]	0.19
	A/California/04/2009	R	S	S	V28I, S31N	-	0.31
	A/California/05/2009	R	S	S	V28I, S31N	-	0.13
	A/California/07/2009	R	S	S	V28I, S31N	-	0.22
	A/New York/18/2009	R	S	S	V28I, S31N	-	0.14
	A/Illinois/10/2009	R	R	S	V28I, S31N	H274Y	3.53
	A/Washington/29/2009	R	R	S	V28I, S31N	H274Y	1.04
A (H2N2)	A/Ann Arbor/6/1960	S	S	S	-	-	0.06
A (H1N1)	A/South Dakota/03/2008 [c)]	S	S	S	-	-	0.13
	A/Texas/14/2008 [c)]	S	S	S	V27T, V28D	-	0.71
A (H1N2)	A/Michigan/09/2007 [c)]	S	S	S	V27I, V28D	-	0.35
A (H4N2)	A/turkey/Minnesota/833/1980	S	S	S	-	-	0.15
	A/turkey/Minnesota/833/1980	S	S	R	-	E119G	0.14
A (H5N1)	A/duck/Vietnam/NCVD93/2007 (clade 2.3.4)	S	S	S	-	-	0.25
	A/duck/Vietnam/NCVD94/2007 (clade 2.3.4)	S	R	R	-	I117V	0.53
	A/chicken/Vietnam/NCVD 103/2007 (clade 2.3.4)	S	S	S	-	I222T	0.20
	A/Vietnam/1203/2004 (clade 1)[d)]	R	S	S	L26I, S31N	-	0.82
	A/Vietnam/HN30408/2005 H274Y (clade 1)[d)]	R	R	S	L26I, S31N	H274Y	0.65
	A/Vietnam/HN30408/2005 N294S (clade 1)[d)]	R	R	R	L26I, S31N	N294S	0.21
A (H7N2)	A/turkey/VA/4529/2002	S	S	S	-	-	0.24
	A/New York/107/2003 [d)]	R	S	S	V28A, S31N	-	1.60

a) Neuraminidase mutation, b) -: Not detected, c) Swine influenza virus clinical isolates, d) Avian influenza virus clinical isolates

Furthermore, sensitivity of favipiravir against existing influenza antiviral drug-(adamantane [amantadine, rimantadine], oseltamivir, zanamivir) resistant strains is as shown in the table below.

Antiviral activity of favipiravir against adamantane (amantadine, rimantadine), oseltamivir, zanamivir-resistant strains

Resistance			Number of strains	EC_{50}value (μg/mL)
Amantadine and rimantadine	Oseltamivir	Zanamivir		
S	S	S	14	0.03-0.94
R	S	S	17	0.07-1.60
S	R	S	6	0.25-0.85
S	S	R	1	0.14
R	R	S	8	0.27-3.53
S	R	R	3	0.13-0.74
R	R	R	4	0.09-0.47

(c) Antiviral activity against clinical isolates in phase III clinical studies (Studies 312 and JP313) (4.2.1.1.35)

The antiviral activity of favipiravir against influenza virus clinical isolates in phase III clinical studies was measured by the plaque reduction assay[13] (Sleeman, et al.). MDCK cells were inoculated with the virus solution, and 1 hour later the inoculation medium was replaced with a measurement medium containing the test drug followed by incubation for several days.[14] After staining with amido black, the plaque-forming inhibitory effect of each test drug was measured using the number of the formed plaques as an indicator. The results are as shown in the table below.

Antiviral activity against clinical isolates obtained from patients before treatment with favipiravir

Type	Number of strains	EC_{50} value(μg/mL)	
		Range	Mean
A (H1N1)[a)]	254	0.045-3.8	0.98
A (H3N2)	40	0.058-0.86	0.23
B	38	0.086-2.3	0.77

a) Type A (H1N1) was pandemic influenza A (H1N1) virus.

Of 552 clinical isolates obtained from patients before and after treatment with favipiravir, 2 isolates (both Type A [H1N1]) showed EC_{50} values of ≥3 μg/mL. In the patient who had given the clinical isolate with an EC_{50} value of 3.8 μg/mL before the treatment, no virus was detected on and after Day 2, and in the other patient who had given the clinical isolate with an EC_{50} value of 4.0 μg/mL on Day 2 (EC_{50} value before the treatment, 2.2 μg/mL), no virus was detected on and after Day 3 or 4. One of the 2 clinical isolates was obtained before the treatment and the other at 2 days after the treatment. In the pre-treatment clinical isolate with an EC_{50} of 3.8 μg/mL, no viruses were detected from Day 2 and thereafter. In the post-treatment clinical isolates with an EC_{50} of 4.0 μg/mL (its pre-treatment EC value was 2.2 μg/mL), no viruses were detected on Day 3 or 4 and thereafter.

The EC_{50} ratio of favipiravir against influenza virus isolates obtained from 1 patient was calculated. The results are as shown in the table below.

Ratio of antiviral activity against isolates from 1 patient before and after the treatment with favipiravir

Day of last virus detection	Number of strains	EC_{50} ratio[a)] range
		Range
Day 2	84	0.25-4.5
Day 3 or 4	121	0.16-4.7
Day of discontinuation	3	0.30-0.61

a) EC_{50} ratio: EC_{50} against post-treatment isolate/EC_{50} against pre-treatment isolates

The EC_{50} value increased ≥4 times after the treatment in 3 strains. The changes of EC_{50} value (EC_{50} ratio) were 0.097 → 0.43 μg/mL (4.5), 0.20 → 0.94 μg/mL (4.7), and 0.12 → 0.50 μg/mL (4.0).

[13] *Antimicrob Agents Chemother*. 2010;54:2517-2524.

[14] The incubation was carried out at 5% CO_2, 35°C for the same period as that of the virus titer assay.

3.(i).A.(1).2) *In vivo* influenza antiviral activity

(a) Therapeutic effect in the mouse infection model

i) Therapeutic effect in the mouse infection model with influenza A (H3N2) and A (H5N1) viruses (4.2.1.1.6; Reference data, 4.2.1.1.5, 4.2.1.1.7, 4.2.1.1.8)

Favipiravir (1 to 300 mg/kg/day), 0.4% carboxymethylcellulose (CMC) solution, or 0.5% methylcellulose (MC) solution was orally administered twice daily (BID) or 4 times daily for 5 days to the mouse infection model,[15] starting 1 hour after the infection. The number of surviving animals was monitored up to 21 days after the infection. As a comparator, oseltamivir phosphate (10 or 20 mg/kg/day) was orally administered BID for 5 days, starting 1 hour after the infection. The results are as shown in the table below.

Therapeutic effects of favipiravir and oseltamivir phosphate in the mouse infection model

Strain [Infectivity titer]	Test drug and comparator	Dose (mg/kg/day)	Number of surviving animals
A/Victoria/3/75 (H3N2) [LD_{100}][a)]	0.4% CMC solution	-	0/20
	Favipiravir	1	0/10
		3	0/10
		10	1/10
		30	7/10**
		100	10/10**
		300	10/10**
	Oseltamivir phosphate	10 b)	5/10*
A/Osaka/5/70 (H3N2) [3×10^3 PFU/Mouse]	0.5% MC solution	-	0/10
	Favipiravir	10	1/10
		30	9/10§
		100	9/10§
A/Duck/MN/1525/81 (H5N1) [LD_{100}][a)]	0.4% CMC solution	-	0/20
	Favipiravir	3	0/10
		10	2/10
		30	8/10**
		100	10/10**
		300	10/10**
A/Duck/MN/1525/81 (H5N1) [LD_{100}][a)]	0.4% CMC solution	-	0/20
	Favipiravir	33	10/10**
		100	10/10**
		300	10/10**
	Oseltamivir phosphate	20 b)	2/10

*: $P < 0.01$, **: $P < 0.001$ vs. control group (Chi-square test with Yates' correction)
§: $P < 0.001$ vs. control group (Kaplan-Meier method, log-rank test)
a) LD_{100}: 100% lethal infection dose, b) calculated as oseltamivir

ii) Inhibition against lung virus replication in the mouse infection model (4.2.1.1.9)

Favipiravir (5, 10, 15, 30 mg/kg/day) or 0.5% MC solution was orally administered BID for 5 days to the mouse infection model,[16] starting 1 hour after the infection. The lung virus titer was measured 6 hours after the last dose to calculate the dose that inhibited the lung virus replication by 90%. The results are as shown in the table below.

[15] Virus solutions were prepared using influenza A/Victoria/3/75 (H3N2), A/Osaka/5/70 (H3N2), and A/Duck/MN/1525/81 (H5N1) viruses, which are know to be lethal in mice. Each virus solution (50 µL) was applied to the nasal cavity to induce infection with the viruses in female BALB/c mice (6 weeks of age or body weight, 18-21 g; n = 10 or 20). The inoculation dose was 3×10^3 PFU/mouse for the A/Osaka/5/70 (H3N2) strain, and the 100% lethal infection dose for the other 2 strains,

[16] A virus solution was prepared using influenza A/Osaka/5/70 (H3N2) virus. The virus solution (50 µL) was applied to the nasal cavity to induce infection with the virus in female BALB/c mice (6 weeks of age, n = 8) in order to make the animals infected with the influenza virus used.

Inhibition of lung virus replication by favipiravir in the mouse infection model

Strain [Infectivity titer]	Test drug	Dose (mg/kg/day)	Lung virus titer (Log PFU/lung)	90% replication inhibition dose[a)] [95% confidence interval (CI)] (mg/kg/day)
A/Osaka/5/70 (H3N2) [3×10^3 PFU/Mouse]	0.5% MC solution	-	7.0 ± 0.11	-
	Favipiravir	5	6.7 ± 0.21*	16 [13-28]
		10	6.4 ± 0.14*	
		15	6.1 ± 0.12*	
		30	5.5 ± 0.12*	

*: $P < 0.001$ vs. control group (Dunnett test)
a) For the calculation, Dx calculation (logistic curve fitting) of SAS release 8.2 (SAS Institute Japan) was used.

iii) Therapeutic effect in the mouse infection model with highly pathogenic avian influenza virus (4.2.1.1.10)

Favipiravir at a dose of 30, 60, or 100 mg/kg/day, oseltamivir phosphate at the dose of 20 mg/kg/day, or 0.5% MC solution was orally administered BID for 5 days or 7 days to the mouse infection model,[17] starting 1 hour after the infection. The number of surviving animals was monitored up to 21 days after the infection. The results are as shown in the table below.

Therapeutic effect in the mouse infection model with highly pathogenic avian influenza A (H5N1) virus

Strain [Infectivity titer]	Test drug and comparator	Dose (mg/kg/day)	Number of surviving animals	
			Dosing regimen	
			BID 5 days	BID 7 days
A/Vietnam/UT3040/2004 (H5N1) [approximately 18 PFU/mouse][a)]	0.5% MC solution	–	0/10	0/10
	Favipiravir	30	2/10*	4/10
		60	4/10***	6/10**
		100	2/10***	10/10***
	Oseltamivir phosphate	20 [b)]	2/10*	2/10

*, **, ***: $P < 0.05$, $P < 0.01$, $P < 0.001$ vs. control group (Kaplan-Meier method, log-rank test)
a) Equivalent to 10 times 50% lethal dose, b) Calculated as oseltamivir

iv) Influences from the timing of the first dose on therapeutic effect in the mouse infection model (Reference data, 4.2.1.1.8, 4.2.1.1.11 to 4.2.1.1.14)

The mouse infection model[18] was generated, and the number of surviving animals was monitored up to 21 days after the infection. Favipiravir was orally administered at a dose of 300 mg/kg/day 4 times daily (QID) for 5 days, starting 1, 24, 36, 48, 60, 72, 84, 96, or 120 hours after the infection. In the control group, 0.4% CMC solution was orally administered QID for 5 days. Favipiravir, for which the first dose was administered 60 or 72 hours after the infection, showed a significant therapeutic effect compared with the control group in mice infected with influenza A/New Caledonia/20/99 (H1N1) virus (number of surviving animals receiving the first dose 60 hours after the infection, 4 of 10 animals in the favipiravir group and 1 of 20 animals in the control group; $P < 0.05$), in mice infected with influenza A/NWS/33 (H1N1) virus (number of surviving animals receiving the first dose 72 hours after the infection, 10 of 10 animals in the favipiravir group and 2 of 20 animals in the control group; $P < 0.001$), and in mice infected with influenza B/Sichuan/379/99 virus (number of surviving animals receiving the first dose 72 hours after the infection, 9 of 10 animals in the favipiravir group and 0 of 20 animals in the control group; $P < 0.001$).[19] In mice infected with influenza A/Duck/MN/1525/81 (H5N1) virus, the 120-hour post-

[17] A virus solution was prepared using highly pathogenic avian influenza A/Vietnam/UT3040/2004 (H5N1) virus isolated from a patient. The virus solution (50 μL) was applied to the nasal cavity to induce infection with the virus in female BALB/c mice (6 weeks of age, n = 10).
[18] Virus solutions were prepared at the lethal levels, using influenza A (H1N1), A (H5N1), and B viruses. Each virus solution (50 μL) was applied to the nasal cavity to induce infection with the viruses in female BALB/c mice (body weight, 18-21 g; n = 10 or 20).
[19] Chi-square test with Yates' correction

infection favipiravir group showed a significant therapeutic effect compared with the control group (3 of 10 animals in the favipiravir group and 0 of 20 animals in the control group; $P < 0.05$).[20]

v) Effect of divided doses on therapeutic effect in the mouse infection model (4.2.1.1.15, 4.2.1.1.16)

Favipiravir at a dose of 10, 30, or 100 mg/kg/day was orally administered once daily to 3 times daily or 6 times daily for 5 days to the mouse infection model,[21] starting 1 hour after the infection, and then 120 hours after the infection, the lungs were homogenized to measure the lung virus titer by the plaque-forming cell assay. Favipiravir at a dose of 10, 20, or 30 mg/kg/day was orally administered once daily to 3 times daily or 6 times daily for 5 days to mice with the infection induced in a similar manner, starting 1 hour after the infection, and the number of surviving animals was monitored up to 21 days after the infection. In the control group, 0.5% MC solution was orally administered 6 times daily for 5 days. The results are as shown in the table below. In mice receiving favipiravir 6 times daily at the dose of 20 mg/kg/day, the surviving effect decreased, but at the dose of 30 mg/kg/day, the number of divided doses did not influence the surviving effect of favipiravir. On the other hand, when the lung virus titer was used as an indicator, 3-time-daily or 6-time-daily treatment at the dose of 30 or 100 mg/kg/day showed a higher therapeutic effect than that of the once-daily treatment.

Effect of divided doses on the number of surviving animals and lung virus titer

Strain [Infectivity titer]	Test drug	Dose (mg/kg/day)	Number of divided doses per day	Number of surviving animals	Lung virus titer (Log PFU/lung) (n = 5)
A/Osaka/5/70 (H3N2) [3×10^3 PFU/Mouse]	0.5% MC solution	–	6	0/10	7.1 ± 0.2
	Favipiravir	10	1	1/10	6.4 ± 0.2$^{\#}$
			2	0/10	6.1 ± 0.2$^{\#}$
			3	1/10	6.1 ± 0.2$^{\#}$
			6	1/10	6.0 ± 0.2$^{\#}$
		20	1	8/10**	
			2	9/10$^{**, \S}$	
			3	9/10**	
			6	4/10*	
		30	1	9/10**	5.6 ± 0.2$^{\#}$
			2	10/10**	5.2 ± 0.3$^{\#}$
			3	10/10**	5.1 ± 0.3$^{\#, \dagger}$
			6	10/10**	5.1 ± 0.2 $^{\#, \dagger}$
		100	1		4.6 ± 0.1 $^{\#}$
			2		3.9 ± 0.1$^{\#, \dagger\dagger}$
			3		3.7 ± 0.3$^{\#, \dagger\dagger}$
			6		3.7 ± 0.1$^{\#, \dagger\dagger}$

*, **: $P < 0.01$, $P < 0.001$ vs. control group (Kaplan-Meier method, log-rank test)
§: $P < 0.05$ vs. each 6-time-daily dose group (Kaplan-Meier method, log-rank test)
#: $P < 0.001$ vs. control group (Tukey test); †, ††: $P < 0.05$, $P < 0.001$ vs. each once-daily dose group (Tukey test)

vi) Therapeutic effect in the immunodeficient mouse infection model with influenza A/Aichi/2/68 (H3N2) virus (4.2.1.1.17)

Favipiravir at a dose of 10, 30, 60, or 100 mg/kg/day was orally administered BID for 14 days to the mouse infection model[22] using severe combined immunodeficient (SCID) mice, starting 1 hour after the infection and the number of surviving animals was monitored up to 21 days after

[20] Chi-square test with Yates' correction
[21] A virus solution was prepared using influenza A/Osaka/5/70 (H3N2) virus. The virus solution (50 μL) was applied to the nasal cavity to induce infection with the virus in female BALB/c mice (6.5 weeks of age).
[22] A virus solution was prepared using influenza A/Aichi/2/68 (H3N2) virus. The virus solution (50 μL) was applied to the nasal cavity to induce infection with the virus in SCID mice (female C.B-17/Icr-scid/scidJcl mice, 7 weeks of age, n = 10).

the infection. Oseltamivir phosphate at the dose of 10 or 20 mg/kg/day or 0.5% MC solution (control) was orally administered on the same schedule.

Therapeutic effect in the SCID mouse infection model

Strain [Infectivity titer]	Test drug and comparator	Dose (mg/kg/day)	Number of surviving animals
A/Aichi/2/68 (H3N2) [7.8×10^4 PFU/Mouse]	0.5% MC solution	-	0/10
	Favipiravir	10	0/10
		30	8/10*
		60	9/10*
		100	10/10*
	Oseltamivir phosphate	10 a)	0/10
		20 a)	0/10

*: $P < 0.001$ vs. control group (Kaplan-Meier method, log-rank test)
a) Equivalent to oseltamivir

3.(i).A.(1).3) Effect of concomitant use

(a) *In vitro* effect of concomitant use (4.2.1.1.18)

MDCK cells were inoculated with influenza A/PR/8/34 (H1N1) virus and spiked with favipiravir and oseltamivir carboxylate at a drug concentration ratio of 5:1 based on their antiviral activity. Cells incubated at 35°C for 2 days were then treated with neutral red. The virus replication inhibition rate was calculated using the cytopathic effect (CPE) measured by the neutral-red intake assay.[23] The effect of concomitant use was analyzed by calculating the combination index (CI) using the median effect method.[24] The calculated CI >1.2 was determined to be antagonistic, while that ≤0.8 was determined to be synergistic.[25] Following concomitant use of favipiravir and oseltamivir carboxylate (concentration ratio, 5:1), CI at 50% virus replication inhibition was 0.66, thus indicating a synergistic effect.

(b) Effect of concomitant use in the mouse infection model (Reference data, 4.2.1.1.19 to 4.2.1.1.21)

Favipiravir (20 mg/kg/day or 25 mg/kg/day) or oseltamivir phosphate (0.03 to 100 mg/kg/day) was orally administered alone BID for 5 days or 7 days or the two drugs were concomitantly administered BID for 5 days or 7 days to the established mouse infection model[26], starting 24 hours after the infection or 2 hours before the infection. The number of surviving animals was monitored up to 21 days after the infection. In the control group, 0.4% CMC solution and sterile water were orally administered. In mice infected with influenza A/NWS/33 (H1N1) or A/Victoria/3/75 (H3N2) virus, favipiravir (20 mg/kg/day, 25 mg/kg/day) or oseltamivir phosphate (0.1 mg/kg/day, 25 mg/kg/day) administered alone presented no therapeutic effect. On the other hand, concomitant use of the two drugs in mice infected with influenza A/NWS/33 (H1N1) virus (favipiravir 20 mg/kg/day + oseltamivir phosphate ≥0.1 mg/kg/day) or A/Victoria/3/75 (H3N2) virus (favipiravir 25 mg/kg/day + oseltamivir phosphate ≥25 mg/kg/day) presented a significant therapeutic effect compared with the control group.[27] In mice infected with influenza A/Duck/MN/1525/81 (H5N1) virus, favipiravir alone (20 mg/kg/day) or oseltamivir phosphate alone (10-40 mg/kg/day) presented no therapeutic effect, but concomitant use of the two drugs (dose, favipiravir 20 mg/kg/day + oseltamivir phosphate ≥10 mg/kg/day) presented a significant therapeutic effect compared with the control group.[28]

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[23] *J Virol Methods.* 2002;106:71-79.
[24] *Adv Enzyme Regul.* 1984;22:27-55.
[25] *Acta Med Okayama.* 2006;60:25-34.
[26] Virus solutions were prepared using influenza A/NWS/33 (H1N1), A/Victoria/3/75 (H3N2), and A/Duck/MN/1525/81 (H5N1) viruses. Each virus solution (50 μL or 90 μL) was applied to the nasal cavity to induce infection with the viruses in female BALB/c mice (body weight, 17-20g; n = 10-20).
[27] $P < 0.001$, Fisher's exact test
[28] $P < 0.001$, Fisher's exact test (favipiravir 20 mg/kg/day + oseltamivir phosphate 10 mg/kg/day or 40 mg/kg/day)
$P < 0.05$, Fisher's exact test (favipiravir 20 mg/kg/day + oseltamivir phosphate 20 mg/kg/day)

3.(i).A.(1).4) Selection of drug-resistant viruses (4.2.1.1.22; Reference data, 4.2.1.1.23, 4.2.1.1.24)

Influenza A/PR/8/34 (H1N1) virus was subcultured in MDCK cells for 30 passages in the presence of favipiravir (low and high concentrations). In the low concentration passage culture, the concentration was increased from the EC_{50} value (0.1 μg/mL), as measured by the plaque reduction assay at the initial passage, to 6.4 μg/mL. In the high concentration passage culture, the concentration was increased from 10 × the EC_{50} value (1 μg/mL) at the initial passage to 16 μg/mL. In the control culture, the virus was subcultured for the same number of passages in the absence of favipiravir. The EC_{50} value was measured by the plaque reduction assay every 5 passages. The EC_{50} values as measured every 5 passages ranged from 0.15 to 0.72 μg/mL in the low concentration passage culture and ranged from 0.098 to 0.53 μg/mL in the high concentration passage culture. The sensitivity was within 5 times that of the control culture at the corresponding passage number (low concentration passage culture, 0.23-0.57 μg/mL; high concentration passage culture, 0.18-0.77 μg/mL). No development of drug-resistance[29] was noted.

The drug-resistance was induced in influenza A/Yokohama/UT2017/2003 (H3N2)[30] and influenza A/Duck/MN/1525/81 (H5N1)[31] virus strains (subjected to 30 and 25 passages, respectively). As a result, the drug-resistance to favipiravir was not developed in the influenza A/Yokohama/UT2017/2003 (H3N2) virus strain (99% inhibitory concentration [IC_{99}] value after 30 passages [yield reduction assay],[32] 0.19 μg/mL in the control culture, 0.18-0.20 μg/mL in culture with favipiravir). The resistance to favipiravir was not developed in the influenza A/Duck/MN/1525/81 (H5N1) virus strain either (IC_{90} value [yield reduction assay], 0.8 μM at the initial passage → 1.4 μM after 25 passages).

3.(i).A.(1).5) Mechanism of action

The applicant considers that the mechanism of action of favipiravir is the selective inhibition of RNA polymerase by favipiravir RTP formed by cellular enzymes in the influenza virus leading to antiviral activity. This is because purine nucleic acid reduced the antiviral activity of favipiravir [see "3.(i).A.(1).5).(a) Effect of nucleic acids on antiviral activity"]; and favipiravir was found to have lower inhibitory effects against human-derived polymerases [see "3.(i).A.(1).5).(d) Inhibitory effects against human-derived DNA and RNA polymerases and selection ratio to influenza virus RNA polymerase"] and against cell growth [see "3.(i).A.(1).5).(g) Inhibitory effect against growth of cultured cells"] compared with the comparator (ribavirin).

(a) Effect of nucleic acids on antiviral activity (4.2.1.1.25)

The effects of spiked purines and pyrimidines on the antiviral activity of favipiravir against influenza were investigated by the plaque reduction assay (Woods, et al.). MDCK cells were infected with influenza A/PR/8/34 (H1N1) virus at approximately 60 PFU/well, and to the culture medium containing favipiravir at the concentration of 6.4 μmol/L (1 μg/mL), purine and pyrimidine nucleic acids and their metabolites were added at 10 times the molar concentration of favipiravir (64 μmol/L). After 2-day incubation, the number of plaques was counted. Using the number of plaques from the virus culture without favipiravir or nucleic acids as the control, the percentage (T/C[33] [%]) was calculated. The number of plaques from the virus culture with favipiravir alone was reduced to 2% of that from the control culture, indicating the presence of antiviral activity. When, however, purine nucleic acids and their metabolites (adenine, guanine,

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[29] Resistance was confirmed when the difference from the culture control was at least 5 times.
[30] IC_{99} value of T-705 = 0.21 μg/mL (yield reduction)
[31] IC_{50} value of T-705 = 0.7 μM (neutral red intake)
[32] *Antimicrob Agents Chemother.* 1998;42:3234-3241.
[33] T: Plaque count of the study group containing favipiravir and nucleic acids, C: Plaque count of study group not containing favipiravir and nucleic acids

adenosine, guanosine, inosine, 2'-deoxyadenosine, 2'-deoxyguanosine, and hypoxanthine) were added to the virus culture with favipiravir, the antiviral activity was reduced (92%, 87%, 90%, 98%, 96%, 117%, 88%, and 116%, respectively). On the other hand, when xanthine, uric acid, and pyrimidine nucleic acids (cytosine, thymine, uracil) were added, the antiviral activity was not reduced (5%, 3%, 7%, 2%, and 3%, respectively).

(b) Identification of intracellular metabolites (4.2.1.1.26)

MDCK cells were incubated in a medium containing favipiravir at 10 μg/mL at 5% CO_2, 37°C for 18 hours, and then metabolites of favipiravir in the cells were analyzed by electrospray ionization in the negative ion mode with the liquid chromatography-mass spectrometer system. The results are as shown in the table below.

Exact mass, estimated composition formula, mass accuracy, and estimated chemical compound at each retention time

Retention time (min)	Exact mass (*m/z*)	Estimated composition formula	Mass accuracy (ppm)	Estimated chemical compound
2.02	527.96252	$C_{10}H_{14}FN_3O_{15}P_3$	-0.39	Favipiravir RTP
2.08	447.99503	$C_{10}H_{13}FN_3O_{12}P_2$	-3.05	Favipiravir RDP
2.50	368.02954	$C_{10}H_{12}FN_3O_9P$	-1.43	Favipiravir RMP
3.26	156.02136	$C_5H_3FN_3O_2$	-0.76	Favipiravir

RTP: Ribosyl triphosphate, RDP: Ribosyl diphosphate, RMP: Ribosyl monophosphate

The peak considered to be that of favipiravir RTP was subjected to fragment analysis. The corresponding fragment ion showed the signal in intensity ratio similar to that of the favipiravir RTP reference standard, demonstrating the presence of favipiravir RTP.

(c) Effect on influenza virus RNA polymerase (4.2.1.1.27)

The inhibitory effects of favipiravir and its intracellular metabolites, favipiravir ribosyl (R), favipiravir ribosyl monophosphate (RMP), and favipiravir RTP, against influenza virus RNA polymerase activity were investigated according to the method[34] of Tomassini, et al.[35] Ribavirin triphosphate (ribavirin TP) was used as the control, which was previously reported to inhibit the influenza virus RNA polymerase activity in the same method. The results are as shown in the table below. Favipiravir, favipiravir R and favipiravir RMP did not show any inhibitory effect against the influenza virus RNA polymerase even at the concentration of 200 μmol/L.

Inhibitory effect against influenza virus RNA polymerase

Substrate	IC_{50} value (μmol/L)	
	Favipiravir RTP	Ribavirin TP
[^{32}P] UTP	12.6	>200
[^{32}P] GTP	0.341	8.90

(d) Inhibitory effects against human-derived DNA and RNA polymerases and selection ratio to influenza virus RNA polymerase (4.2.1.1.28, 4.2.1.1.29)

To investigate the inhibitory effect of favipiravir RTP against human-derived DNA polymerases α, β, and γ, [8-^{3}H] deoxyguanosine-5'-triphosphate ([^{3}H] dGTP) and [methyl-^{3}H] thymidine-5'-triphosphate ([^{3}H] dTTP) were used as the substrates to measure the radiation activities of the enzyme reaction products. The results are as shown in the table below.

[34] *Antimicrob Agents Chemother*. 1994;38:2827-2837.

[35] The inhibition rate (n = 3, mean ± standard deviation) against intake of [α-^{32}P] uridine-5'-triphosphate ([^{32}P] UTP) or [α-^{32}P] guanosine-5'-triphosphate ([^{32}P] GTP) was calculated, which were added as substrates, into RNA using the RNA polymerase solution prepared from virus particles of influenza A/PR/8/34 (H1N1) virus.

Inhibitory effects against human-derived DNA polymerase α, β, and γ

Human-derived DNA polymerase	Substrate	Inhibition rate (%)			
		Favipiravir RTP (μmol/L)		Ribavirin TP (μmol/L)	
		100	1000	100	1000
α	dGTP	1.61	-1.81	-1.47	63.0
	dTTP	-1.82	-9.12	8.78	65.0
β	dGTP	1.12	13.5	22.7	63.8
	dTTP	-2.36	9.08	23.1	50.8
γ	dGTP	-4.10	11.7	1.54	24.8
	dTTP	1.93	41.2	1.83	27.1

To investigate the inhibitory effect of favipiravir RTP against human-derived RNA polymerase II and the selection ratio relative to human-derived RNA polymerase II (ratio of the IC_{50} value against human-derived RNA polymerase II to that against influenza virus RNA polymerase), [^{3}H] GTP was used as the substrate to measure the radiation activities of the enzyme reaction products. The results are as shown in the table below.

Inhibitory activity against human-derived RNA polymerase II and selection ratio

Test drug	IC_{50} value (μmol/L)		Selection ratio
	Human-derived RNA polymerase II	Influenza virus RNA polymerase[a)]	
Favipiravir RTP	905	0.341	2650
Ribavirin TP	849	8.90	95.4

a) The IC_{50} value against influenza virus RNA polymerase was the value obtained by using [^{32}P]GTP as the substrate [see "3.(i).A.(1).5).(c) Effect on influenza virus RNA polymerase"].

(e) Effect on IMPDH (4.2.1.1.30)

The inhibitory effect of favipiravir RMP against inosine monophosphate dehydrogenase (IMPDH) was investigated according to the method of Hodges, et al.[36] Ribavirin monophosphate (ribavirin MP) was used as the control, which was previously reported to inhibit IMPDH.[37] The IC_{50} values of favipiravir RMP and ribavirin MP against IMPDH were >1000 and 2.0 μmol/L (95% confidence interval [CI], 1.9-2.1 μmol/L), respectively. Ribavirin MP inhibited IMPDH, but favipiravir RMP did not.

(f) Inhibitory effects against DNA and RNA syntheses in cultured cells (4.2.1.1.31)

The inhibitory effects of favipiravir against DNA and RNA syntheses in MDCK cells, human lung epithelial A549 cells, and human myeloid K-562 cells were investigated using ribavirin as the comparator.[38] The results are as shown in the table below.

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[36] The extract of MDCK cells was used as the crude enzyme solution of IMPDH, and [^{14}C] inosine-5'-monophosphate (IMP) was used as the substrate. The formation rate was determined based on the area of [^{14}C] xanthosine-5'-monophosphate (XMP) from the enzymatic reaction product identified by radiochromatography, and then IC_{50} was calculated by logistic regression (*J Biol Chem.* 1989;264:18137-18141.).

[37] *Proc Natl Acad Sci U S A.* 1973;70:1174-1178.

[38] [6-^{3}H] thymidine or [5-^{3}H] uridine was added to cells incubated with or without the test drug for 1 day, and at 3 hours after the addition, the intracellular radioactivity was measured. Using the radioactivity without the test drug as the control, DNA synthesis and RNA synthesis inhibition rates were calculated. The concentrations of favipiravir and ribavirin were determined in consideration of their solubility in the medium and cell proliferation inhibitory concentration.

Inhibitory effects against DNA and RNA syntheses in cultured cells (%)

Test drug	Concentration (μg/mL)	MDCK cells		A549 cells		K-562 cells	
		DNA synthesis inhibition rate	RNA synthesis inhibition rate	DNA synthesis inhibition rate	RNA synthesis inhibition rate	DNA synthesis inhibition rate	RNA synthesis inhibition rate
Favipiravir	200	NT	NT	NT	NT	<0	23.0
	500	33.5	12.8	10.6	<0	9.3	44.7
	1000	28.7	25.4	< 0	<0	48.4	71.9
	2000	57.6	44.1	6.0	11.8	NT	NT
Ribavirin	10	NT	NT	NT	NT	82.5	67.5
	20	NT	NT	NT	NT	86.7	75.8
	50	99.6	99.3	76.7	50.8	88.5	81.1
	100	99.6	98.0	74.4	59.1	NT	NT
	200	99.3	97.1	67.0	32.0	NT	NT

NT: Not tested

(g) Inhibitory effect against growth of cultured cells (4.2.1.1.32)

The cell growth inhibitory effect of favipiravir against MDCK cells, A549 cells, and K-562 cells was investigated using oseltamivir carboxylate, amantadine, and ribavirin as controls.[39] The results are as shown in the table below.

Inhibitory effect against growth of cultured cells

Cultured cells	CC_{50} value (μg/mL)			
	Favipiravir	Oseltamivir carboxylate	Amantadine	Ribavirin
MDCK cells	>2000	>2000	130	37
A549 cells	>2000	>2000	93	150
K-562 cells	910	>2000	90	6.2

3.(i).A.(1).6) Other pharmacology studies

(a) Influenza antiviral activity of favipiravir hydroxide (M1) (4.2.1.1.33)

The influenza antiviral activity of M1, a major metabolite of favipiravir, was measured by the plaque reduction assay using MDCK cells. As a result, the EC_{50} value of M1 against influenza A/PR/8/34 (H1N1) virus strain was >100 μg/mL, indicating that M1 did not show antiviral activity.

(b) *In vitro* activity and *in vivo* therapeutic effect of favipiravir against other RNA viruses (*Antimicrob Agents Chemother.* 2005;49:2378-2386.)

According to the reference, favipiravir showed antiviral activity against *Bunyaviridae* (La Crosse encephalitis virus, Punta Toro virus, Rift Valley fever virus, Phlebotomus fever virus) and *Arenaviridae* (Junin virus, Pichinde virus, Tacaribe virus), both of which cause viral hemorrhagic fever, to an extent comparable to that of ribavirin.

[39] XTT reagent was added to cells incubated with or without the test drug for 3 days, followed by measurement at OD 450 nm. The drug concentration without the test drug at which the absorbance decreased to 50% was determined as the 50% cytotoxicity value (CC_{50}).

(c) Efficacy evaluation in the cynomolgus monkey infection model with highly pathogenic avian influenza virus (Reference data, 4.2.1.1.34)

Female cynomolgus monkeys were inoculated with highly pathogenic avian influenza A [redacted] (H5N1) virus isolated from a clinical sample to induce infection with the virus.[40] The high doses of favipiravir (initial dose, 300 mg/kg/day; second dose, 150 mg/kg/day), the low doses of favipiravir (initial dose, 180 mg/kg/day; second dose, 90 mg/kg/day), oseltamivir phosphate (100 mg/kg/day), or 0.5% MC solution (control) was administered orally once daily for 6 days to the animals.[41] In both favipiravir high-dose group and low-dose group, 1 of 3 animals died 4 days and 5 days after the infection, respectively. Histopathological examination of the dead animals showed no serious changes in any part except for the lungs, and the lung virus titer in the favipiravir group, including the surviving animals, was comparable to that in the control group. In the oseltamivir phosphate group, the lung virus titer was significantly lower than that in the control group.[42] Blood levels of cytokines (interferon [IFN] -γ, monocyte chemoattractant protein [MCP] -1, interleukin [IL] -6, IL-8, tumor necrosis factor [TNF] -α) were measured over time after the infection. These cytokine levels were not clearly different among the favipiravir group, oseltamivir phosphate group, and control group. In the oseltamivir phosphate group and control group, no animals died.

The applicant explained that the trough blood concentrations in the favipiravir group at 24 hours after the treatment which were estimated by simulation, were approximately 10 μg/mL in the high-dose group and approximately 1 μg/mL in the low-dose group, but actually after the first dose, the blood concentrations were below the lower limit of quantitation (<0.1 μg/mL) in all animals in both the high-dose group and low-dose group, and the subsequent concentrations remained lower than the estimated values, while the oseltamivir phosphate group was exposed to the drug above the efficacy exposure level (serum trough concentration, ≥0.0311 μg/mL).

3.(i).A.(2) Secondary pharmacodynamics (4.2.1.2.1, 4.2.1.2.2, 4.2.1.2.4; Reference data, 4.2.1.2.3)

For the regulatory application, 4 secondary pharmacodynamic studies were conducted. A summary of the major studies and the results are as shown in the table below.

[40] Female cynomolgus monkeys (2-3 years of age, n = 3) were inoculated by application of the virus at the infectivity titer of 6.7×10^7 PFU/monkey to the trachea (4.5 mL), nasal cavity (1.0 mL, 0.5 mL/nostril), oral (1.0 mL), and conjunctiva (0.2 mL, 0.1 mL/eye). The virus inoculation was carried out immediately after the first dose, and the treatment with favipiravir and the virus inoculation were carried out under anesthesia (ketamine 5 mg/kg, xylazine 1 mg/kg).

[41] With reference to the data from the 2-week repeated oral dose toxicity study in cynomolgus monkeys in which favipiravir was administered BID [see 4.2.3.2.5] and based on the simulation results of the blood concentration profile following the once-daily treatment in cynomolgus monkeys, thedoses were selected. The low dose was the dose that would provide the area under the plasma concentration-time curve (AUC) equivalent to that at the dose of 60 mg/kg/day, at which the efficacy was confirmed in the mouse infection model, and the high dose was the dose at which no serious toxicity was caused in cynomolgus monkeys.

[42] *: $P < 0.05$ vs. control group (Dunnett test)

Summary of secondary pharmacodynamic studies and the results

<table>
<tr><th>Pharmacologic action to be evaluated</th><th>Animal species/strain</th><th>Spiked concentration</th><th>Results</th></tr>
<tr><td>Effect on proliferation of human bone marrow hematopoietic progenitor cells</td><td>Bone marrow CD34 positive cells</td><td>0.0128-1000 µg/mL (incubated in erythroblast cell differentiation medium for 7 days, and then in granulocytic/monocytic cell differentiation medium for 10 days)</td><td>Inhibitory effect against growth of bone marrow cells (IC_{50} value, µg/mL)
<table>
<tr><th>Cell type</th><th>Favipiravir</th><th>Zidovudine</th><th>Ribavirin</th></tr>
<tr><td>Burst-forming unit -erythroid (BFU-E)</td><td>539</td><td>0.0814</td><td>0.599</td></tr>
<tr><td>Colony forming unit-granulocyte/monocyte (CFU-GM)</td><td>170</td><td>2.87</td><td>0.745</td></tr>
</table></td></tr>
<tr><td>Effect on mitochondria in human hepatoma-derived HepG2 cells</td><td>HepG2 cells</td><td><u>Favipiravir</u>
30-3000 µmol/L (4.71-471 µg/mL)

<u>Zidovudine</u>
0.3-300 µmol/L (0.08-80.2 µg/mL)

<u>Zalcitabine</u>
0.3-300 µmol/L (0.06-63.4 µg/mL)

(incubated for 3 days and 9 days)</td><td><u>Favipiravir</u>
3-day incubation: No effect on cell growth, lactic acid production, or mitochondrial DNA up to 3000 µmol/L
9-day incubation: Cell growth inhibition (64.8% of the control) at 3000 µmol/L, but no effects on lactic acid production or mitochondrial DNA amount
<u>Zidovudine</u>
3-day incubation: At 30 and 300 µmol/L, cell growth was inhibited (66.5% and 42.9% of the control, respectively), lactic acid production increased (1.43 and 2.12 times the control, respectively), but no effect on the amount of mitochondrial DNA
9-day incubation: At 3, 30, and 300 µmol/L, cell growth was inhibited (66.8%, 24.8%, and 3.60% of the control, respectively), and at 30 and 300 µmol/L, lactic acid production increased (3.20 and 11.8 times the control, respectively), but no effect on the amount of mitochondrial DNA
<u>Zalcitabine</u>
3-day incubation: At 300 µmol/L, cell growth was inhibited (58.6% of the control), lactic acid production increased (1.71 times the control), and at 3, 30, and 300 µmol/L, mitochondrial DNA decreased (42.8%, 35.0%, and 33.4% of the control, respectively).
9-day incubation: At 3, 30, and 300 µmol/L, cell growth was inhibited (60.8%, 27.6%, and 5.20% of the control, respectively), lactic acid production increased (1.77, 3.88, and 8.95 times the control, respectively), and mitochondrial DNA decreased (≤5% of the control at any concentration).</td></tr>
<tr><td rowspan="2">Effect on binding of various receptors</td><td>Animal- or human-derived receptors, enzymes</td><td>1000 µmol/L (157 µg/mL)</td><td>Inhibition against binding of human PR-B by 96%
No inhibition against binding of bovine PR
No inhibition against binding of rat AR, muscarine receptor, 5-HT_1, 5-HT_2, opioid receptor, thyroid hormone receptor, or steroid 5α reductase
No inhibition against binding of guinea pig 5-HT_4
No inhibition against binding of human CCK_1, CCK_2, D_1, D_{2L}, D_3, ERα, ERβ, H_1, H_2, NT_1, 5-HT_3, 5-HT_{5A}, serotonin transporter, VIP_1, or aromatase (CYP19)</td></tr>
<tr><td>Human-derived receptors</td><td>31.25-1000 µmol/L (4.91-157 µg/mL)</td><td>No inhibition against binding of human progesterone receptor (common ligand binding site of isoforms)</td></tr>
</table>

PR-B, PR: Progesterone receptors; AR: Androgen receptor; 5-$HT_{1\ to\ 5A}$: Serotonin receptors
CCK_1, CCK_2: Cholecystokinin receptors; D_1, D_{2L}, D_3: Dopamine receptors; ERα, ERβ: Estrogen receptors
H_1, H_2: Histamine receptor; NT_1: Neurotensin receptor; VIP_1: Vasoactive intestinal peptide receptor

3.(i).A.(3) Safety pharmacology (4.2.1.3.1 to 4.2.1.3.6)

For the regulatory application, 6 safety pharmacology studies were conducted. A summary of the major studies and the results are shown below.

Test substance, favipiravir

Tissue to be evaluated	Animal species/strain	Route of administration	Dose[a)] or spiked concentration (mg/kg)	Sex and number of animals/group	Noteworthy findings
Central nervous system	Mouse /ICR	Orally	30, 125, 500, 2000	3M	No abnormalities in clinical condition or behavior (modified Irwin method) at 30, 125, and 500 mg/kg. Decreased locomotor activity, abnormal gait, flaccid posture, decrease in grooming, appearance of jumping behavior, decreased passivity, decreased orientation, hypersensitized touch response, decreased grip strength, decreased traction, decreased righting reflex, and decreased body temperature at 2000 mg/kg.
Cardiovascular system	Dog/beagle	Orally	15, 50, 150 (dosing interval, 6-8 days)	4M	No effects on blood pressure (systolic, diastolic, mean), heart rate, or electrocardiographic (ECG) parameters (PR, QRS, QT, QTc) (telemetry method) up to 20 hours after the treatment.
	HEK293 cells (hERG expressed)	*in vitro*	40, 200, 1000 μmol/L (6.28-157 μg/mL)	5	No effects on hERG current at 40 or 200 μmol/L (patch-clamp method). Mild suppression at 1000 μmol/L (suppression rate from the baseline, 2.7% in the solvent control group vs. 8.1% at 1000 μmol/L).
Respiratory system	Rat/SD	Orally	200, 600, 2000	6M	No effects on respiratory rate, tidal volume, or minute ventilation volume up to 8 hours after the treatment (Whole body plethysmograph method).

a) Unless otherwise specified, single-dose administration.

Test substance, M1

Tissue to be evaluated	Animal species/strain	Route of administration	Dose[a)] or spiked concentration (mg/kg)	Sex and number of animals/group	Noteworthy findings
Cardiovascular system	Dog/beagle	Intravenously	30	2M	No effects on blood pressure (systolic, diastolic, mean), heart rate, or ECG parameters (PR, QRS, QT, QTc) (telemetry method) up to 8 hours after the treatment. Plasma M1 concentration at the end of the treatment, 68.2 μg/mL, the mean value in 2 animals (individual value, 69.5 and 66.9 μg/mL).
	HEK293 cells (hERG expressed)	*in vitro*	20, 100, 500 μmol/L (3.46-86.6 μg/mL)	5	No effects on hERG current (patch-clamp method).

a) Unless otherwise specified, single-dose administration.

3.(i).B Outline of the review by PMDA

3.(i).B.(1) Antiviral activity against clinical isolates

PMDA considers as follows:

According to the data submitted in the application, *in vitro* studies on sensitivity in various laboratory strains demonstrated the antiviral effect, and studies on sensitivity in clinical isolates obtained between 1992 and 2009 showed no changes in sensitivity to favipiravir over time. Based on the above, favipiravir is expected to show an antiviral activity against influenza A and B virus strains.

Favipiravir has a mechanism of action different from those of the existing influenza antiviral

drugs (amantadine, rimantadine,[43] oseltamivir, zanamivir), and no cross-resistance occurred in the strains which is resistant to the existing influenza antiviral drugs. Non-clinical data indicate that favipiravir is expected to show an antiviral activity even against these drug-resistant strains.

The investigation of sensitivity to favipiravir in virus clinical isolates obtained in phase III clinical studies (Studies 312 and JP313) showed that the sensitivity decreased in 3 of 208 isolates during the treatment period of favipiravir, but all the decreases were equivalent to 4- to 5-time increase of the resistance (EC_{50} value, 0.43-0.94 μg/mL). In patients from whom virus with decreased sensitivity was isolated, no particular clinical signs attributable to the decreased sensitivity were noted.

As described above, no currently available information indicates that clear selection of drug-resistant viruses will occur even during the clinical use of favipiravir. It is, however, necessary to continue to collect the information on the drug-resistant viruses, because development potential of viruses resistant to favipiravir cannot be completely ruled out [for the details, see "3.(i).B.(2) Selection of favipiravir-resistant viruses"].

3.(i).B.(2) Selection of favipiravir-resistant viruses

The study for selection of favipiravir-resistant viruses [see "3.(i).A.(1).4) Selection of resistant viruses"] showed that 30 passages in the presence of favipiravir did not lead to selection of the drug-resistant viruses. Regarding this result, PMDA asked the applicant to explain whether or not an additional study for selection of the resistant viruses has been planned.

The applicant responded as follows:
In the study for selection of the drug-resistant viruses, the virus culture underwent 30 passages, which was 2 times the maximum number of passages (15 passages) which are reported to have shown the development of viruses resistant to the existing influenza antiviral drugs in the study for drug-resistance induction. As a result, no favipiravir-resistant viruses were selected, but taking into account that favipiravir has a new mechanism of action, the virus culture after the 30th passage is planned to be additionally investigated. In this study, the favipiravir concentration in the virus culture will be started at the EC_{50} value and then increased in every passage, and the active form of oseltamivir (oseltamivir carboxylate) will be used as the comparator. If sensitivity of the virus is not decreased at the 30th passage, the passage will be continued for the investigation. This planned study differs from the previous one in the following points.

Since differences among the isolates possibly affect the selection of drug-resistant viruses, this study will use influenza A/FM/1/47 (H1N1) virus different from influenza A/PR/8/34 (H1N1) virus, which failed to select the drug-resistant viruses in the previous study.

The sensitivity of the cultured isolate will be measured at the 10th, 15th, 20th, 25th, and 30th passages. At the 30th passage, plaque purification will be performed in the presence of the drug to investigate whether or not viruses with decreased sensitivity can be selected. If the sensitivity is not decreased at the 30th passage, the condition will be modified such as combining plaque purification methods to facilitate selection of the drug-resistant viruses.

Favipiravir is an influenza antiviral drug with a new mechanism of action and it is therefore important to characterize the favipiravir-resistant virus. In the future, various studies in addition to the above will be performed to facilitate early selection of the drug-resistant viruses, using the information on the clinical isolates as reference.

[43] Unapproved in Japan

PMDA accepted the applicant's response stating that the study for selection of the drug-resistant viruses will be continued. The information obtained from the study should be immediately provided to healthcare professionals.

3.(i).B.(3) Efficacy of favipiravir against highly pathogenic avian influenza A (H5N1) virus

In vitro studies demonstrated the antiviral activity of favipiravir against avian influenza virus strains including highly pathogenic strain [see "3.(i).A.(1).1).(b) Antiviral activity against various influenza virus clinical isolates"]. Also, *in vivo* studies in mice showed significant therapeutic effect of favipiravir compared with the control [see "3.(i).A.(1).2).(a).i) Therapeutic effect in the mouse infection model with influenza A (H3N2) virus and influenza A (H5N1) virus" and "3.(i).A.(1).2).(a).iii) Therapeutic effect in the mouse infection model with highly pathogenic avian influenza virus"]. On the other hand, *in vivo* studies in cynomolgus monkeys [see "3.(i).A.(1).6).(c) Efficacy evaluation in the cynomolgus monkey infection model with highly pathogenic avian influenza virus"] showed that the serum favipiravir concentration was below the quantitation limit, but death occurred only in the favipiravir group.

The applicant stated that the efficacy could not be evaluated in cynomolgus monkeys because the serum favipiravir concentration was below the quantitation limit. Regarding this matter, PMDA considers it necessary to provide the currently available information (including the fact that clinical efficacy against virus subtype H5N1 strains has not been investigated at present) to healthcare professionals appropriately so that they will not have over-expectations on the clinical efficacy of favipiravir in patients infected with highly pathogenic avian influenza virus, only based on the results of *in vitro* studies on the sensitivity and results of *in vivo* (mouse infection model) studies on the therapeutic effect. In addition, Study [redacted] in patients infected with influenza A [redacted] virus is planned to be conducted. The results from this study should be also presented to healthcare professionals appropriately.

Concerning the death of cynomolgus monkeys in this study, the applicant discussed that the serum favipiravir concentration was below the quantitation limit and cynomolgus monkeys in the favipiravir group died of viral pneumonia. In addition to this discussion, the conclusion of PMDA on the results of non-clinical toxicity study additionally conducted to investigate the cause of death in cynomolgus monkeys [see 4.2.3.7.2.1 to 4.2.3.7.2.2 and 4.2.3.7.7.20 to 4.2.3.7.7.22] will be discussed in the toxicity section [see "3.(iii).B.(5) Deaths in the pharmacology study in monkeys infected with influenza virus"].

3.(i).B.(4) Safety pharmacology

3.(i).B.(4).1) Effect on central nervous system

PMDA considers as follows:

Taking into account that mice treated with favipiravir at the dose of 2000 mg/kg presented signs suggestive of the depression of the central nervous system (CNS) (decreased locomotor activity, flaccid posture, decrease in grooming), and that intracerebral transfer of favipiravir was found in rats and monkeys [see 4.2.2.3.1 and 4.2.2.3.2], effects of favipiravir on the central nervous system cannot be ruled out. However, the exposure to favipiravir in mice at the no observed effect level (500 mg/kg) (maximum plasma concentration [C_{max}] [mean], 338 μg/mL; see 4.2.3.7.7.4) is 6.6 times that of favipiravir given in accordance with the proposed dosage regimen (C_{max} [mean], 51.5 μg/mL), clinical use of favipiravir do not seem to cause any particular issues. The effect on the CNS will be discussed in the Clinical data section [see "4.(iii).B.(2).5) Pediatric and adolescent patients"].

3.(i).B.(4).2) ECG QT interval (QT) prolongation risk of favipiravir

PMDA considers as follows:

In the studies of the effect on the hERG current as a cardiovascular parameter, the suppression of

the hERG current was observed at the concentration of 1000 μmol/L (157 μg/mL, 3.0 times the human C_{max}), but the QT interval (QT) prolongation risk of favipiravir is considered to be low, because the rate of suppression relative to the baseline was as mild as 8.1%; and in the telemetry study (dogs), no effects on blood pressure (systolic, diastolic, mean), heart rate, or ECG parameters (ECG PR interval [PR], ECG QRS wave [QRS], QT, ECG corrected QT interval [QTc]) were observed even at the oral dose of 150 mg/kg (C_{max} [mean], 268 μg/mL; 5.2 times the human C_{max}) until 20 hours have passed after the treatment [see "3.(i).A.(3) Safety pharmacology"].

3.(ii) Summary of pharmacokinetic studies

3.(ii).A Summary of the submitted data

^{14}C-labeled or unlabeled favipiravir was orally or intravenously administered to mice, rats, dogs, and monkeys and pharmacokinetics of the drug was investigated. Drug concentrations in biological samples from animals treated with favipiravir were determined by the high performance liquid chromatography (HPLC) -UV method, and radioactivity levels in biological samples from animals treated with ^{14}C-labeled favipiravir were determined with the liquid scintillation counter (LSC) and HPLC system connected with a radioactivity detector (Radio-HPLC). Tissue distribution of the radioactivity was determined by autoradioluminography.

3.(ii).A.(1) Absorption[44]

3.(ii).A.(1).1) Bioavailability (4.2.2.2.1)

A single oral or single intravenous dose of 8 mg/kg of favipiravir was administered in female mice. The plasma concentrations of favipiravir and favipiravir hydroxide (M1) changed with time similarly between oral and intravenous administration. The area under the plasma concentration-time curve (AUC) from time 0 to infinity was 37.3 μg·hr/mL in mice treated orally and 38.3 μg·hr/mL in mice treated intravenously; the bioavailability was thus 97.6%.

3.(ii).A.(1).2) Dose correlation (4.2.2.2.2, 4.2.3.2.1, 4.2.3.2.3, 4.2.3.2.5)

Single oral doses of 3 to 30 mg/kg of favipiravir were administered to female mice and repeated oral doses of 6.5 to 100 mg/kg of favipiravir BID were administered for 28 days to male rats. C_{max} and AUC values of favipiravir and M1 increased almost proportionally to the dose level in the single dose and on Day 1 of the repeated dose. The ratio of M1 to favipiravir in terms of AUC ($AUC_{M1}/AUC_{favipiravir}$ ratio) was 0.06 to 0.09 in female mice and 0.01 to 0.02 in male rats, presenting almost constant values among the dose levels. The pharmacokinetic linearity was confirmed in these animal species. On the other hand, the elimination half-life of favipiravir ($t_{1/2}$) extended with increasing dose level on Day 1 in studies where repeated oral doses of 5 to 150 mg/kg of favipiravir BID were administered for 28 days to male dogs and where repeated doses of 50 to 150 mg/kg of favipiravir BID were administered for 14 days to male monkeys. The C_{max} of favipiravir administered as the second dose and AUC ($AUC_{0\text{-}24}$) up to 24 hours after the treatment showed more than dose proportional increases. The $AUC_{M1}/AUC_{favipiravir}$ ratio tended to decrease at the dose of ≥50 mg/kg BID in male dogs and tended to decrease with increasing dose level (50, 100, 150 mg/kg BID) in male monkeys. Pharmacokinetic non-linearity was confirmed in dogs and monkeys.

3.(ii).A.(1).3) Sex differences (4.2.3.7.7.4, 4.2.3.2.1, 4.2.3.2.3, 4.2.3.2.5)

No sex differences were observed in C_{max} or $AUC_{0\text{-}24}$ of favipiravir, or the $AUC_{M1}/AUC_{favipiravir}$ ratio on Day 1 in studies where oral doses of 6.5 to 100 mg/kg of favipiravir BID were administered for 28 days to male and female rats and oral doses of 5 to 50 mg/kg of favipiravir BID were administered for 28 days to male and female dogs. On the other hand, in a study where oral doses of 50 to 150 mg/kg of favipiravir BID were administered for 14 days to male and

[44] In this section, a summary of the pharmacokinetic data in the repeat-dose toxicity studies (4.2.3.2.1, 4.2.3.2.3, 4.2.3.2.5) and other toxicity studies (4.2.3.7.7.4) are provided.

female monkeys, C_{max} and AUC_{0-24} of favipiravir, and the $AUC_{M1}/AUC_{favipiravir}$ ratio on Day 1 showed no sex differences at the doses of 50 mg/kg BID and 150 mg/kg BID, but the C_{max} and AUC_{0-24} of favipiravir in female monkeys at the dose of 100 mg/kg BID were 0.4 to 0.7 times and 0.3 times those in male monkeys, respectively, and the $AUC_{M1}/AUC_{favipiravir}$ ratio in female monkeys was 2.09, which was higher than that in male monkeys (0.77).[45] Following repeated oral doses of 15 to 500 mg/kg of favipiravir BID for 1 day to male and female mice, the C_{max} and AUC_{0-24} of favipiravir in female mice were 1.2 to 1.9 times and 1.5 to 2.0 times those in male mice, respectively. The $AUC_{M1}/AUC_{favipiravir}$ ratios (0.03-0.05) in female mice were lower than those in male mice (0.09-0.12), showing a sex difference in plasma pharmacokinetics of favipiravir.

3.(ii).A.(1).4) Repeat-dose administration (4.2.2.2.1, 4.2.3.2.1, 4.2.3.2.3, 4.2.3.2.5)

Following repeated oral doses of 8 mg/kg of favipiravir QID for 5 days to female mice, the area under the plasma concentration-time curve of favipiravir at steady state (AUC_{τ}) was 36.3 μg·hr/mL, and The $AUC_{M1}/AUC_{favipiravir}$ ratio was 0.09; both parameters were comparable to those following a single oral dose (AUC, 37.3 μg·hr/mL; The $AUC_{M1}/AUC_{favipiravir}$ ratio, 0.06). Favipiravir was orally administered BID for 28 days at doses of 6.5 to 100 mg/kg to male rats or at doses of 5 to 50 mg/kg to male dogs. The C_{max} and AUC_{0-24} of favipiravir (on the day of the final dose) were 0.9 to 1.6 times and 1.0 to 1.3 times those on Day 1, respectively, in male rats and 1.2 to 1.5 times and 1.3 to 1.4 times those on Day 1, respectively, in male dogs. The $AUC_{M1}/AUC_{favipiravir}$ ratio on the day of the final dose was 0.02 in male rats and 0.02 to 0.04 in male dogs, which were comparable to those on Day 1 (male rats, 0.01-0.02; male dogs, 0.03-0.05). Following repeated oral doses of 50 to 150 mg/kg of favipiravir BID for 14 days to male monkeys, The C_{max} and AUC_{0-24} of favipiravir on the day of the final dose were 2.4 to 7.8 times and 4.4 to 6.1 times higher than those on Day 1, respectively, while the $AUC_{M1}/AUC_{favipiravir}$ ratio on the day of the final dose was 0.04 to 0.25, which was lower than that on Day 1 (0.45-1.91). The above data indicated the effects of the repeated doses on the plasma pharmacokinetics.

3.(ii).A.(2) Distribution

3.(ii).A.(2).1) Tissue distribution in rats and monkeys (4.2.2.3.1, 4.2.2.3.2)

Following a single oral dose of 20 mg/kg of ^{14}C-labeled favipiravir to male rats, the maximum radioactivity levels were reached at 0.5 to 1 hours after dosing in all tissues[46] except for the small intestine, cecum, and fur and then decreased to ≤5.7% of the maximum level at 96 hours in all tissues except for the fur.[47] The maximum radioactivity level (mean) in each tissue was lower than the maximum plasma radioactivity level (51.4 μg eq./mL) except for that in the stomach (74.2 μg eq./g).[48] The maximum radioactivity levels (mean) were reached in the trachea and lungs (trachea, 20.5 μg eq./g; lung, 21.7 μg eq./g) at 0.5 and 1 hour after dosing, respectively, and their ratios relative to the plasma radioactivity level were 0.40 and 0.50, respectively. Following a single oral dose of 20 mg/kg of ^{14}C-labeled favipiravir to male monkeys, the maximum radioactivity levels were reached at 0.5 hours after dosing and then decreased to ≤2.8% of the maximum level at 24 hours in all tissues except for the bones.[49] The maximum radioactivity level in each tissue was lower than the maximum plasma radioactivity level (39.5 μg eq./mL) except

[45] The applicant discussed as follows: in the favipiravir 100 mg/kg BID group, many females showed relatively high CL/F values (apparent total systemic clearance following the oral dose) , and many males showed relatively low CL/F values, but in the other dose groups (50 mg/kg and 150 mg/kg BID), no differences were found in CL/F between males and females; and therefore, the difference in plasma pharmacokinetics between males and females observed in the 100 mg/kg BID dose group was not attributable to the sex difference but was attributable to the individual variability in metabolic clearance (individual variability in metabolizing capacity).

[46] The maximum concentration was 26.4 μg eq./g in the small intestine at 4 hours after dosing, 20.8 μg eq./g in the cecum at 8 hours, and 0.359 μg eq./g in the fur at 24 hours.

[47] The radioactivity level in the fur at 96 hours after dosing was 0.193 μg eq./g.

[48] The effect on the testis was observed in toxicity studies in rats, but the radioactivity level in the testis reached the maximum (16.1 μg eq./g) at 1 hour after dosing. This level was lower than the radioactivity level in the plasma (43.2 μg eq./mL at 1 hour) and then decreased in parallel with that in the plasma until 24 hours after dosing.

[49] The radioactivity level in the bone at 24 hours after dosing was 0.594 μg eq./g.

for that in the kidney (105 μg eq./g), and their ratios relative to the plasma radioactivity level were ≤0.72.[50] The maximum radioactivity level was reached in the lungs (lung, 20.3 μg eq./g) at 0.5 hours after dosing, and its ratio relative to the plasma radioactivity level was 0.51.

The tissue distribution of ^{14}C-labeled favipiravir in pigmented (Long-Evans) rats following a single oral dose of 20 mg/kg, measured by whole-body autoradioluminography, was comparable to that in albino rats. There was no pigmented-tissue (eyes, skin, fur) specific distribution or persistence of favipiravir.

3.(ii).A.(2).2) Lung concentrations of favipiravir ribosyl triphosphate (RTP) in mice (4.2.2.2.2)

Following a single oral dose of 20 mg/kg of favipiravir to female mice (of the same strain as that in the influenza virus infection model), the maximum lung concentration (mean) of favipiravir RTP (active form) was reached at 4 hours after dosing (0.683 μg/g lung), and its ratio relative to the plasma concentration of favipiravir (9.11 μg/mL) was 0.02 in terms of molar concentration. The half life ($t_{1/2}$) of favipiravir RTP in the lungs was 4.21 hours.[51]

3.(ii).A.(2).3) Distribution in fetuses (4.2.2.3.3)

Following a single oral dose of 20 mg/kg of ^{14}C-labeled favipiravir to rats in the organogenesis period (Gestation day 12) or perinatal period (Gestation day 19), the radioactivity levels in dam tissues and fetuses (whole-body) in the organogenesis period were not clearly different from those in the perinatal period, and the maximum levels were reached at 0.5 hours after dosing in almost all tissues including the fetuses. The maximum radioactivity level in each tissue was lower than the plasma radioactivity level in dams (organogenesis period, 47.4 μg eq./mL; perinatal period, 42.6 μg eq./mL) except for that in their stomach (organogenesis period, 87.4 μg eq./g; perinatal period, 89.1 μg eq./g). The radioactivity levels in the fetus and fetal tissues were 0.37 to 1.72 times the plasma radioactivity level in dams, and comparable to the ratio of the radioactivity level in the placenta to the plasma radioactivity level in dams (0.52-1.30).

3.(ii).A.(2).4) *In vitro* serum protein binding rate (5.3.2.1.1, 5.3.2.1.2) and distribution rate in blood cells (4.2.2.3.1, 4.2.2.3.2)

The *in vitro* protein binding rates of ^{14}C-labeled favipiravir in mouse, rat, rabbit, dog, and human serum samples were almost constant in the concentration range examined (0.3-30 μg/mL), the rates were 8.3% to 10.9% in mouse serum, 53.7% to 57.9% in rat serum, 56.4% to 59.8% in rabbit serum, 23.9% to 31.5% in dog serum, and 53.4% to 54.4% in human serum. Following a single oral dose of 20 mg/kg of ^{14}C-labeled favipiravir to rats and monkeys, the distribution rate in blood cells ranged from 16.30% to 24.99% at 8 hours after dosing and then ranged from 36.30% to 73.26% at 24 hours post-dose and thereafter, showing an increase over time. The *in vitro* protein binding rate of M1 in human serum was 28.8% to 36.9% in the concentration range examined (0.5-50 μg/mL). The rates of binding of favipiravir to human serum albumin and α_1-acid glycoprotein were 65.0% and 6.5%, respectively, indicating that favipiravir mainly binds to albumin.

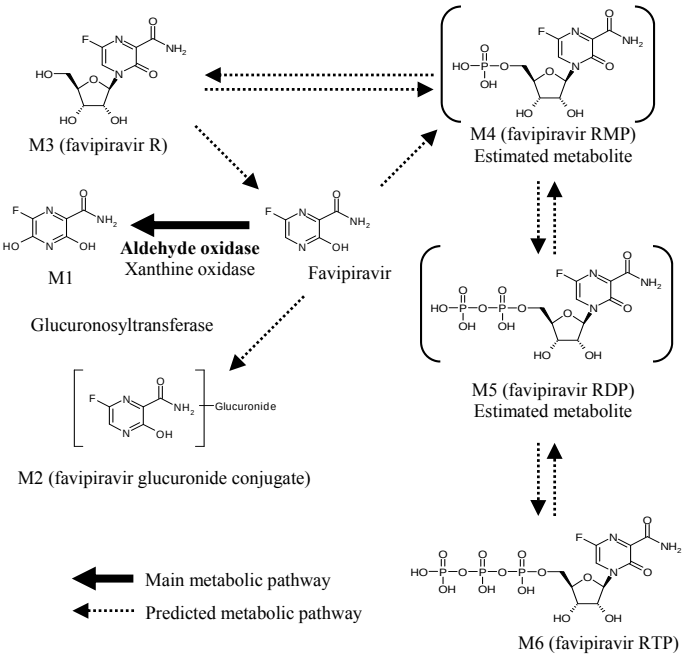
3.(ii).A.(3) Metabolism

3.(ii).A.(3).1) *In vivo* metabolism (4.2.2.2.2, 4.2.2.3.1, 4.2.2.3.2, 4.2.2.4.1 to 4.2.2.4.3)

The metabolites of favipiravir were investigated in the plasma, urine, bile, feces, and tissues from rats and monkeys receiving a single oral dose of ^{14}C-labeled favipiravir, and in the lungs of the mice receiving a single oral dose of favipiravir. The metabolic pathway of favipiravir predicted from the results is shown below.

[50] The radioactivity level in the testis of monkeys reached the maximum (8.15 μg eq./g) at 0.5 hours after dosing, which was lower than that in the plasma (39.5 μg eq./mL at 0.5 hours).

[51] $t_{1/2}$ of favipiravir in the plasma was 2.05 hours.



Predicted metabolic pathway

R: Ribosyl, RMP: Ribosyl monophosphate, RDP: Ribosyl diphosphate, RTP: Ribosyl triphosphate

A single oral dose of 20 mg/kg of ^{14}C-labeled favipiravir was administered to rats to investigate the main metabolites. At 0.5, 4, and 8 hours after dosing, favipiravir (accounting for 84.36%-93.53% of the radioactivity recovered) was mainly detected in the plasma, cerebrum, and skeletal muscle and favipiravir (28.33%-69.50%) and M1 (10.75%-34.44%) were mainly detected in the lungs, liver, kidney, and testis. M1 (urine, 43.03%; feces, 42.81%; bile, 51.99% [0-6 hours] and 55.04% [6-24 hours]) was mainly detected in the urine, feces, and bile at 0 to 24 hours after dosing. In the urine, M1 was followed by M2 (22.76%) and favipiravir (15.62%), and in the bile, M1 was followed by favipiravir (0-6 hours, 26.40%; 6-24 hours, 23.93%). A single oral dose of 20 mg/kg of ^{14}C-labeled favipiravir was administered to monkeys to investigate the main metabolites. Favipiravir (25.91%-53.16%) and M1 (36.20%-70.84%) were mainly detected in the plasma and testis at 0.5 and 4 hours after dosing, and M1 (0-8 hours, 95.35%; 8-24 hours, 75.13%) was mainly detected in the urine at 0 to 24 hours after dosing.

3.(ii).A.(3).2) *In vitro* metabolism

(a) *In vitro* metabolism study in human liver microsomes (5.3.2.2.2)

In an *in vitro* metabolism study of ^{14}C-labeled favipiravir (60 μmol/L) using human liver microsomes (protein concentration, 1 mg/mL), the percentage (over time) of favipiravir with and without the nicotinamide adenine dinucleotide phosphate (reduced form) (NADPH) generating system was 98.5% to 98.8% and 96.9% to 98.8%, respectively. No NADPH- or time-dependent favipiravir metabolism was observed.

(b) *In vitro* metabolism studies in human hepatic cytosol (5.3.2.2.2 to 5.3.2.2.3)

In the *in vitro* metabolism study of ^{14}C-labeled favipiravir (60 μmol/L) using human hepatic cytosol (protein concentration, 5 mg/mL), M1 was formed both with and without the NADPH generating system. The amount of M1 increased with the NADPH generating system, showing that favipiravir is metabolized to M1 mainly by NADPH-independent enzymes and partially by

NADPH-dependent enzymes in human hepatic cytosol.

In the *in vitro* metabolism inhibitory study of ^{14}C-labeled favipiravir (60 μmol/L) using human hepatic cytosol (protein concentration, 5 mg/mL), menadione and isovanillin (aldehyde oxidase [AO] inhibitors) and allopurinol (xanthine oxidase [XO] inhibitor) inhibited formation of M1 in a concentration-dependent manner (concentrations examined; 1, 10, 100 μmol/L), and the inhibition rate at 100 μmol/L was 73.6% for menadione, 52.6% for isovanillin, and 27.3% for allopurinol.

Correlation of the metabolism of favipiravir to M1 with the AO and XO activities was investigated in individual human hepatic cytosol samples (8 male subjects, 8 female subjects). As a result, the M1 formation activity is significantly correlated to the AO activity (correlation coefficient, 0.675; *P*-value, 0.004), showing that favipiravir is metabolized to M1 mainly by AO. On the other hand, there was no correlation of the M1 formation activity to the XO activity.

(c) *In vitro* metabolism study in human peripheral blood mononuclear cells (PBMC) (5.3.2.3.2)

In the *in vitro* metabolism study of favipiravir (300-1200 μmol/L) using human PBMC (pool of cells from 8 healthy adult male subjects), the results showed that favipiravir RTP is formed in PBMC in a concentration- and time-dependent manner. The $t_{1/2}$ of favipiravir RTP after removal of favipiravir was 2.05 hours.

3.(ii).A.(4) Excretion

3.(ii).A.(4).1 Urinary and fecal excretion (4.2.2.3.2, 4.2.2.5.1)

Following a single oral dose of 20 mg/kg of ^{14}C-labeled favipiravir to fasted male rats, the cumulative radioactivity excretion rate (mean) in urine, feces, and expired air up to 96 hours was 83.06%, 19.97%, and 0.04% of the dosed radioactivity, respectively. Following a single oral dose of 20 mg/kg of ^{14}C-labeled favipiravir to male monkeys, the cumulative radioactivity excretion rate in the urine and feces up to 24 hours was 91.14% and 4.32% of the dosed radioactivity, respectively.

3.(ii).A.(4).2 Biliary excretion (4.2.2.5.2)

Following a single oral dose of 20 mg/kg of ^{14}C-labeled favipiravir to fed male rats (bile duct-cannulated), the cumulative radioactivity excretion rate (mean) in the bile, urine, and feces at 48 hours was 16.17%, 59.88%, and 3.83% of the dosed radioactivity, respectively. Following a single oral dose of 20 mg/kg of ^{14}C-labeled favipiravir to normal animals, the fecal excretion rate (mean) of the radioactivity up to 48 hours was 19.64%, leading to the discussion that the fecal excretion mainly occurs through the bile.

3.(ii).A.(4).3 Excretion in milk (4.2.2.3.3)

Following a single oral dose of 20 mg/kg of ^{14}C-labeled favipiravir to lactating rats (13-14 days after delivery), the maximum milk radioactivity level was reached at 4 hours after dosing, followed by a decrease with time. C_{max}, AUC, time to maximum plasma concentration (t_{max}), and $t_{1/2}$ (mean) of the milk radioactivity were 69.9 μg eq./mL, 876 μg eq.·hr/mL, 4.00 hours, and 3.92 hours, respectively. C_{max}, AUC, and t_{max} of the milk radioactivity were higher than the plasma radioactivity (45.8 μg eq./mL, 329 μg eq.·hr/mL; 1.00 hour, 3.60 hours; respectively).

3.(ii).A.(5) Pharmacokinetic drug interactions

3.(ii).A.(5).1 Effects on human hepatic cytochrome P450 (CYP) (5.3.2.2.5 to 5.3.2.2.7)

In the *in vitro* CYP inhibitory study, the inhibitory effects of favipiravir against major human hepatic CYP isoforms (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4) activity were investigated in human liver microsome (favipiravir concentrations examined, 8-800 μmol/L). As a result, favipiravir inhibited the CYP2C8 activity in a concentration-dependent manner, with an IC_{50} of

477 μmol/L (74.9 μg/mL). The metabolic activities of the other CYP isoforms in the presence of favipiravir at the maximum concentration (800 μmol/L [126 μg/mL])[52] were all ≥60% of the control, and IC_{50} values were >800 μmol/L (126 μg/mL) for any isoforms. M1 (concentrations examined, 0.123-270 μmol/L), the major metabolite of favipiravir, decreased the CYP2E1 activity to 72.6% of the control at the maximum concentration (270 μmol/L [46.7 μg/mL]), but hardly inhibited activities of the other CYP isoforms with IC_{50} values of >270 μmol/L (46.7 μg/mL) for any isoforms.

In the *in vitro* CYP induction study, the effects of favipiravir on human hepatic CYP isoforms (CYP1A2, 2C9, 2C19, 3A4) activity were investigated in fresh human primary hepatocytes. As a result, favipiravir increased the expression of the CYP isoforms up to 1.7 times (mean) as compared with the control in the concentration range examined (8-800 μmol/L), and the CYP induction of favipiravir was ≤6.6% of those of the positive controls (omeprazole and rifampicin) for each CYP isoform.

3.(ii).A.(5).2 Effects on AO activity (5.3.2.2.8)

In the *in vitro* inhibitory study, the inhibitory effects of favipiravir against the AO activity were investigated in human hepatic cytosol. As a result, the residual metabolic activity (phthalazone formation activity) of phthalazine, a substrate of AO, decreased in a favipiravir concentration (20-6000 μmol/L)-dependent and preincubation time (0-60 minutes)-dependent manner, showing irreversible inhibition (mechanism based inhibition) of AO by favipiravir.

3.(ii).A.(5).3 Effects on XO activity (5.3.2.2.11)

In the *in vitro* inhibitory study, the inhibitory effects of favipiravir against the XO activity were investigated in human hepatic cytosol. As a result, favipiravir did not inhibit metabolism of 1-methylxanthine, a metabolite of theophylline which is a substrate of XO, in a concentration (30-3000 μmol/L)-dependent or preincubation time (5 minutes, 60 minutes)-dependent manner.

3.(ii).A.(5).4 Interaction with acetaminophen (5.3.2.2.9)

In the *in vitro* inhibitory study, the inhibitory effects of favipiravir and M1 against acetaminophen metabolism were investigated in human liver S9. As a result, favipiravir did not inhibit glucuronidation metabolism of acetaminophen in the concentration range examined (30-3000 μmol/L), but inhibited the sulfate conjugation metabolism (IC_{50} = 150 μmol/L [23.6 μg/mL]). M1 did not inhibit glucuronidation or sulfate conjugation metabolism of acetaminophen in the concentration range examined (3-300 μmol/L).

3.(ii).A.(5).5 Interaction with oseltamivir (5.3.2.2.10)

In the *in vitro* inhibitory study, the inhibitory effects of favipiravir and M1 against oseltamivir metabolism were investigated in human liver S9. As a result, favipiravir inhibited de-esterification of oseltamivir in the concentration range examined (30-3000 μmol/L) (residual activity at 3000 μmol/L [471 μg/mL], 71.7%), and the IC_{50} was ≥3000 μmol/L. M1 did not inhibit de-esterification of oseltamivir in the concentration range examined (3-300 μmol/L).

3.(ii).A.(6) Other pharmacokinetics

3.(ii).A.(6).1 P-glycoprotein (P-gp) (5.3.2.3.4, 5.3.2.3.5)

A membrane fraction from the human MDR1-expressing cells was used to investigate P-gp substrate recognition. As a result, favipiravir (5-1000 μmol/L) and M1 (1-500 μmol/L) did not increase the adenosinetriphosphatase (ATPase) activity in a concentration-dependent manner, suggesting that neither of them would act as a substrate of P-gp. In addition, investigation in LLC-

[52] The concentration was higher than the estimated maximum plasma concentration of favipiravir (78.9 μg/mL [Study JP111]) in humans treated with the proposed dosage regimen.

GA5-CoL300 cells[53] showed that favipiravir (5 mmol/L) and M1 (1 mmol/L) decreased the P-gp transportation activity of the standard substrate to 81.9% and 85.2% (mean) of the control, respectively.[54]

3.(ii).A.(6).2 Other (non-P-gp) transporters (5.3.2.3.6)

S2 cells and HEK293 cells were used to investigate non-P-gp transporters substrate recognition (human organic anion transporters [hOAT1, hOAT2, hOAT3, hOAT4], human organic cation transporters [hOCT1, hOCT2, hOCT3], human organic anion transport polypeptide [hOATP2], human urate transporter [hURAT1]). Results showed that favipiravir did not act as the substrate of any of the 9 transporters examined. In fact, favipiravir and M1 inhibited activities of various transporters. Favipiravir inhibited the transporters (hOAT1, hOAT3, and hURAT1)-mediated uptake of their standard substrates at 800 μmol/L (126 μg/mL), decreasing their uptake activity (mean) to 30.9%, 50.0%, and 65.7% of the control, respectively. M1 inhibited the transporters (hOAT1, hOAT3, and hURAT1)-mediated uptake of their standard substrates at 300 μmol/L (51.9 μg/mL), decreasing their uptake activity (mean) to 45.4%, 57.7%, and 31.0% of the control, respectively. Furthermore, favipiravir inhibited hURAT1 cells-mediated urate uptake concentration-dependently, while M1 enhanced the uptake concentration-dependently.

3.(ii).A.(6).3 Tissue coloring (4.2.2.3.1; Reference data, 4.2.2.7.1 to 4.2.2.7.3)

In various toxicity studies in mice, rats, and dogs [see 4.2.3.1.1 to 4.2.3.1.3, 4.2.3.2.1, 4.2.3.2.3], pale yellow or yellow fur, nails or foot pads were observed. Coloring on the fur was investigated. After administration of 7 oral doses of 300 mg/kg of favipiravir to shaved male rats, colored fur was observed only in the fur grown during the treatment period, and the colored part emitted fluorescence under UV irradiation. Autoradioluminography of the fur in shaved male rats receiving 5 oral doses of 300 mg/kg of ^{14}C-labeled favipiravir showed that the radioactive part matched with the colored part. Based on the above, to identify components in the colored fur, extraction in sodium hydroxide (10 mmoL/L), radiochromatography, and accrate mass spectrometry were performed. As a result, of multiple components extracted,[55] one was estimated to be a modified favipiravir component with the original fluoro group substituted by the mercapto group. The whole-body autoradioluminography on male rats 96 hours after single oral dose of 20 mg/kg of ^{14}C-labeled favipiravir showed that the radioactivity was mostly eliminated in all tissues except for the fur [see "3.(ii).A.(2).1 Tissue distribution in rats and monkeys"].

3.(ii).B Outline of the review by PMDA

3.(ii).B.(1) Sex differences

$AUC_{0\text{-}24}$ in female mice was 1.5 to 2.0 times that in male mice, showing a sex difference. PMDA thus asked the applicant to explain sex differences in pharmacokinetics of favipiravir, including study data in humans.

The applicant responded as follows:

Favipiravir 600 mg was orally administered to healthy adult US male and female subjects (aged 29-58 years, Studies US102 and US103), the plasma favipiravir concentration profile in male subjects was comparable to that in female subjects. Of the plasma pharmacokinetic parameters of favipiravir (geometric mean [coefficient of variation [CV%]) in male and female subjects, C_{max} was 20.4 (13.7) μg/mL and 24.2 (25.0) μg/mL, AUC was 45.2 (25.0) μg·hr/mL and 43.2 (27.2) μg·hr/mL, and $t_{1/2}$ (mean ± standard deviation [SD]) was 1.4 ± 0.2 hours and 1.2 ± 0.1 hours, respectively. As with the above, no clear differences between male and female subjects

[53] Human P-gp expressing LLC-PK1 cells (pig tubular cell strain)

[54] The concentration in the study was higher than that in the plasma predicted in humans treated in accordance with the proposed dosage regimen.

[55] Whether or not this ingredient has antiviral activity has not been investigated. The applicant explained that the estimated structure of the component in the colored fur could be actually that of a degradation product of the component formed during the extraction process because it was not extracted in organic solvent but extracted in sodium hydroxide solution.

were observed in any other pharmacokinetic parameter. Favipiravir 400 mg was also orally administered to Japanese healthy elderly male and female subjects (aged 65-77 years, Studies JP104 and JP107), the plasma favipiravir concentration profile in male subjects was comparable to that in female subjects, and no clear differences between male and female subjects were found in the pharmacokinetic parameters (C_{max}, 18.0 [25.8] μg/mL in male subjects, 20.1 [24.2] μg/mL in female subjects; AUC, 59.1 [23.0] μg·hr/mL in male subjects, 55.0 [23.6] μg·hr/mL in female subjects; $t_{1/2}$, 2.0 ± 0.3 hours in male subjects, 1.7 ± 0.3 hours in female subjects, etc.). On the other hand, following oral administration of favipiravir at doses of 15 to 500 mg/kg BID to mice, The AUC_{0-24} of favipiravir in females was 1.5 to 2.0 times higher than that in males, showing the sex difference. According to reports, favipiravir is metabolized to M1 by AO in human hepatic cytosol, and the AO activity in female mice is lower than that in male mice, showing the sex difference.[56,57] The $AUC_{M1}/AUC_{favipiravir}$ ratio in female mice was as low as 0.30 to 0.56 times that in male mice, indicating that the M1 formation activity in females was lower than that in males. The sex difference in mice was considered attributable to the sex difference in metabolism into M1, which is involved in the major elimination pathway of favipiravir. On the other hand, after repeated oral administration of favipiravir BID to rats, dogs, and monkeys, the plasma pharmacokinetics of favipiravir did not show clear sex differences [see "3.(ii).A.(1).3) Sex differences"]. According to the reports, in rats and humans, the AO activity did not indicate clear sex differences,[57,58] and dogs have little AO activity.[57,59]

Based on the above, the sex differences in plasma pharmacokinetics of favipiravir observed in mice is considered attributable to a mouse-specific difference in AO activity between males and females.

PMDA has accepted the above applicant's response, confirming that no clear sex differences are found in plasma pharmacokinetics of favipiravir in humans. The results was the same as shown in the currently available non-clinical study data (rats, dogs, monkeys).

3.(ii).B.(2) Distribution in target tissues

PMDA asked the applicant to explain the distribution of favipiravir and favipiravir RTP in target tissues of influenza virus infection.

The applicant responded as follows:

Following a single oral dose of 20 mg/kg of favipiravir to female mice (mice in the same strain as that of the influenza A/Osaka/5/70 [H3N2] virus infection model), the lung concentration of favipiravir RTP increased more slowly than the plasma concentration of favipiravir and reached the maximum level of 0.683 μg/g (1.29 μmol/kg) at 4 hours after dosing. At this time point, the molar concentration ratio of the plasma concentration of favipiravir RTP to the plasma concentration of favipiravir (9.11 μg/mL [58.0 μmol/L]) was 0.02. The $t_{1/2}$ of favipiravir RTP in the mouse lungs was 4.21 hours, indicating that favipiravir RTP in the lungs was more slowly eliminated than favipiravir in plasma ($t_{1/2}$, 2.05 hours). However, the cumulative rate {R:1/[1-exp (-ke·τ)]} at steady state was estimated to be 1.16, indicating that the lung concentration of favipiravir RTP following repeated doses would not remarkably increase compared with that after a single dose. The above cumulative rate was calculated based on the 1-compartment model, assumed from the lung concentration profile of favipiravir RTP, and the dosing interval (τ) of 12 hours, assumed from the elimination rate constant (ke, 0.165).

The concentration profile of favipiravir RTP in the non-lung respiratory system tissues such as upper respiratory tract (nasal cavity, pharynx, larynx) and lower respiratory tract (trachea,

[56] *Biochem.J.* 1999;341:71-80.
[57] *Bioorg Med Chem.* 2006;14:62-66.
[58] *IUBMB Life.* 2001;51:249-253.
[59] *IUBMB Life.* 1999;48:607-611.

bronchus) has not been investigated. Following oral administration of ^{14}C-labeled favipiravir at 20 mg/kg in rats, however, the radioactivity level in the trachea (20.5 μg eq./g at 0.5 hours) was comparable to that in the lungs (21.7 μg eq./g at 1 hour), showing the profile in parallel with the plasma radioactivity level profile. The whole-body autoradioluminograms of rats and monkeys at 0.5 hours after single oral dose of 20 mg/kg of ^{14}C-labeled favipiravir showed that radioactivity was distributed in tissues around the nasal cavity, pharynx, larynx, and trachea (only in monkeys) at a level lower than or comparable to that in the lungs. The distribution of favipiravir in the non-lung respiratory system tissues was considered comparable to that in the lungs. In addition, favipiravir RTP was considered to be formed in cells in the non-lung respiratory system tissues as well, because it was confirmed to be formed in human PBMC *in vitro*.

Furthermore, in order to clarify the relationship of the efficacy of favipiravir with exposure to favipiravir RTP, the relationships of the lung concentration of favipiravir RTP with the therapeutic effect of favipiravir and inhibitory effect against the lung virus replication were investigated. The results have indicated that the therapeutic effect 21 days after the infection in mice infected with influenza virus [A/Osaka/5/70(H3N2)] [see 4.2.1.1.16] will be dependent on the duration in which a certain lung concentration of favipiravir RTP is maintained;[60] and the inhibitory effect against the lung virus replication 48 hours after the infection[61] will be dependent on C_{min}[62] of the lung concentration of favipiravir RTP. These PK/PD parameters are considered to be useful indicators of the clinical efficacy. However, favipiravir RTP is chemically and biologically unstable and it is impossible to determine the human lung concentration of favipiravir RTP. The lung concentration of favipiravir RTP in humans treated with favipiravir in accordance with the proposed dosage regimen was, thus, estimated from the measured plasma concentrations of favipiravir through the simulation model in which the non-binding rate of favipiravir in blood, distribution in the lungs, and metabolism into favipiravir RTP were taken into account. As a result, C_{min} up to 48 hours after the first dose on Day 1 mostly remained ≥0.3 μmol/kg, and T >0.4 μmol/kg was also found at ≥50%.

The above results indicated that the estimated lung concentration of favipiravir RTP in humans met the indicators of PK/PD parameters based on the lung concentration of favipiravir RTP in mice, showing that the efficacy of favipiravir at the proposed dosage regimen can be expected.

PMDA considers as follows:
It has been confirmed that in animals treated with ^{14}C-labeled favipiravir, the radioactivity, as revealed by the whole-body autoradioluminography, was distributed in the respiratory system tissues other than the trachea and lungs, although the radioactivity level profiles in these tissues have not been investigated. According to the simulation model in which the non-binding rate of favipiravir in blood, distribution in the lungs, and metabolism into favipiravir RTP were taken into account, the lung concentration of favipiravir RTP in humans treated with favipiravir at the proposed dosage regimen is predicted to reach the therapeutic level. In addition, the distribution in the trachea and lungs was confirmed to be comparable based on the radioactivity level profile. It is thus expected that therapeutic concentration can be reached in these tissues. This model is, however, mainly based on the assumption,[63] and the derived result is pure speculation. It is, therefore, necessary to determine the clinical efficacy of favipiravir in patients with influenza virus infection based on the clinical data.

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[60] In the case of T >0.4 μmol/kg was ≥50%, the survival rate on 21 days after the infection was ≥90% (correlation coefficient, 0.9958).

[61] *Int J Infect Dis.* 2008;12:E170-171.

[62] C_{min} ≥0.3 μmol/kg: The replication inhibition rate of the lung virus 48 hours after the infection was ≥90% (correlation coefficient, 0.9376)

[63] Hypothesis 1: Enzyme involved in conversion and degradation into favipiravir RTP in the lung is the same as that in PBMC (the Michaelis-Menten constant [Km] of the enzyme in the lung is the same as that in PBMC). Hypothesis 2: The ratio of the enzyme amount in the lung with respect to that in PBMC in humans is the same as the ratio in mice (the ratio of the maximum velocity [Vmax] of the enzyme in PBMC with respect to that in the lung in humans is the same as the ratio in mice).

3.(ii).B.(3) Tissue distribution following repeated doses

In consideration of the effect of repeated oral doses of favipiravir on the plasma pharmacokinetics, which was observed in monkeys, PMDA asked the applicant to explain the possibility that the tissue distribution following the repeated oral doses is different from that following the single oral dose (such as accumulation in specific tissues).

The applicant responded as follows:
Following a single oral dose of 20 mg/kg of ^{14}C-labeled favipiravir to rats, the radioactivity in the Harderian gland, adrenal gland, epididymis, and fur was more slowly eliminated ($t_{1/2}$, 20.8-24.3 hours) than that in the liver and kidney, which changed in parallel with the plasma radioactivity level. In the fur, the maximum concentration was reached at 24 hours and $t_{1/2}$ was not determined, but the radioactivity level at 24 hours decreased to approximately 50% by 96 hours post-dose. The cumulative rates in the Harderian gland, adrenal gland, epididymis, and fur estimated from their radioactivity level profiles following single administration are considered to be higher than those in the other tissues. The $t_{1/2}$ of the radioactivity in the Harderian gland (24.3 hours), which was the longest, was approximately 2 times the dosing interval in the repeat-dose toxicity study. The tissue concentration following repeated doses is thus considered to be not remarkably different from the value estimated from the data following the single dose. In the 1-month repeat-dose toxicity study in rats (dose, 13-200 mg/kg/day), no histopathological changes were found in the Harderian gland, adrenal gland, epididymis, or fur [see "3.(iii).A.(2).1) One-month oral dose study in rats"].

Following a single oral dose of 20 mg/kg of ^{14}C-labeled favipiravir to monkeys, the radioactivity level in the bone at 24 hours post-dose was 44.0% of the maximum concentration; the radioactivity tended to be more slowly eliminated in the bone than in the plasma. When favipiravir was orally administered BID at 50 to 150 mg/kg for 14 days to monkeys, the exposure ($AUC_{0\text{-}24}$) to favipiravir in the plasma on the day of the final dose increased to 4.4 to 6.1 times that on Day1; the plasma pharmacokinetics was affected by the repeated doses. The tissue favipiravir concentration in animals treated with repeated doses of favipiravir was considered to be higher than the value estimated from the data from animals treated with single-dose favipiravir. On the other hand, the change in plasma pharmacokinetics due to repeated doses, associated with the decrease in the $AUC_{M1}/AUC_{favipiravir}$ ratio, is possibly caused by decreased metabolic clearance of favipiravir. The tissue distribution of favipiravir was thus considered to be dependent only on the change in plasma favipiravir concentrations. The radioactivity levels in all tissues except for the bone changed in parallel with the plasma radioactivity level. Therefore, the tissue favipiravir concentration following 14-day treatment with favipiravir may increase in line with the change in plasma pharmacokinetics and reach 6 times that following the single dose, as in the case with the plasma favipiravir concentration. In addition, as the radioactivity in the bone was more slowly eliminated than that in other tissues, the increase in favipiravir concentration in the bone is possibly greater than that in the other tissues. However, in the 2-week repeat-dose toxicity study in monkeys (dose, 100-300 mg/kg/day), no histopathological changes were observed in the bone [see "3.(iii).A.(2).3) Two-week oral dose study in monkeys"].

Although the change in plasma pharmacokinetics following repeated oral doses possibly increases the tissue concentration to the level higher than that following single oral dose, the toxicity study data have indicated that the accumulation of the drug in the tissue is unlikely to cause histopathological changes in the dose range examined (50-150 mg/kg BID for 14 days). PMDA thus has concluded that the above applicant's view is acceptable.

3.(iii) Summary of toxicology studies

3.(iii).A Summary of the submitted data

Toxicity studies of favipiravir conducted include single-dose toxicity studies, repeat-dose toxicity studies, genotoxicity studies, reproductive and developmental toxicity studies, and other toxicity

studies (immunotoxicity studies, phototoxicity studies, testis toxicity studies, juvenile animal toxicity studies, toxicity studies for concomitant use with anesthetics, toxicity studies of metabolites and impurities).

3.(iii).A.(1) Single-dose toxicity (4.2.3.1.1 to 4.2.3.1.3; Reference data, 4.2.3.2.4, 4.2.3.1.5)

Single-dose toxicity was evaluated in oral dose studies and intravenous dose studies in mice as well as in oral dose studies in rats and dogs. Acute toxicity in monkeys was evaluated in the dose-finding study [see Reference data, 4.2.3.2.4], which was a 2-week repeated oral dose toxicity study. The approximate lethal dose was determined to be >2000 mg/kg in oral and intravenous dose studies in mice, >2000 mg/kg in oral dose studies in rats, and >1000 mg/kg in dogs and monkeys. Findings in oral dose studies include pale yellow fur or nails in both mice and rats and reduction in body weight gain in rats at ≥500 mg/kg, and transient reduction in body weight gain in both mice and rats and stained fur in the abdomen and perianal region, and transient weight loss in rats at 2000 mg/kg. Findings in intravenous dose studies in mice include pale yellow fur at ≥1000 mg/kg and decreased locomotor activity and transient weight loss at 2000 mg/kg. Data from studies in dogs were submitted as the reference data. According to the data, decreased locomotor activity, vomiting, and weight loss occurred in the animals receiving a single oral dose of 1000 mg/kg, but tended to be reversible on Day 6 or 8. Regarding acute toxicity in monkeys, in the dose-finding study for the 2-week repeated oral dose toxicity study, no toxicological changes were observed on the first day of the BID treatment at 1000 mg/kg/day, but on the following day and thereafter, decreased locomotor activity and vomiting were observed.

3.(iii).A.(2) Repeat-dose toxicity study

To evaluate repeat-dose toxicity, oral dose studies in rats and dogs (1 month) and oral dose study in monkeys (2 weeks) were conducted. Major findings following administration of favipiravir included effects on the hematopoietic tissues (decreases in erythrocyte-related parameters, associated with decreased myelopoiesis), effects on the liver (increases in alkaline phosphatase [ALP], alanine aminotransferase [ALT], aspartate aminotransferase [AST], and total bilirubin, increased liver weight, and vacuolization in hepatocytes), and testis toxicity. To evaluate the effects on the hematopoietic tissues, repeated oral dose toxicity studies (3 days, 7 days, 2 weeks, 1 month, and 3 months) in rats were conducted. The AUC[64] value in healthy adult Japanese male subjects[65] treated with favipiravir in accordance with the proposed dosage regimen (oral administration of 1200 mg [first dose] and 400 mg [second dose] on Day 1, followed by 400 mg/dose BID from Day 2 to Day 5) was compared with the $AUC_{0\text{-}t}$[66] values obtained at the no observed adverse effect levels (NOAEL) (rats, 32 mg/kg/day; dogs, 10 mg/kg/day; monkeys, 100 mg/kg/day) in the oral dose studies. The AUC in humans was approximately 0.58 to 0.87 times that in rats, approximately 0.23 to 0.27 times that in dogs, and approximately 0.9 to 1.3 times that in monkeys, and the C_{max}[67] in humans was approximately 0.75 to 0.87 times that in rats, approximately 0.21 to 0.24 times that in dogs, and approximately 2.1 to 2.2 times that in monkeys.

3.(iii).A.(2).1) One-month oral dose study in rats (4.2.3.2.1)

Favipiravir was orally administered BID to SD rats at a dose of 0 (vehicle, 0.5% methylcellulose solution), 13, 32, 80, or 200 mg/kg/day for 1 month. Decreases in phospholipid (PL) and total cholesterol (TC) were observed in the ≥32 mg/kg/day groups, but these changes in the 32 mg/kg/day group were determined to have no toxicological significance, because no related other changes (decreased food consumption, findings suggesting liver disorder, etc.) were observed, and they were mild. On the other hand, changes in PL and TC observed in the ≥80 mg/kg/day groups were accompanied by the related other changes (decreased food consumption, reduction in body weight gain, increased ALP or ALT) and they were therefore considered to be of

[64] Area under the plasma concentration-time curve per day
[65] Multiple high-dose study (Study JP111)
[66] Area under the plasma concentration-time curve on day of the final dose
[67] Maximum plasma concentration

toxicological significance. Findings in the ≥80 mg/kg/day groups included reduction in body weight gain, pale yellow fur and nails, decreases in hemoglobin (Hb) and hematocrit (Ht), increased ALP as well as decreased lung weight. The pale yellow fur and nails were considered to be of little toxicological significance, because these findings were not accompanied by shedding of the fur or nails or their abnormal elongation, or histopathological changes. Death occurred in 1 of 30 animals in the 200 mg/kg/day group. Findings in the dead animal included congestion and edema in dark red lungs, atrophy of the thymus and spleen, ascites and abdominal subcutaneous oedema, bladder distension (brown urine retention), hemorrhage and inflammatory cell infiltration in dark red urinary bladder, vesicular gland, and prostate, renal tubular dilation, oedema in the prostate gland, inflammatory cell infiltration in the abdominal muscle, and dentin degeneration in the incisor. Urine retention in the urinary bladder was found in this animal, which suggested that urination disorder caused oedema, leading to circulatory disturbance and then resulting in death. In the surviving animals at the dose of 200 mg/kg/day, findings included fractured incisor and decreased food consumption; urinalysis showed decreased urinary sodium (Na), potassium (K) and chlorine (Cl); hematology showed decreases in red blood cell (RBC) count and reticulocyte count, prolongations of prothrombin time (PT) and activated partial thromboplastin time (APTT); bone marrow examination showed increases in granulocyte ratio and ratio of granulocytes to erythroblasts (M/E ratio); and clinical chemistry showed increases in ALT, total bilirubin, albumin, albumin/globulin (A/G) ratio, triglyceride (TG), and Na, decreases in total protein (TP) and K, and changes in protein fraction. Additional findings included decreases in pituitary gland, salivary gland, thymus, kidney, adrenal gland, testis, epididymis, and ovary weights and increased cecum weight. Histopathological findings included decreased myelopoiesis, cyst formation in the dental pulp/odontoblast layer of the incisor, dentin degeneration, inflammatory cell infiltration in the dental pulp, and necrotic tissue. The effects on the incisor were considered to be related to the tooth type of rats, which have open-rooted teeth continuously growing throughout the life of the animal due to mitotic proliferation of tooth germ, because such effects were not found in dogs or monkeys (rooted teeth). The risk in humans (rooted teeth) is thus considered low. All of these changes were reversible or tended to be reversible during the 1-month recovery period. Based on the above, the NOAEL in this study was determined to be 32 mg/kg/day.

3.(iii).A.(2).2) One-month oral dose study in dogs (4.2.3.2.3)

Favipiravir was orally administered to beagle dogs at a dose of 0 (gelatin capsule), 10, 30, or 100 mg/kg/day BID for 1 month. In addition, in the high-dose group (100 [300] mg/kg/day), animals received favipiravir at 300 mg/kg/day until Day 6 and then 100 mg/kg/day on Day 7 and thereafter. In the ≥30 mg/kg/day groups, vomiting, weight loss, decreased food consumption, and decreased reticulocyte count were the most prominent in Week 1 or 2, but these changes tended to be reversible thereafter. Clinical chemistry showed increased creatinine. Findings in the ≥100 mg/kg/day groups were loose stool or diarrhea, white fur, and pale yellow foot pads; hematology showed increases in white blood cell count (WBC), neutrophil count, and fibrinogen as well as prolonged APTT; and clinical chemistry showed increases in AST, ALT, lactate dehydrogenase (LDH), TG, and blood urea nitrogen (BUN). In addition, findings possibly associated with the deteriorated clinical condition (weight loss, decreased food consumption) included decreased respiratory rate and prolongations of QT and QTc as well as decreases in calcium (Ca) and K. The pale yellow fur and foot pads were considerd to be of little toxicological significance, because these findings were not accompanied by shedding of the colored tissues or their abnormal elongation, or histopathologically abnormal changes. In the 100 [300] mg/kg/day group, 1 of 5 animal was sacrificed in a moribund condition on Day 11, and another one was found dead on Day 25. Findings in these animals were decreases in food consumption and body weight and histopathology findings included hemorrhagic necrosis and inflammatory cell infiltration in the lungs, hemorrhage in the stomach or intestine, bilateral seminiferous epithelial degeneration and sperm hypoplasia in the testis, atrophy of the prostate and epididymis, epithelial degeneration and dilation of the renal tubule, and hemorrhage in the urinary bladder. In addition, findings possibly

associated with the deteriorated clinical condition were bacterial infection (lungs, foot pads), atrophy of the thymus and pancreas, hypoplasia of the sternal bone marrow, splenic white pulp atrophy and decreased extramedullary hematopoiesis of the spleen, lymphocyte hypoplasia in the lymph node, clear gastric chief cells, and decreased glycogen in the hepatocytes. Other changes in the 100 [300] mg/kg/day group (including surviving animals) were increased urine bilirubin; hematology showed decreases in RBC, Hb, Ht, lymphocytes, and eosinophils and prolonged PT; and clinical chemistry showed changes in protein fraction. Furthermore, findings possibly associated with the deteriorated clinical condition were decreases in respiratory rate and pulse rate, prolonged ECG PR interval (PR), decreased urine volume, increased urine specific gravity, and decreases in ALP, creatine kinase (CK), TP, albumin, A/G ratio, TG, and electrolyte as well as decreased prostate weight. In the testis in 1 of 5 animals subjected to necropsy at the end of the treatment period, bilateral seminiferous epithelial degeneration and severe bilateral sperm hypoplasia as well as atrophy of the prostate were observed. All of these changes were reversible or tended to be reversible during the treatment period or 1-month recovery period. Based on the above, the NOAEL in this study was determined to be 10 mg/kg/day.

3.(iii).A.(2).3) Two-week oral dose study in monkeys (4.2.3.2.5)

Favipiravir was orally administered to cynomolgus monkeys at a dose of 0 (solvent, 0.5% methylcellulose solution), 100, 200, or 300 mg/kg/day BID for 2 weeks. Findings in the ≥200 mg/kg/day groups were decreases in body weight and food consumption; hematology showed increased fibrinogen; and clinical chemistry showed increased TG. Findings in the 300 mg/kg/day group were salivation; urinalysis showed decreased urinary Cl, decreased urine pH, increased urine specific gravity, and increased ketone body; hematology showed prolonged PT and decreases in RBC, Hb, and Ht; clinical chemistry showed increases in AST and ALT and decreases in TC, blood glucose, and albumin; and increased liver weight, vacuolization of the hepatocytes, and decreased mucus of the mucosal epithelial in the cecum. Changes in hematology and clinical chemistry parameters were reversible after the 4-week recovery period, and other changes were reversible after the 8-week recovery period. There were no effects on the reproductive organs (abnormalities in the blood testosterone and inhibin B concentration as well as testis, epididymis, vesicular gland, prostate, and ovary weights, and histopathological abnormalities in the reproductive organs). Based on the above, the NOAEL in this study was determined to be 100 mg/kg/day.

3.(iii).A.(2).4) Oral dose studies in rats (Reference data, 4.2.3.2.7 to 4.2.3.2.13)

To investigate the effects on the hematopoietic tissues, 3-day, 7-day, and 2-week repeated oral dose toxicity studies were conducted in SD rats. Also, to evaluate changes in reticulocyte count and blood erythropoietin (EPO) over time, 1-month repeated oral dose toxicity study as well as 3-month repeated oral dose toxicity study were conducted.

In the 3-day dose study, decreases in reticulocyte count and myeloid erythroblast cells ratio were observed in the 1000 mg/kg/day group but resolved after 7 days of withdrawal. In the 7-day dose study, findings included decreased reticulocyte count in the ≥300 mg/kg/day groups and myeloid hypoplasia and changes in the liver in the 1000 mg/kg/day group. In the 2-week dose study, decreases in reticulocyte count and myeloid erythroblast cells ratio as well as decreased hematopoiesis in the spleen were observed in the 300 mg/kg/day group, but these findings were resolved after 2 weeks of withdrawal. In this study, the drug was administrated once or twice daily, but the changes in administration frequency did not affect the toxicity. In the 1-month dose study, the reticulocyte count decreased to approximately half of that in the control group after 1 week of treatment in the 300 mg/kg/day group, but did not further decrease at Week 2 and thereafter and then reached the level comparable to that in the control group (the reticulocyte count gradually decreased with the growth) at the end of the treatment period. On the other hand, there was no effect on the blood EPO concentration. In the 3-month dose study, findings included decreases in RBC and Hb, increased ALT, and sperm cells retained in the testis in the ≥100

mg/kg/day groups and death in 1 of 5 animals, decreased Ht and effect on the testis in the 300 mg/kg/day group.

3.(iii).A.(3) Genotoxicity (4.2.3.3.1.1 to 4.2.3.3.1.3, 4.2.3.3.2.1 to 4.2.3.3.2.3; Reference data, 4.2.3.3.1.4, 4.2.3.3.1.5, 4.2.3.3.2.4, 4.2.3.2.5)

To evaluate the genotoxicity, bacterial reverse mutation assay and unscheduled DNA synthesis assay in rat hepatocytes following oral administration (up to 2000 mg/kg/day) were conducted. Both assays showed negative results.

In the chromosomal aberration assay in mammalian cultured cells (Chinese hamster lungs [CHL/IU] cells), favipiravir induced chromosomal aberration. Furthermore, in the mouse lymphoma TK assay, favipiravir induced mutations irrespective of the metabolic activation. To elucidate the mechanism, mechanistic studies were conducted [see Reference data, 4.2.3.3.1.4, 4.2.3.3.1.5]. As a result, when fewer cells were treated with favipiravir, and when nucleic acids precursors were added to the test system, no structural chromosome aberrations were induced. In mammalian cultured cells treated with favipiravir, imbalance among amounts of intracellular nucleic acids (deoxyadenosine triphosphate [dATP], deoxyguanosine triphosphate [dGTP], deoxycytidine triphosphate [dCTP], deoxythymidine triphosphate [dTTP]) was observed. The chromosomal aberrations induced by favipiravir were considered attributable to the effect mediated by the imbalanced intracellular nucleic acid pool, but not to the direct DNA damaging effect, as in the case with similar antiviral nucleoside analogs.[68,69,70]

In the myeloid micronucleus assay in rats receiving oral favipiravir, those treated at 1000 mg/kg/day for 2 days showed negative results, but those treated at 2000 mg/kg/day for 2 days in which death occurred (1 of 5 animals) showed mildly increased frequency of protoerythrocytes with micronucleus. The effect of favipiravir on rat body temperature was investigated. In animals treated at 2000 mg/kg/day for 2 days, the body temperature decreased [see Reference data, 4.2.3.3.2.5], and abnormalities such as respiratory irregularity and lateral position suggesting hypoxic condition were observed. Since decreased body temperature and hypoxic condition increased the frequency of secondary micronucleus development according to reports,[71,72,73] the genotoxicity risk of favipiravir has been considered low. In the 2-week repeated oral dose toxicity study in mice [see Reference data, 4.2.3.2.6], the frequency of protoerythrocytes with micronucleus in the myeloid tissue was not increased in animals treated at 1000 mg/kg/day.

3.(iii).A.(4) Carcinogenicity

No carcinogenicity studies have been conducted for the following reasons: favipiravir is planned to be used for a short period in clinical setting; no precancerous lesions were noted in the repeat-dose toxicity studies; there was no accumulation or persistence of favipiravir in any specific tissue [see 4.2.2.3.1, 4.2.2.3.2]; and there were no local tissue reactions attributable to long-term retention of unchanged favipiravir or the metabolites in the repeat-dose toxicity studies. Of the genotoxicity studies [see "3.(iii).A.(3) Genotoxicity"], the chromosomal aberration assay in mammalian cultured cells and mouse lymphoma TK assay showed positive results, but the study for elucidation of the mechanism [see Reference data, 4.2.3.3.1.4, 4.2.3.3.1.5] suggested that the positive results would be attributable to an indirect effect based on the imbalanced intracellular nucleic acid pool. The positive result in the rat micronucleus assay is considered attributable to decreased body temperature and hypoxic condition. Based on these discussions and other

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68 "Copegus tablet 200 mg" Summary of product applications for manufacturing approval (2.4 Nonclinical Overview, 2005:1-42)
69 "Famciclovir and Famvir tablet 250 mg" Summary of product applications for manufacturing approval (d. Toxicity, 2008:1-103)
70 *Mutat Res.* 1994;318:1-64.
71 *Mutat Res.* 2000;471:81-86.
72 *Mutat Res.* 2007;627:78-91.
73 *Jikeikai Medical Journal.* 1993;108:71-78.

genotoxicity data, favipiravir is unlikely to develop genotoxicity in the body. Furthermore, pyrazinamide, which is structurally similar to favipiravir, induced chromosomal aberration presumably by inhibiting synthesis of nucleic acid precursors,[74,75] but tested negative for carcinogenicity.[76] Based on these results, favipiravir was considered unlikely to have carcinogenic potential.

3.(iii).A.(5) Reproductive and developmental toxicity

To evaluate reproductive and developmental toxicity, studies of fertility and early embryonic development to implantation in rats, embryo-fetal development studies in mice, rats, and rabbits, and a rat study on pre- and postnatal development, including maternal function were conducted. As the reference data, the results from embryo-fetal development studies in monkeys were submitted. In a study of fertility in rats, effects on the testis and sperm and decreased fertility were observed in males and anestrus was observed in females at the high-dose. In the embryo-fetal development studies, findings indicative of teratogenicity were noted in mice, rats, rabbits, and monkeys, and decreases in live fetal body weight and in the number of live fetuses were found. In the study on pre- and postnatal development, including maternal function, a decrease in the number of live offspring, an increase in the number of dead offspring, a decrease in the survival of the offspring at 4 days after birth, and a reduction in body weight gain of the offspring were noted, but there were no effects on the other growth and development of the F_1 offspring and F_2 fetuses. Placental transfer and milk excretion of favipiravir in rats [see "3.(ii).A.(2).3) Distribution in fetuses" and "3.(ii).A.(4).3) Excretion in milk"] have been noted.

3.(iii).A.(5).1) Fertility and early embryonic development to implantation

(a) Study in rats (4.2.3.5.1.1 to 4.2.3.5.1.2)

Favipiravir was orally administered BID to male SD rats at a dose of 0 (vehicle, 0.5% methylcellulose solution), 30, 60, 100, or 200 [300] mg/kg/day (in the 200 [300] mg/kg/day group, the dose was started at 300 mg/kg/day but decreased to 200 mg/kg/day on Day 35 and thereafter) and to female SD rats at a dose of 0 (vehicle, 0.5% methylcellulose solution), 30, 60, 100, or 200 mg/kg/day. The treatment in males was continued for 98 to 100 days, from 63 days before mating through the mating period until the day before necropsy, while that in females was continued from 14 days before mating through the mating period until Gestation day 7. During the treatment period, males and females treated at the same dose were mated, and cesarean section was performed on Gestation day 20. General toxicological effects on the parent animals observed in the ≥30 mg/kg/day groups included pale yellow to yellow fur, nails, or tail and reduction in body weight gain as well as, in males, decreases in testis and epididymis weights and prostatitis. The pale yellow to yellow fur, nails, or tail was considered to be of little toxicological significance, because there were no disorders, such as shedding of the colored tissues and their abnormal elongation; and in the repeat-dose toxicity studies in rats and dogs [see "3.(iii).A.(2).1) One-month oral dose study in rats" and "3.(iii).A.(2).2) One-month oral dose study in dogs"], no histopathological changes were found in the colored tissues. In the ≥60 mg/kg/day groups, fractured incisor and decreased food consumption in females during the gestation period were observed; in the ≥100 mg/kg/day groups, decreased type A spermatogonium count per Sertoli cell was noted in the quantitative analysis of the seminiferous tubule at each stage. In the 200 [300] mg/kg/day group, of 24 animals, 1 animal was sacrificed in a moribund condition, and 10 animals died, and decreasing trends of the counts of spermatocytes at the pre-leptotene stage, spermatocytes at the pachytene stage, and sperm cells were observed. The effects on the reproductive function in parent animals observed included decreases in sperm vitality and motile sperm rate in males and increased preimplantation loss rate in females in the ≥30 mg/kg/day groups, and increased incidence of sperm morphological defects in males in the ≥60 mg/kg/day

[74] *Mutat Res.* 1977;48:215-224.
[75] *Mutat Res.* 1994;321:1-5.
[76] *Natl Cancer Inst Carcinog Tech Rep Ser.* 1978;48:1-107.

groups. In the ≥100 mg/kg/day groups, the numbers of fertile males and pregnant females decreased. In the 100 mg/kg/day and 200 mg/kg/day groups each including 24 females, 2 females and 0 females, respectively, became pregnant. In the 200 mg/kg/day group, the estrous cycle observation showed females with continuous anestrus. There were no effects on the mating ability. Regarding the effects on the offspring, increased postimplantation mortality associated with the increased numbers of early embryonic losses and resorbed embryos were noted in the ≥30 mg/kg/day groups. In the ≥30 mg/kg/day groups, decreases in live fetal count and live fetal body weight as well as increased sex ratio (increased percentage of male fetuses) were noted, but no abnormalities were found on the external of the live fetuses. In the ≥100 mg/kg/day groups, there were no live fetuses. Based on the above, the NOAELs were determined to be <30 mg/kg/day all for general toxicity and reproductive function of parent animals as well as development of the offspring.

(b) Study in rats (supplemental study) (4.2.3.5.1.3)

In the study of fertility and early embryonic development to implantation in rats [see "3.(iii).A.(5).1).(a) Study in rats"], the fertility of the parent animals and development of the offspring were affected at the lowest dose of 30 mg/kg/day. A supplemental study was conducted to investigate which of the male and female parent animals were responsible for the effects. Favipiravir was orally administered BID to male and female SD rats at a dose of 0 (vehicle, 0.5% methylcellulose solution), 3, 10, or 30 mg/kg/day followed by mating with untreated animals. The treatment was continued in males for 78 to 80 days, from 63 days before mating through the mating period until the day before necropsy, while it was continued in females from 14 days before mating through the mating period until Gestation day 7. Cesarean section was performed on Gestation day 20. In the male treatment study, decreased epididymis weight was noted in the 30 mg/kg/day group, but there were no effects on the sperm, reproductive organs at the histopathological examination, mating rate, or fertility rate, and there were no effects on the embryo-fetal development at the cesarean section of the mated non-treated females. In the female treatment study, a reduction in body weight gain noted on Gestation day 7 and thereafter as the effect on the parent animals in the 30 mg/kg/day group, but there were no effects on the mating rate or gestation rate. The effects on the offspring included decreased live fetal body weight in females in the 10 mg/kg/day group, increased postimplantation mortality, a decrease in the number of live fetuses, increased sex ratio, decreased live fetal body weight in males and females, and increased placenta weight for males in the 30 mg/kg/day group. In both male and female treatment studies, pale yellow fur or nails were found in parent animals treated with favipiravir at 30 mg/kg/day, but considered to be of little toxicological significance, because there were no abnormal findings, such as shedding of the colored tissues and their abnormal elongation; and because no histopathological changes were found in the colored tissues in the repeat-dose toxicity studies in rats and dogs [see "3.(iii).A.(2).1) One-month oral dose study in rats" and "3.(iii).A.(2).2) One-month oral dose study in dogs"]. Based on the above, the NOAELs were determined to be 30 mg/kg/day in males and 10 mg/kg/day in females for general toxicity, and 30 mg/kg/day in both males and females for reproductive function. The NOAELs for development of the offspring were 30 mg/kg/day and 3 mg/kg/day, respectively, in male and female treatment studies.

(c) Study in rats (comparison of the treatment timing, before and after gestation) (Reference data, 4.2.3.5.1.4)

In the supplemental study in rats of the study of fertility and early embryonic development to implantation [see "3.(iii).A.(5).1).(b) Study in rats (supplemental study)"], increased postimplantation mortality and decreased live fetal body weight were observed in females treated with favipiravir 30 mg/kg/day. This study was conducted to investigate the relationship between the toxicity on embryo-fetal development and treatment timing. Favipiravir was orally administered BID to pregnant SD rats at a dose of 0 (vehicle, 0.5% methylcellulose solution) or 30 mg/kg/day. Animals were treated with favipiravir (i) from 14 days before mating throughout

the mating period, (ii) from Gestation day 0 to Gestation day 7, (iii) from Gestation day 0 to Gestation day 3, and (iv) from Gestation day 4 to Gestation day 7, and cesarean section was performed on Gestation day 20. As a result, no abnormalities were found in fetuses in the animals treated (i) from 14 days before mating throughout the mating period and (iv) from Gestation day 4 to Gestation day 7. In fetuses in the animals treated (ii) from Gestation day 0 to Gestation day 7, a decrease in the number of live fetuses, increased postimplantation mortality, decreased live fetal body weight, and increased sex ratio were noted, and in those treated (iii) from Gestation day 0 to Gestation day 3, decreased live fetal body weight was observed. Based on the above results, embryo-fetal abnormalities were not attributable to the treatment before mating but to the treatment during the gestation period (early pregnancy period).

(d) Study in rats (comparison with antiviral drugs) (Reference data, 4.2.3.5.1.5)

Ribavirin (RBV) and valacyclovir (VACV) are existing antiviral nucleoside analogs which have been reported to affect early embryonic development in non-clinical studies. To compare the effects on early embryonic development, RBV (30, 100 mg/kg/day), VACV (100, 200, 400 mg/kg/day) or favipiravir (10, 30 mg/kg/day) was orally administered BID to pregnant SD rats from Gestation day 0 to Gestation day 7 followed by cesarean section on Gestation day 20. There were no effects of favipiravir on maternal animals, a reduction in body weight gain and an increase in the number of maternal animals with all embryos resorbed were observed in the RBV 100 mg/kg/day group, and, a reduction in body weight gain was observed in the VACV 400 mg/kg/day group. The effects on embryo-fetal development observed in the favipiravir 30 mg/kg/day group included increases in postimplantation loss rate and early embryonic mortality, increased sex ratio, and decreased live fetal body weight. On the other hand, in the RBV ≥30 mg/kg/day groups, increases in postimplantation loss rate and early embryonic mortality, decreased live fetal body weight, and increased incidence of fetal external abnormalities were observed, and in the VACV 400 mg/kg/day group, increases in postimplantation loss rate and early embryonic mortality and decreased live fetal body weight were observed, but there were no changes in the incidence of external abnormalities. The exposures (AUC) in rats at the doses of favipiravir 30 mg/kg/day, RBV 30 mg/kg/day, and VACV 400 mg/kg/day were 0.79, 0.085, and 4.9 times, respectively, the exposure in humans (mean AUC, for favipiravir, the value in humans who received favipiravir in accordance with the proposed dosage regimen[77]).

3.(iii).A.(5).2) Embryo-fetal development

(a) Study in mice (4.2.3.5.2.1)

Favipiravir was orally administered BID to pregnant ICR mice at a dose of 0 (vehicle, 0.5% methylcellulose solution), 30, 100, 300, or 1000 mg/kg/day from Gestation day 6 to Gestation day 15 followed by cesarean section on Gestation day 18. General toxicity findings in the maternal animals included decreased food consumption as well as yellow fur and nails in the ≥300 mg/kg/day groups, and a reduction in body weight gain and abortion (7 of 21 maternal animals) or maternal animals with all embryos resorbed (5 of 21 maternal animals) in the 1000 mg/kg/day group. Findings in these maternal animals were hemorrhage in the urinary tract and reproductive organs, decreased locomotor activity, and decreased body temperature. Death occurred in 1 animal on Gestation day 17. The yellow fur and nails were considerd to be of little toxicological significance, because there were no disorders, such as shedding of the colored tissues and their abnormal elongation; and in the repeat-dose toxicity studies in rats and dogs [see "3.(iii).A.(2).1) One-month oral dose study in rats" and "3.(iii).A.(2).2) One-month oral dose study in dogs"], no histopathological changes were found in the colored tissues. The effects on embryo-fetal development included decreased live fetal body weight, decreased placenta weight, increased incidence of external abnormalities (head, tail), and decreased ossification count in the ≥300 mg/kg/day groups, and increased postimplantation loss rate, a decrease in the number of

[77] 633 μg·hr/mL (Multiple high-dose study in healthy adult Japanese male subjects [Study JP111])

live fetus count, increased visceral abnormality incidence (brain, cardiovascular), increased incidence of skeletal abnormality (fused sternebrae, sternebra morphological defect, fused cervical vertebral arch), and increased incidence of skeletal variation (complete extra rib, extra lumbar spine) in the 1000 mg/kg/day group. Based on the above, the NOAELs were determined to be 100 mg/kg/day for general toxicity in maternal animals and embryo-fetal development and 300 mg/kg/day for reproductive function in maternal animals.

(b) Study in rats (4.2.3.5.2.3)

Favipiravir was orally administered BID to pregnant SD rats at a dose of 0 (vehicle, 0.5% methylcellulose solution), 6, 20, 60, or 200 mg/kg/day from Gestation day 7 to Gestation day 17 followed by cesarean section on Gestation day 20. General toxicity findings in the maternal animals included pale yellow fur or nails and reduction in body weight gain in the ≥60 mg/kg/day groups, and decreased food consumption, little defecation or no-feces, loose stool, and maternal animals with all fetuses dead (4 of 19 animals) in the 200 mg/kg/day group. The pale yellow fur and nails were considered to be of little toxicological significance, because there were no abnormal changes, such as shedding of the colored tissues and their abnormal elongation; and because no histopathological changes were found in the colored tissues in the repeat-dose toxicity studies in rats and dogs [see "3.(iii).A.(2).1) One-month oral dose study in rats" and "3.(iii).A.(2).2) One-month oral dose study in dogs"]. The effects on embryo-fetal development included a trend toward a decrease in or decreased live fetal body weight, decreased placenta weight, and increased skeletal variation incidence (extra lumbar spine) in the ≥60 mg/kg/day groups and increased postimplantation loss rate, a decrease in the number of live fetuses, increased visceral abnormality incidence (cardiovascular, thymus), increased skeletal variation incidence (complete extra rib, short extra rib), and decreased ossification count in the 200 mg/kg/day group. Based on the above, the NOAELs were determined to be 20 mg/kg/day for maternal general toxicity and embryo-fetal development and 60 mg/kg/day for maternal reproductive function.

(c) Combination study of male fertility and embryo-fetal development toxicity in rats (4.2.3.5.2.4)

To investigate whether or not favipiravir treatment in male rats before mating affects the incidence of fetal abnormalities, favipiravir was orally administered BID to male SD rats at a dose of 0 (vehicle, 0.5% methylcellulose solution), 20, 60, or 200 mg/kg/day for 43 to 45 days, from 30 days before mating through the mating period to the day before necropsy. Furthermore, favipiravir was orally administered BID to pregnant rats at the same dose as that for male rats to be mated from Gestation day 7 to Gestation day 17, throughout the fetal organogenesis period, followed by cesarean section on Gestation day 20. General toxicity findings in male and female parent animalsduring the treatment and withdrawal periods in the ≥60 mg/kg/day groups were yellow fur, nails, or tail but they were considered to be of little toxicological significance, because there were no abnormal changes, such as shedding of the colored tissues and their abnormal elongation and because no histopathological changes were found in the colored tissues in the repeat-dose toxicity studies in rats and dogs [see "3.(iii).A.(2).1) One-month oral dose study in rats" and "3.(iii).A.(2).2) One-month oral dose study in dogs"]. Other general toxicity findings in the male parent animals included decreased epididymis weight, dilation of the seminiferous tubule, and retention of sperm cells in the ≥60 mg/kg/day groups and decreased testis weight, atrophy of the seminiferous tubule, and degeneration of spermatocytes in the 200 mg/kg/day group. At the end of the 13-week withdrawal period, mild atrophy of the seminiferous tubule occured in the 20 mg/kg/day group, but the change was within a range of the historical data and no abnormalities were observed at the histopathological and sperm examinations at the end of the treatment period. Therefore, the change was considered unrelated to favipiravir. The degeneration of spermatocytes in the 60 mg/kg/day group, atrophy and vacuolization of the seminiferous tubule in the ≥60 mg/kg/day groups, and decreased testis and epididymis weights in the 200 mg/kg/day group remained from the end of the treatment period, and they were not reversibile, compared with those

at the end of the treatment. In maternal animals, reduction in body weight gain and decreased food consumption were observed in the 200 mg/kg/day group. Although there were no effects on mating rate and fertility rate in male parent animals, the effects on the reproductive function revealed by the sperm examination included decreased motile sperm rate, trend toward a decrease in or decreased sperm vitality, and increased incidence of sperm morphological defect in the ≥60 mg/kg/day groups. At the end of the 13-week withdrawal period, trend toward a decrease in or decreased sperm vitality and trend toward an increase in or increased incidence of sperm morphological defect were observed in the ≥60 mg/kg/day groups and decreased motile sperm rate in the 200 mg/kg/day group. These effects, however, tended to be reversible compared with those at the end of the treatment. In the 200 mg/kg/day group, abortion and all embryos resorbed occurred in 3 and 5 of 17 maternal animals, respectively. The effects on embryo-fetal development included decreases in live fetal body weight and placenta weight and increased incidence of skeletal variation (extra lumbar spine) in the ≥60 mg/kg/day groups, increased postimplantation loss rate, a decrease in the number of live fetuses, increased incidence of visceral abnormality (cardiovascular), and decreased ossification count in the 200 mg/kg/day group. Based on the above, the NOAELs were determined to be 20 mg/kg/day for general toxicity and reproductive function in male parent animals and embryo-fetal development and 60 mg/kg/day for general toxicity and reproductive function in maternal animals.

(d) Study in rats (comparing with antiviral drugs) (Reference data, 4.2.3.5.2.6)

RBV and VACV that are existing antiviral nucleoside analogs and have been reported to affect embryos and fetuses in non-clinical studies were used as control in this study. RBV (3, 10 mg/kg/day), VACV (200, 400 mg/kg/day), or favipiravir (30, 100 mg/kg/day) was orally administered BID to pregnant SD rats from Gestation day 7 to Gestation day 17, followed by cesarean section on Gestation day 20, to compare the effects on embryos and fetuses among the drugs. No embryo-fetal abnormalities were observed in the favipiravir 30 mg/kg/day group, but decreased live fetal body weight and increased incidences of visceral abnormality and skeletal variation were noted in the favipiravir 100 mg/kg/day group, RBV ≥3 mg/kg/day groups, and VACV ≥200 mg/kg/day groups. Furthermore, increased postimplantationloss rate, a decrease in the number of live fetuses, decreased live fetal body weight, and delayed ossification were observed in the RBV 10 mg/kg/day group and VACV 400 mg/kg/day group. In addition, increased skeletal abnormality incidence was observed in the RBV 10 mg/kg/day group, but neither favipiravir nor VACV affected the incidence of skeletal abnormality even at the doses leading to a decrease in the number of live fetuses or decreased live fetal body weight. The exposures (AUC) in rats at the doses of favipiravir 30 and 100 mg/kg/day, RBV 3 mg/kg/day, and VACV 200 mg/kg/day were 0.79 and 3.4, 0.014, and 2.3 times, respectively, the exposure in humans (mean AUC, for favipiravir, the value in humans who received favipiravir in accordance with the proposed dosage regimen[78]).

(e) Study in rabbits (4.2.3.5.2.8)

Favipiravir was orally administered BID to pregnant NZW rabbits at doses of 0 (vehicle, 0.5% methylcellulose solution), 30, 100, 300, 600 or 1000 mg/kg/day from Gestation day 6 to Gestation day 18 followed by cesarean section on Gestation day 29. Of 11 animals in the 1000 mg/kg/day group, 5 animals died or were found in a moribund condition on Gestation day 12 to Gestation day 15. The remaining surviving animals discontinued the treatment, and a new dose level of 600 mg/kg/day was selected. As the general toxicological effect on maternal animals, pale yellow fur was found in the ≥300 mg/kg/day groups but determined to have little toxicological significance, because there were no disorders, such as shedding of the colored tissues and their abnormal elongation; and in the repeat-dose toxicity studies in rats and dogs [see "3.(iii).A.(2).1) One-month oral dose study in rats" and "3.(iii).A.(2).2) One-month oral dose study in dogs"], no histopathological changes were observed in the colored tissues. At the dose of 600 mg/kg/day,

[78] 633 μg·hr/mL (Multiple high-dose study in healthy adult Japanese male subjects [Study JP111])

death (3 of 11 animals) and abortion (1 of 11 animals) occurred, and decreased food consumption and reduction in body weight gain were observed from Gestation day 15 to Gestation day 24. Preterm delivery or abortion occurred in 1 animal each in the 30 and 300 mg/kg/day groups (1 of 22 animals and 1 of 21 animals, respectively) and were concidered to be caused by incidental malnutrition due to decreased food consumption but not by favipiravir. The effects on embryo-fetal development included a trend toward to a decrease in live fetal body weight, increased skeletal abnormality incidence (hemicentrum of the cervical vertebral body), and increased incidence of skeletal variation (extra lumbar spine, extra ossificated sternebra, complete extra rib) in the 600 mg/kg/day group. Based on the above, the NOAELs were determined to be 300 mg/kg/day all for general toxicity and reproductive function in maternal animals as well as embryo-fetal development.

(f) Study in monkeys (Reference data, 4.2.3.5.2.9)

Favipiravir was orally administered BID to pregnant cynomolgus monkeys at a dose of 0 (vehicle, 0.5% methylcellulose solution), 50, 100, or 200 mg/kg/day from Gestation day 20 to Gestation day 50 followed by cesarean section on Gestation day 100. There were no effects of favipiravir on the maternal animals. Of 5 animals in the 200 mg/kg/day group, 1 animal was found to have fetuses with external abnormalities of polyhydramnios, cleft palate, local oedema, and abdominal distension as well as ascites retention, pulmonary oedema, swelling of the liver, and foci of discoloration. Furthermore, of the other animals, fetuses with local oedema (1 of 5 animals) and with cleft palate (1 of 5 animals) were noted. These abnormalities are not included in the historical data at the laboratory and are considered to be attributable to favipiravir but not spontaneous findings.

3.(iii).A.(5).3) Rat study for effects on pre- and postnatal development, including maternal function (4.2.3.5.3.1)

Favipiravir was orally administered BID to pregnant SD rats at a dose of 0 (vehicle, 0.5% methylcellulose solution), 10, 30, or 100 mg/kg/day from Gestation day 7 to 20 days after delivery. In F_0 maternal animals, yellow fur, nails, or tail was found in the ≥30 mg/kg/day groups but considered to be of little toxicological significance, because there were noabnormal changes, such as shedding of the colored tissues and their abnormal elongation and because no histopathological changes were observed in the colored tissues in the repeat-dose toxicity studies in rats and dogs [see "3.(iii).A.(2).1) One-month oral dose study in rats" and "3.(iii).A.(2).2) One-month oral dose study in dogs"]. In the 100 mg/kg/day group, reduction in body weight gain, decreased food consumption, and mild prolongation of the mean gestation period were noted. The mild prolongation of the mean gestation period was considered to be unrelated to favipiravir, but due to the fact that a greater proportion of the maternal animals had 22 days of the gestation period in the 100 mg/kg/day group compared with the control group; the individual gestation periods in both groups were similar (21 or 22 days). The effects on F_1 offspring included a decrease in the number of live offspring, an increase in the number of dead offspring, decreased survival of the offspring at 4 days after birth, yellow fur (until 53 days after birth), and reduction in body weight gain in the 100 mg/kg/day group. There were no effects on F_1 maternal animals and F_2 fetus. Based on the above, the NOAELs were determined to be 30 mg/kg/day for general toxicity and 100 mg/kg/day for reproductive function in F_0 maternal animals and 30 mg/kg/day in F_1 offspring.

3.(iii).A.(6) Other toxicity studies

3.(iii).A.(6).1) Immunotoxicity studies

T cell dependent antibody production study in rats and study for the effects on cytokine production on human peripheral blood mononuclear cells were conducted to investigate the effects of favipiravir on immunity.

(a) T cell dependent antibody production study (4.2.3.7.2.1)

Favipiravir was orally administered BID to SD rats at a dose of 0 (vehicle, 0.5% methylcellulose

solution), 13, 32, or 80 mg/kg/day for 1 month, and 6 days before necropsy, sheep red blood cells (SRBCs) were injected into the tail vein for immunization. The anti-SRBC specific antibody titer in the serum collected on the day of necropsy was determined. In the 80 mg/kg/day group, reduction in body weight gain was observed, but the effects on immunity were ruled out since there were no changes in the thymus or spleen weight, or anti-SRBC specific antibody titer.

(b) *In vitro* effects on cytokine production (Reference data: 4.2.3.7.2.2)

The *in vitro* effects of favipiravir and favipiravir hydroxide (M1) on LPS-induced cytokine production (IL-1β, IL-6, IL-8, TNF-α) were investigated using human peripheral blood mononuclear cells. As a result, favipiravir at 30, 100, and 300 μg/mL and favipiravir hydroxide (M1) at 10, 30, and 100 μg/mL did not affect the cytokine production.

3.(iii).A.(6).2) Toxicity studies of the metabolites

Toxicity studies of M1 conducted include genotoxicity studies, a 2-week repeated oral dose toxicity study in rabbits, and reproductive and developmental toxicity studies in rats.

(a) Genotoxicity study (4.2.3.7.5.1 to 4.2.3.7.5.2; Reference data, 4.2.3.7.5.4 to 4.2.3.7.5.5)

Bacterial reverse mutation assay and chromosomal aberration assay in mammalian cells (CHL/IU cells) of M1 were conducted. As a preliminary investigation, bacterial reverse mutation assay and *in vitro* micronucleus study in mammalian cells (CHL/IU cells) were conducted. All of these assays showed negative results.

(b) Two-week repeated oral dose study in rabbits (Reference data, 4.2.3.7.5.3)

Following administration of favipiravir, a greater amount of M1 was formed in rabbits than in dogs and rats. Favipiravir was thus orally administered BID to Japanese white male rabbits at a dose of 0 (vehicle, 0.5% methylcellulose solution), 100, 200, or 600 mg/kg/day for 2 weeks. Of 3 animals in the 600 mg/kg/day group, 1 animal died. In the dead animal, decreases in body weight and food consumption, swelling, bleaching, and fine yellowish white spots on the cut surface of the kidney, and crystal deposition, inflammatory cell infiltration, hemorrhage, and mineralization in the tubular and renal pelvis in the kidney were found. In the surviving animals, pale yellow fur, increased TG, bile duct hyperplasia and inflammatory cell infiltration in the portal area in the liver were found. The crystal deposition in the kidney was not observed in any of the studies in rats, dogs [see "3.(iii).A.(2).1) One-month oral dose study in rats" and "3.(iii).A.(2).2) One-month oral dose study in dogs"] and monkeys in which M1 formation would be comparable to that in rabbits [see "3.(iii).A.(2).3) Two-week oral dose study in monkeys"]. This finding is thus considered attributable to rabbit-specific urine composition, characterized by abundant calcium carbonate, ammonium phosphate, and magnesium.

(c) Study for effects of M1 on early embryonic development to implantation in rats (4.2.3.7.5.6)

M1 was intravenously administered once daily to pregnant SD rats at doses of 0 (saline with the pH adjusted to approximately 9 by addition of sodium hydroxide[79]), 25, 50, or 100 mg/kg/day from Gestation day 0 to Gestation day 7. There were no effects of M1 on maternal animals or embryo-fetal development. Based on the above, the NOAELs were determined to be 100 mg/kg/day both for maternal general toxicity as well as embryo-fetal development.

(d) Embryo-fetal development study of M1 in rats (4.2.3.7.5.7)

M1 was intravenously administered once daily to pregnant SD rats at a dose of 0 (saline with the pH adjusted to approximately 9 by addition of sodium hydroxide[79]), 25, 50, or 100 mg/kg/day

[79] The pH of the M1 dosing solution was approximately 9.8, and thus to saline for the vehicle control group, sodium hydroxide was added to adjust the pH before dosing.

from Gestation day 7 to Gestation day 17. There were no effects of M1 on maternal animals or embryo-fetal development. Based on the above, the NOAELs were determined to be 100 mg/kg/day all for general toxicity and reproductive function in maternal animals and embryo-fetal development.

3.(iii).A.(6).3) Toxicity studies of impurities (Reference data, 4.2.3.7.6.1 to 4.2.3.7.6.3)

Substance I (percentage composition, [redacted]%) and Substance K (percentage composition, [redacted]%) were impurities contained in the drug substance batch (Lot JI103S) for the phase I clinical study (Study JP101), but the drug substance batches used in the toxicity studies before the start of this clinical study contained these impurities at a level below the detection limit or <[redacted]%. To ensure the safety of both impurities, single oral dose toxicity study in rats [see Reference data, 4.2.3.7.6.1], bacterial reverse mutation assay [see Reference data, 4.2.3.7.6.2], and rat micronucleus assay [see Reference data, 4.2.3.7.6.3] were conducted with the drug substance in the same batch. There were no marked differences in acute toxicity in rats between Lot JI103S and Lot EA102Q (Substance I, below the detection limit; Substance K, <[redacted]%), and Lot JI103S tested negative for genotoxicity.

No toxicity studies of impurities other than the above toxicity studies have been conducted, because the drug substance batches other than this batch contain Substance I at a level below the detection limit and Substance K at ≤[redacted]%, and no impurities exceeding the qualification threshold are contained in the drug substance conforming to the proposed specifications (individual related substances ≤[redacted]%; total related substances ≤[redacted]%).

3.(iii).A.(6).4) Phototoxicity studies

Phototoxicity studies in mice and guinea pigs were conducted to evaluate the phototoxicity of favipiravir. The results have indicated that favipiravir has phototoxicity. Precautions are therefore required for clinical use of favipiravir.

(a) Phototoxicity study in mice (4.2.3.7.7.1)

Favipiravir was orally administered as a single dose to female BALB/c mice at a dose of 30, 100, or 300 mg/kg followed by UVA irradiation for 4 hours. At 30 minutes and 24, 48, and 72 hours after the end of the irradiation, the auricular skin was macroscopically observed, and the macroscopic changes were rated on a 1-to-5 point scale. In the 100 mg/kg group, changes of a score of 1 (slight erythema) or of score of 2 (clear erythema) were observed in 5 of 5 animals at 30 minutes and 24 hours after the end of the irradiation, but at 72 hours, the change of a score of 1 was observed in 1 of 5 animals. A resolving trend was thus confirmed. At the dose of 300 mg/kg, changes of a score of 2 were observed in 5 of 5 animals at all observation timepoints, and there were no changes in score over time.

(b) Phototoxicity study in guinea pigs (comparison with quinolones) (Reference data, 4.2.3.7.7.2)

A phototoxicity study was conducted in guinea pigs to compare the phototoxicity between favipiravir and quinolones, sparfloxacin (SPFX), ciprofloxacin (CPFX), or levofloxacin (LVFX). As a result, the phototoxicity was observed following single intravenous dose of 100 mg/kg of favipiravir, but the severity was milder than that of SPFX and CPFX and comparable to that of LVFX at the same dose.

3.(iii).A.(6).5) Testis toxicity study

To evaluate the testis toxicity of favipiravir, 2-week oral dose studies in mice, rats, and rabbits were conducted. These animals were selected to investigate differences in sensitivity among animal species. To investigate the relationship between the treatment period and testis toxicity threshold, single and 1-week oral dose studies were conducted in rats. The resultant study data were compared with those from the 2-week oral dose study. To evaluate the reversibility of the

testis toxicity, 2-week oral dose study in rats and 6-week oral dose study in monkeys were conducted. The treatment period of the study in monkeys (6 weeks) was selected based on the sperm formation period of cynomolgus monkeys taking 42 days.[80] Two-week oral dose studies were conducted in mice and rats to compare the testis toxicity of favipiravir with that of the existing antiviral nucleoside analogs of which testis toxicity in non-clinical studies was reported. The testis toxicity studies used sexually matured animals[81] appropriate for evaluation of testis toxicity. As a result, rodents (especially rats) are more sensitive to testis toxicity of favipiravir than rabbits and monkeys. On the other hand, in monkeys treated at 150 mg/kg/day for a period corresponding to the sperm formation period (6 weeks), there were no effects on the testis. According to the study data in rats, the testis toxicity of favipiravir developed at doses of ≥100 mg/kg/day (2-week treatment) and ≥60 mg/kg/day (6-week treatment); as with the severity of the testis toxicity, the development of toxicity depended on the treatment period. The studies in rats have demonstrated reversibility of the testis toxicity.

(a) Two-week oral dose study in mice (4.2.3.7.7.3 to 4.2.3.7.7.5)

Favipiravir was orally administered BID to male ICR mice (11 weeks of age) at a dose of 0 (vehicle, 0.5% methylcellulose solution), 30, 100, 300, or 1000 mg/kg/day for 2 weeks. Necropsy was performed at Weeks 1 and 2 of treatment as well as Weeks 4 and 8 of recovery to evaluate the testis toxicity. In the 1000 mg/kg/day group, death occurred in 17 of 30 animals by Day 1 of recovery, and decreases in body weight and food consumption (resolved after the withdrawal) were observed, but no abnormalities were revealed by the necropsy, or weight measurement, or histopathological examination of the reproductive organs. In the 1000 mg/kg/day group, increased incidence of morphological defect was revealed by the sperm examination at Weeks 1 and 2 of treatment, and decreases in counts of spermatogonium cells, spermatocytes at the pre-leptotene stage, spermatocytes at the pachytene stage, and round sperm cells per Sertoli cell revealed by the quantitative analysis of the seminiferous tubule at each stage atWeek 2 of treatment. It has been, however, considered that it remains unclear whether decreases of these reproductive cells were caused by direct effects of favipiravir or were non-specific changes attributable to decreases in body weight and food consumption in the animals. No abnormalities were revealed by the examination during the recovery period. Based on the above, the NOAEL in this study was determined to be 300 mg/kg/day for testis toxicity.

(b) Two-week oral dose study in mice (comparison with antiviral drugs) (Reference data, 4.2.3.7.7.6)

RBV, VACV, and valganciclovir (VGCV), of which testicular toxicity in non-clinical studies has been reported, were used as control in this study. Favipiravir (100, 300 mg/kg/day), RBV (150, 500 mg/kg/day), VACV (100, 300 mg/kg/day), or VGCV (30, 100, 300 mg/kg/day) was orally administered BID to male ICR mice (11 weeks of age) for 2 weeks for weight measurement and histopathological examination of the testis, epididymis, vesicular gland, and prostate. There were no effects on the testis even at the highest dose of favipiravir (300 mg/kg/day) or RBV (500 mg/kg/day). On the other hand, there were effects on the testis at the dose of VACV 300 mg/kg/day and at the dose of VGCV ≥30 mg/kg/day. The exposures (AUC) in mice at the doses of favipiravir 300 mg/kg/day and RBV 500 mg/kg/day exceeded the exposure in humans (mean AUC, for favipiravir, the value in humans who received favipiravir in accordance with the proposed dosage regimen[82]) (1.8 and 3.1 times, respectively), but those in mice at the doses of VACV 300 mg/kg/day and VGCV 30 mg/kg/day were comparable to or below that in humans.

(c) Single and 1-week oral dose studies in rats (4.2.3.7.7.8 to 4.2.3.7.7.9; Reference data, 4.2.3.7.7.7)

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[80] *Toxicol Pathol.* 2007;35:395-404.
[81] *Toxicol Pathol.* 2002;30:507-520.
[82] 633 μg·hr/mL (Multiple high-dose study in healthy adult Japanese male subjects [Study JP111])

A single dose of favipiravir was administered to male SD rats (12 weeks of age) at 0 (vehicle, 0.5% methylcellulose solution) or 1000 mg/kg for weight measurement of the testis, epididymis, vesicular gland, and prostate and histopathological examination of the testis. As a result, 5 days after administration, decreases in weights of the left testis, epididymis, vesicular gland, and prostate, changes possibly related to weight loss, were observed, but no histopathological changes were observed.

Favipiravir was orally administered BID to male SD rats (12 or 13 weeks of age) at a dose of 0 (vehicle, 0.5% methylcellulose solution), 30, 60, or 100 mg/kg/day for 1 week. In the preceding study, favipiravir was orally administered BID only at the dose of 100 mg/kg/day for 1 week for weight measurement and histopathological examination of the testis, epididymis, vesicular gland and prostate. In this preceding study, a decreasing trend of testis weight and multinucleated giant cell formation and atrophy of the seminiferous tubule were observed in 1 of 5 animals in the 100 mg/kg/day group. However, these changes were considered unrelated to favipiravir, since no abnormalities were observed in the supplemental study, and no such findings were observed in other studies in rats. The NOAEL was determined to be 100 mg/kg/day for testis toxicity in this study.

(d) Two-week oral dose study in rats (4.2.3.7.7.10 to 4.2.3.7.7.11)

Favipiravir was orally administered BID to male SD rats (13 weeks of age) at a dose of 0 (vehicle, 0.5% methylcellulose solution), 30, 100, or 300 mg/kg/day for 2 weeks for sperm examination, weight measurement and histopathological examination of the testis, epididymis, vesicular gland, and prostate, and quantitative analysis on the seminiferous tubule in each stage. In addition, on Day 14 of treatment and on Day 28 of recovery, blood hormone (testosterone, FSH, LH, progesterone) concentration was measured. In the ≥100 mg/kg/day groups, reduction in body weight gain or decreased body weight and decreased food consumption were observed, but these findings were reversible or tended to be reversible during the 28-day recovery period. Furthermore, in the 300 mg/kg/day group, decreased locomotor activity was observed, and death occurred by Day 2 of recovery (8 of 40 animals, including 1 animal due to dosing error). Regarding the effects on the testis, no abnormalities were found in the 100 mg/kg/day group during the treatment period, but findings on Day 28 of recovery included trend toward decreases in sperm count, motile sperm rate, and sperm vitality, and trend toward an increase in the incidence of sperm morphological defect as well as retention of sperm cells in the testis revealed by the histopathological examination. In the 300 mg/kg/day group, findings included decreased weights of the testis, epididymis, vesicular gland, or prostate and dilation of seminiferous tubule on Day 5 of treatment and thereafter; degeneration/necrosis of the seminiferous epithelium on Day 7 of treatment and thereafter; vacuolization of the Sertoli cells, interstitial hemorrhage, and neutrophil infiltration on Day 10 of treatment and thereafter; and necrosis of the interstitial cells and Sertoli cells on Day 14 of treatment. The sperm examination showed decreased sperm count on Day 10 of treatment and thereafter and decreases in motile sperm rate and sperm vitality on Day 14 of treatment. Changes on Day 28 of recovery included increased incidence of sperm morphological defect revealed by the sperm examination, in addition to the changes found on Day 14; retention of the sperm cells, atrophy of the seminiferous tubule, and mineralization revealed by the histopathological examination. Changes in blood hormone concentrations included decreases in testosterone and FSH concentrations as well as increased progesterone concentration in the 300 mg/kg/day group on Day 14 of treatment. The quantitative analysis on the seminiferous tubule at each stage showed no abnormalities. In the supplemental study, favipiravir was orally administered BID to male SD rats (12 weeks of age) at a dose of 0 (vehicle, 0.5% methylcellulose solution) or 60 mg/kg/day for 2 weeks for measurement and histopathological examination of the testis, epididymis, vesicular gland, and prostate, no effects on the testis were observed. Based on the results of the above 2 studies, the NOAEL of 2-weeks favipiravir treatment was determined to be 60 mg/kg/day for testis toxicity.

(e) Two-week oral dose study in rats (investigation for the reversibility) (4.2.3.7.7.12)

Favipiravir was orally administered BID to male SD rats (12 weeks of age) at a dose of 0 (vehicle, 0.5% methylcellulose solution), 30, 100, or 200 mg/kg/day for 2 weeks followed by necropsy at Week 2 of treatment and at Weeks 4, 13, and 26 of recovery for weight measurement and histopathological examination of the testis, epididymis, vesicular gland, and prostate. At Week 31 of recovery, weight of the testis, epididymis, vesicular gland, and prostate was measured. In the ≥100 mg/kg/day groups, reduction in body weight gain or decreased body weight were noted during the treatment period, but all of these findings were reversible during the recovery period. The effects on the testis found during the treatment period included decreased weights of epididymis, vesicular gland, and prostate, degeneration of the seminiferous epithelium, and dilation of the seminiferous tubule in the 200 mg/kg/day group at Week 2 of treatment. Findings observed during the recovery period included retention of sperm cells in the 100 mg/kg/day group at Week 4 of recovery, and decreased epididymis weight, retention of sperm cells, decreased seminiferous epithelium, and dilation of the seminiferous tubule in the 200 mg/kg/day group at Week 4 of recovery. These changes were not found at Week 13 or 26 of recovery. Based on the above results, the effects on the testis observed in the ≥100 mg/kg/day groups were considered to have resolved following the 13-week withdrawal period.

(f) Two-week oral dose study in rats (comparison with antiviral drugs) (Reference data, 4.2.3.7.7.13 to 4.2.3.7.7.14)

RBV, VACV, and VGCV, and famciclovir (FCV), of which testicular toxicity in non-clinical studies has been reported, were used as control in this study. Favipiravir (100, 200 mg/kg/day), RBV (80, 160, 250, 500 mg/kg/day), VACV (150, 300, 450, 900 mg/kg/day), VGCV (50, 100, 200, 300, 600 mg/kg/day), or FCV (200, 400, 1000 mg/kg/day) was orally administered BID to male SD rats (12 weeks of age) for 2 weeks, followed by necropsy at Week 2 of treatment and at Week 4 of recovery for weight measurement and histopathological examination of the testis, epididymis, vesicular gland, and prostate. Findings after favipiravir treatment included a reduction in body weight gain or decreased body weight in the ≥100 mg/kg/day groups during the treatment period, decreased weights of epididymis, vesicular gland, and prostate and degeneration of spermatocytes and dilation of the seminiferous tubule in the testis in the 200 mg/kg/day group at Week 2 of treatment, and retention of sperm cells and cell residue in the epididymis in the 200 mg/kg/day group at Week 4 of recovery. The effects on the testis were observed in the favipiravir 200 mg/kg/day group, in the RBV ≥250 mg/kg/day groups, in the VACV ≥300 mg/kg/day groups, in the VGCV ≥50 mg/kg/day dose groups, and in the FCV ≥400 mg/kg/day dose groups. The exposures (AUC) in rats at the doses of favipiravir 200 mg/kg/day, VACV 300 mg/kg/day, and FCV 400 mg/kg/day, at which testis toxicity was observed, were 5.4, 3.7, and 2.2 times, respectively, the exposure in humans (mean AUC, for favipiravir, the value in humans who received favipiravir in accordance with the proposed dosage regimen[83]), but the exposrues in rats at the doses of RBV 250 mg/kg/day and VGCV 50 mg/kg/day were comparable to or below that in humans.

(g) Two-week oral dose study in rabbits (4.2.3.7.7.15)

Favipiravir was orally administered BID to male NZW rabbits (21 weeks of age) at a dose of 0 (vehicle, 0.5% methylcellulose solution), 200, or 600 mg/kg/day for 2 weeks. On Days 7 and 14 of treatment and on Days 28 and 56 of recovery, seminal fluid was collected for sperm examination, and on Day 14 of treatment and on Day 56 of recovery, necropsy was carried out for histopathological examination of the testis, epididymis, vesicular gland, and prostate. In the 600 mg/kg/day group, death occurred in 2 of 7 animals by Day 10 of treatment, and in the surviving animals, decreases in body weight and food consumption were observed but resolved following the withdrawal. The effects on the testis included decreased seminal fluid volume on Days 7 and 14 of treatment and decreased weight and atrophy of the vesicular gland and prostate

[83] 633 μg·hr/mL (Multiple high-dose study in healthy adult Japanese male subjects [Study JP111])

on Day 14 of treatment at the dose of 600 mg/kg/day, but all of these findings were determined to be non-specific changes attributable to malnutrition associated with the decreased food consumption. No abnormalities were observed during the recovery period. Based on the above, the NOAEL was determined to be 600 mg/kg/day for testis toxicity.

(h) Six-week oral dose study in monkeys (4.2.3.7.7.16)

Favipiravir was orally administered BID to male cynomolgus monkeys (5-6 years of age) at a dose of 0 (vehicle, 0.5% methylcellulose solution), 70, 100, or 150 mg/kg/day for 6 weeks. At Week 6 of treatment and at Weeks 4 and 12 of recovery, blood hormone (testosterone, inhibin B) concentrations were measured, and necropsy was carried out for weight measurement and histopathological examination of the testis, epididymis, vesicular gland, and prostate. Hematology and clinical chemistry were also performed. No effects on the testis were observed at any dose, and the clinical chemistry showed increased TG in the 150 mg/kg/day group at Week 6 of treatment but it resolved after the 4-week recovery period. Based on the above, the NOAEL was determined to be 150 mg/kg/day for testis toxicity.

3.(iii).A.(6).6) Juvenile animal toxicity studies

With a view to the use of favipiravir in children, 1-month repeated oral dose studies in juvenile dogs and rats were conducted. In the 1-month repeated dose study, the dose at which death occurred in juvenile dogs was lower than that in adult dogs, and toxicity findings specific to juvenile animals such as degeneration and necrosis of hepatocytes, degeneration and necrosis of papillary muscle in the heart, atrophy and degeneration of skeletal muscle fiber, and gait disturbance were observed. It has been therefore determined that use of favipiravir in children should be carefully considered.

(a) One-month oral dose study in juvenile dogs (4.2.3.7.7.17)

Favipiravir was orally administered BID to juvenile beagle dogs (8 weeks of age) at a dose of 0 (gelatin capsule), 15, 30, 60, or 100 mg/kg/day for 1 month. In the 60 mg/kg/day group, death occurred in 9 of 12 animals on Day 20 of treatment and thereafter. Findings included decreased appetite on Day 10 of treatment and thereafter and decreased locomotor activity, abnormal position, abnormal respiration, abnormal feces, abnormal light reflex, pale oral mucosa, auricle, or conjunctiva, vomiting, and low body temperature on Day 18 of treatment and thereafter. Of 12 animals in the 100 mg/kg/day group, 5 animals died by Day 15 of treatment, and the 7 surviving animals were withdrawn from Day 16 of treatment, but 6 animals died during the withdrawal period. In dead animals in the 60 and 100 mg/kg/day groups, hemorrhagic necrosis of hepatocytes, pulmonary infarction, thrombus in the lungs or liver, systemic oedema or vascular dilation, localized hemorrhagic fibrinous pneumonia, degeneration/necrosis or mineralization of papillary muscle in the heart, degeneration of skeletal muscle fiber, and atrophy or regression of lymphoid tissue were observed. Furthermore, in 2 animals in the 100 mg/kg/day group which died during the withdrawal period, decreased myeloid nucleated cell count was found, and in 1 of 12 animals in the 60 mg/kg/day group, systemic bacterial embolism was observed. Findings suggesting inflammatory changes and bacterial infection in the lungs observed in the dead animals were considered as the secondary changes associated with the deteriorated clinical condition. Findings in the surviving animals in the 60 mg/kg/day group at the end of the treatment period include yellow fur; decreases in RBC, Hb, Ht, lymphocyte, eosinophil, platelet, and fibrinogen, increases in WBC, neutrophil, and monocyte, and prolongations of PT and APTT revealed by hematology; increases in AST, ALT, LDH, BUN, total bilirubin, and blood glucose, and decreases in TP, albumin, electrolyte revealed by clinical chemistry; and degeneration of skeletal muscle fiber revealed by the histopathological examination. Findings in the surviving animal (1 of 12 animals) in the 100 mg/kg/day group included yellow fur during the treatment and recovery periods, and slight vascular dilation in the liver and gallbladder, and mild oedema in the gallbladder at the end of the recovery period. Based on the above, the NOAEL in this study was determined to be 30 mg/kg/day.

(b) One-month oral dose study in juvenile rats (Reference data, 4.2.3.7.7.18)

Favipiravir was orally administered BID to juvenile rats (6 days of age) at a dose of 0 (vehicle, 0.5% methylcellulose solution), 50, 100, or 300 mg/kg/day for 1 month. Findings included pale yellow fur and nails, reduction in body weight gain, and decreases in Ht and MCV in the ≥50 mg/kg/day groups; and abnormal gait, decreased Hb, decreased creatinine, increased CK, atrophy of skeletal muscle fiber, and multinucleated giant cell formation and vacuolization of the Sertoli cells in the testis in the 100 mg/kg/day group. Of 32 animals in the 300 mg/kg/day group, 17 animals died by Day 6 of treatment, and all the surviving animals discontinued the treatment on the same day and were sacrificed in a moribund condition. The major findings in the 300 mg/kg/day group included decreased reticulocyte count, increases in AST, ALT, and ALP, pleural fluid, atrophy and vacuolization of the skeletal muscle fiber, and degeneration and coagulation necrosis of hepatocytes. The abnormal gait and atrophy of skeletal muscle fiber observed in the 100 mg/kg/day group were reversible or tended to be reversible following the recovery period. Based on the above, the NOAEL in this study was determined to be <50 mg/kg/day.

3.(iii).A.(6).7) Toxicity study of concomitant use with anesthetics (4.2.3.7.7.20 to 4.2.3.7.7.22)

In the influenza virus infection study in monkeys [see 4.2.1.1.34], death occurred in the favipiravir group. In this study, however, anesthetics (ketamine, xylazine) were used when favipiravir was administered. To investigate the toxicological interaction of these anesthetics with favipiravir, 6-day repeated concomitant use toxicity studies were conducted in rats and cynomolgus monkeys. While favipiravir was orally administered, the anesthetics were intramuscularly administered. As a result, the concomitant use of favipiravir with the anesthetics (ketamine, xylazine) did not clearly intensify the toxicity. Although the concomitant use with the anesthetics tended to prolong t_{max} of favipiravir or prolonged $t_{1/2}$, these effects were mild. Based on the above, the concomitant use with the anesthetics was considered unlikely to cause serious adverse events.

3.(iii).B Outline of the review by PMDA

3.(iii).B.(1) Effects on embryos and fetuses

Concerning the effects on embryos and fetuses observed in the reproductive and developmental toxicity studies, PMDA asked the applicant to discuss the relevant risk in humans.

The applicant responded as follows:

In studies investigating the effects on the early embryonic development in rats [see "3.(iii).A.(5).1).(a) Study in rats" and "3.(iii).A.(5).1).(b) Study in rats (supplemental study)"], increased preimplantation loss rate, increased postimplantation mortality associated with increased early embryonic loss and resorbed embryo count, and decreased live fetal body weight were observed. Furthermore, studies investigating the effects on the early embryonic development in rats (comparison of the treatment timing, before and after gestation) [see "3.(iii).A.(5).1).(c) Study in rats (comparison of the treatment timing, before and after gestation)"] suggested that the treatment during the early stage of pregnancy, in which a pregnancy test may give a negative result in humans, may cause delayed development of embryos or embryo mortality. In the embryo-fetal development studies in rats, mouse, rabbits, and monkeys [see "3.(iii).A.(5).2) Embryo-fetal development"], teratogenicity was observed in any animal species. In the embryo-fetal development studies, the exposure at NOAEL in any animal species was comparable to or less than the exposure (mean AUC)[84] in humans, while the exposure at the teratogenic dose was 1.9 to 19 times that in humans. The maximum exposure (maximum AUC)[85] in humans who received favipiravir in accordance with the proposed dosage regimen was nearly comparable to or more than the exposure at the teratogenic dose in mice, rats, and monkeys. It cannot be ruled

[84] 633 μg·hr/mL (Multiple high-dose study in healthy adult Japanese male subjects [Study JP111])
[85] 1593 μg·hr/mL (Multiple high-dose study in healthy adult Japanese male subjects [Study JP111])

out that fetal abnormalities may occur in humans who have received favipiravir in accordance with the proposed dosage regimen. The use of favipiravir in women who are pregnant or may possibly be pregnant should therefore be contraindicated as a rule. For females of childbearing potential, the appropriate contraception period after the end of the treatment is considered to be 7 days in which the plasma favipiravir and M1 concentrations will decrease to below the lower limit of quantitation, even when individual variability in the pharmacokinetics are taken into account. M1, a metabolite of favipiravir, is considered to have no embryo-fetal risk in humans, because the maximum exposure to M1[86] in humans who have received favipiravir in accordance with the proposed dosage regimen is smaller than the exposure to M1[87] at the NOAEL in the reproductive and developmental toxicity studies of M1 in rats [see "3.(iii).A.(6).2).(c) Study for effects of M1 on early embryonic development to implantation in rats" and "3.(iii).A.(6).2).(d) Embryo-fetal development study of M1 in rats"] (rat/human ratio: C_{max}, 12.9; AUC, 1.3), and because after the contraception period (7 days), the plasma M1 concentration in humans will decrease to below the lower limit of quantitation (0.02 μg/mL) which is <1/9800 times C_{5min} of M1[88] at the NOAEL for embryo-fetal development in the reproductive and developmental toxicity studies of M1.Since whether or not favipiravir is distributed into the seminal fluid in rats has not been ascertained, careful measures should be taken for contraception in male patients. For this reason, contraception should be used by male patients whose partner is of childbearing potential, and thus male patients whose partner is a woman who is pregnant or may possibly be pregnant should be advised to use condoms so that favipiravir will not be distributed into the uterus. The appropriate contraception period with condoms for men who have taken favipiravir is considered to be up to 7 days after the end of the treatment, based on the fact that in the study for seminal fluid distribution in healthy adult US male subjects (Study US107),[89] the favipiravir concentration in the seminal fluid decreased to below the lower limit of quantitation in all the subjects in 7 days after the end of the treatment.

Concerning the potential effects of sperm from favipiravir-treated male animals on the early embryos and fetuses, the following findings have been obtained: (1) there were no embryo-fetal effects in a study in which male rats treated with favipiravir were mated with untreated female animals [see "3.(iii).A.(5).1).(b) Study in rats (supplemental study)"]; (2) there were no effects on the mean number of implantation sites and mean preimplantation loss rate even in the 200 mg/kg/day group in which abnormalities were shown by the sperm examination changes and changes were found in the testis in male rats in the embryo-fetal study using favipiravir-treated male rats for mating [see "3.(iii).A.(5).2).(c) Combination study of male fertility and embryo-fetal development toxicity in rats"]; (3) favipiravir is unlikely to induce the genotoxicity in the body [see "3.(iii).A.(3) Genotoxicity"]; and (4) the embryo-fetal studies in rats [see "3.(iii).A.(5).2).(b) Study in rats" and "3.(iii).A.(5).2).(c) Combination study of male fertility and embryo-fetal development toxicity in rats"] suggested that favipiravir given to male animals to be mated will not aggravate the fetal toxicity of favipiravir given to pregnant female animals. Based on the above, the early-embryo and fetal toxicity is unlikely to develop in humans due to the sperm from a favipiravir-treated male.

PMDA considers as follows:
The reproductive and developmental toxicity study data suggested that favipiravir may cause delayed development or death of embryos during the early stage of pregnancy, in which a pregnancy test may give a negative result in humans. Also, the teratogenicity of favipiravir was observed in all the animal species (4 species) assessed in embryo-fetal developmental studies; and the favipiravir exposure causing teratogenicity in animals is comparable to that in humans treated

[86] C_{max} (maximum) of M1 following the first dose of 1200 mg on Day 1, 15.2 μg/mL; the estimated daily AUC (maximum), 89.55 μg·hr/mL (Multiple high-dose study in healthy adult Japanese male subjects [Study JP111]).
[87] C_{5min} of M1, 196 μg/mL; AUC_{0-t} of M1, 113 μg·hr/mL (toxicokinetics study of M1 in rats [CTD 4.2.3.7.5.8])
[88] C_{5min} of M1, 196 μg/mL (toxicokinetics study of M1 in rats [CTD 4.2.3.7.5.8])
[89] Clinical study report to be completed in [redacted]

with favipiravir in accordance with the proposed dosage regimen. Thus, favipiravir has raised considerable concern about the teratogenic risk in humans.

In Japan, influenza antiviral drugs are widely prescribed for patients with influenza virus infection in general. In consideration of the remarkable differences in reproductive and developmental toxicity between favipiravir and other drugs in the same class, treatment with favipiravir may have higher teratogenic risk than that with other drugs in the same class in clinical practice. Therefore, the clinical use of favipiravir should be carefully considered in light of the resultant risks and benefits, and healthcare providers in the clinical practice should be thoroughly cautioned of the matter.

In addition, favipiravir should be contraindicated for women who are pregnant or may possibly be pregnant, and women of childbearing potential and men whose partner is of childbearing potential should be advised to use contraception. Additionally, the precautionery statement about the early-embryo toxicity and teratogenicity of favipiravir should be provided in the WARNING section of the package insert. Furthermore, adequate measures should be taken to avoid the treatment with favipiravir in women at the early stage of pregnancy, in which a pregnancy test may give a negative result. The contraception period proposed by the applicant is accepted because the period should be long enough to ensure that the favipiravir concentration in blood in females and in seminal fluid in males will decrease to below the lower limit of quantitation by the end of the contraception period, taking into account individual variability in the pharmacokinetics. Intended patients and clinical positioning of favipiravir will be discussed in the Clinical data section in consideration of the embryo-fetal risk and clinical data [see "4.(iii).B.(2).1) Teratogenicity risk"].

3.(iii).B.(2) Effects on hematopoietic tissues

Concerning the effects on the hematopoietic tissues observed in the repeat-dose toxicity studies, PMDA asked the applicant to discuss the mechanism of development and risk in humans.

The applicant responded as follows:

In the 1-month repeated oral dose toxicity studies of favipiravir in rats and dogs [see "3.(iii).A.(2).1) One-month oral dose study in rats" and "3.(iii).A.(2).2) One-month oral dose study in dogs"] and 2-week repeated oral dose toxicity study in monkeys [see "3.(iii).A.(2).3) Two-week oral dose study in monkeys"], decreases in RBC, Ht, Hb, or reticulocyte count or decreased myelopoiesis (only in rats) were noted at doses of ≥80 mg/kg/day, ≥30 mg/kg/day, and 300 mg/kg/day, respectively.

However, given that at the dose levels leading to the above findings in the repeat-dose toxicity studies, reduction in body weight gain (rats) or decreased body weight and decreased food consumption (dogs, monkeys) were noted and changes in erythrocyte-related parameters were small; and that the changes in feed efficiency and food consumption are known to affect the erythrocyte-related parameters,[90] it was considered that the decreases in RBC, Ht, Hb, or reticulocyte count or decreased myelopoiesis observed in the repeat-dose toxicity studies do not reflect the direct effects of favipiravir on hematopoietic tissues but may be the secondary changes associated with the deteriorated clinical condition.

On the other hand, in the secondary pharmacodynamics studies, the effects of favipiravir on differentiation and proliferation of human bone marrow hematopoietic progenitor cells (myeloid CD34 positive cells) into burst-forming unit-erythroid (BFU-E) and colony forming unit-granulocyte/monocyte (CFU-GM) were investigated. As a result, favipiravir inhibited the differentiation and proliferation into BFU-E and CFU-GM (IC_{50} value, BFU-E, 539 μg/mL; CFU-

[90] Histopathology of preclinical toxicity studies (3rd edition). London: *Academic Press*. 2007:99-159.

GM, 170 μg/mL) [see 4.2.1.2.1]. It cannot be, therefore, ruled out that direct actions of favipiravir on the hematopoietic tissues are partially involved.

The AUC values at the NOAEL for the hematopoietic tissues in the repeat-dose toxicity studies in rats, dogs, and monkeys (32, 10, 200 mg/kg/day) were compared with the exposure (mean AUC)[91] in humans who received favipiravir in accordance with the proposed dosage regimen. The AUC values in rats and dogs were smaller than that in humans, but the AUC value in monkeys was 4.6 to 4.7 times that in humans and 1.8 to 1.9 times the maximum exposure (maximum AUC)[92] in humans, indicating certain difference. In addition, at the minimum toxic dose for the hematopoietic tissues in rats and dogs (80 and 30 mg/kg/day, respectively), changes in hematological parameters were small without histopathological changes. The AUC at this dose in dogs was comparable to the mean AUC in humans, and that in rats was comparable to the maximum AUC in humans. Furthermore, as described above, the IC_{50} value of favipiravir in the *in vitro* study in human bone marrow hematopoietic progenitor cells was greater than the C_{max} (mean)[93] in humans who received favipiravir in accordance with the proposed dosage regimen.

In consideration of these results and currently available clinical data, the use of favipiravir in patients at the proposed dosage regimen is unlikely to have significant effects on the hematopoietic tissues.

PMDA considers as follows:
The above response is acceptable. Given that the currently available clinical data have not suggested the risk of favipiravir on the hematopoietic tissues [see "4.(iii).B.(2) Safety"], the effects on the hematopoietic tissues have not raised particular concerns at present. However, the collection of information about the effects on the hematopoietic tissues should be continued in the future because the information obtained from the clinical use of favipiravir are limited.

3.(iii).B.(3) Hepatotoxicity
Concerning the effects on the liver found in the repeat-dose toxicity studies, PMDA asked the applicant to discuss the mechanism of development and risk in humans.

The applicant responded as follows:
In the 1-month repeated oral dose toxicity study in rats [see "3.(iii).A.(2).1) One-month oral dose study in rats"], increased blood ALP at ≥80 mg/kg/day and increases in blood ALT and total bilirubin at 200 mg/kg/day were observed, but no treatment-related histopathological changes in the liver were found in any animal including ones at 200 mg/kg/day which died during the study. In the 1-month repeated oral dose toxicity study in dogs [see "3.(iii).A.(2).2) One-month oral dose study in dogs"], increases in blood AST and ALT were observed at ≥100 mg/kg/day, and in animals at 100 [300] mg/kg/day which died during the study, decreased glycogen in the hepatocytes attributable to the deteriorated nutritional status was found, but no histopathological changes were observed in the liver in the surviving animals including ones at 100 [300] mg/kg/day. In the 2-week repeated oral dose toxicity study in monkeys [see "3.(iii).A.(2).3) Two-week oral dose study in monkeys"], increases in blood AST and ALT, increased liver weight, and histopathological vacuolization of the hepatocytes were observed at 300 mg/kg/day. The vacuolization of the hepatocytes observed in the study in monkeys is generally known to be induced by excessive fluid accumulation in the intracellular space that is attributable to cell membrane damage, as well as by the dilation of the endoplasmic reticulum resulting from intracellular water retention and impaired protein metabolism and/or from invaginated cell membrane attributable to increased hepatic sinusoidal pressure.[94] The effects of favipiravir on

[91] 633 μg·hr/mL (Multiple high-dose study in healthy adult Japanese male subjects [Study JP111])
[92] 1593 μg·hr/mL (Multiple high-dose study in healthy adult Japanese male subjects [Study JP111])
[93] 51.5 μg/mL (Multiple high-dose study in healthy adult Japanese male subjects [Study JP111])
[94] Japanese Society of Toxicologic Pathology (Tokyo), *Journal of Toxicologic Pathology.* 2000:179-213.

the liver are considered to result from its action on the cell membrane of the hepatocytes. In the 2-week repeated oral dose toxicity study in rabbits [see "3.(iii).A.(6).2).(b) Two-week repeated oral dose study in rabbits"], bile duct hyperplasia and inflammatory cell infiltration in the portal area possibly related to M1 were observed in the liver at 600 mg/kg/day, but these changes were mild, and there were no hepatic parameter abnormalities suggesting decreased hepatic function. The effects on the liver were therefore considered weak.

The favipiravir exposures in the repeat-dose toxicity studies were compared with that in humans who received favipiravir in accordance with proposed dosage regimen. Results indicated that there were no safety margins in comparison with the exposure at the NOAEL for the liver in the studies in rats and dogs (32 mg/kg/day and 30 mg/kg/day, respectively), while the exposure at the NOAEL (200 mg/kg/day) for the liver in the study in monkeys had a safety margin approximately 2 times the maximum exposure (maximum AUC)[95] in humans who received favipiravir in accordance with the proposed dosage regimen. In the studies in rats and dogs, even at the minimum toxic dose, which led to the exposure almost comparable to or approximately 2 times the maximum exposure[95] in humans, findings were only mildly increased hepatic enzyme parameters without histopathological changes, and these parameters did not increase remarkably with increasing exposure. Furthermore, no effects on the liver were observed in monkeys treated with favipiravir for 6 weeks at the dose leading to the exposure exceeding the maximum exposure[95] in humans [see "3.(iii).A.(6).5).(h) Six-week oral dose study in monkeys"]. In consideration of these results and currently available clinical data, the use of favipiravir in patients at the proposed dosage regimen is unlikely to have serious effects on the liver.

PMDA considers as follows:
The above response is acceptable. Given that the currently available clinical data have not suggested the serious effects of favipiravir on the liver [see "4.(iii).B.(2) Safety"], the effects on the liver have not raised particular concerns at present. However, the collection of information about the effects on the liver should be continued in the future because the information obtained from the clinical use of favipiravir are limited.

3.(iii).B.(4) Testis toxicity

Concerning the testis toxicity observed in the repeat-dose toxicity studies, PMDA asked the applicant to discuss the mechanism of development and risk in humans.

The applicant responded as follows:
To investigate the mechanism of the testis toxicity of favipiravir, histopathological examinations were performed chronologically in the 2-week dose testis toxicity study in rats [see "3.(iii).A.(6).5).(d) Two-week oral dose study in rats"]. In this study, at the dose of 300 mg/kg/day, dilation of the seminiferous tubule were observed on Day 5 of treatment and thereafter and degeneration/necrosis of the seminiferous epithelium were observed on Day 7 of treatment and thereafter. As the result of examination of the animals with slight changes on the seminiferous epithelium, the affected tissue was found to consist of the spermatocytes. In another 2-week dose testis toxicity study in rats [see "3.(iii).A.(6).5).(e) Two-week oral dose study in rats (investigation for the reversibility)"], degeneration of the seminiferous epithelium was observed at 200 mg/kg/day. The spermatocytes were affected in this study as well. Furthermore, in the combination study of male fertility and embryo-fetal development toxicity in rats [see "3.(iii).A.(5).2).(c) Combination study of male fertility and embryo-fetal development toxicity in rats"], degeneration of the spermatocytes was observed at ≥60 mg/kg/day. It is thus considered that the spermatocytes will be one of the target cell types of favipiravir in the testis. Dilation of the seminiferous tubule was observed at ≥200 mg/kg/day in the 2-week dose testis toxicity study in rats and at ≥60 mg/kg/day in the combination study of male fertility and embryo-fetal

[95] 1593 μg·hr/mL (Multiple high-dose study in healthy adult Japanese male subjects [Study JP111])

development toxicity in rats, but the quantitative analysis on the seminiferous tubule at each stage performed in the 2-week dose testis toxicity study in rats showed no abnormalities in seminiferous epithelium count per Sertoli cell [see "3.(iii).A.(6).5).(d) Two-week oral dose study in rats"]. The dilation of the seminiferous tubule was considered to be unrelated to shedding of the seminiferous epithelium. It is known that functional changes of Sertoli cells (increased production of seminiferous tubule fluid) can cause dilation of the seminiferous tubule,[96] and the retention of sperm cells found in the 2-week dose testis toxicity study in rats and the combination study of male fertility and embryo-fetal development toxicity in rats is also the finding reflecting impaired function of Sertoli cells.[96] Furthermore, in the 2-week dose testis toxicity study in rats [see "3.(iii).A.(6).5).(d) Two-week oral dose study in rats"], vacuolization of the Sertoli cells was observed at 300 mg/kg/day. Sertoli cells are also considered to be target cells of favipiravir. In the case where the spermatogonium cells are the primary target cells, the counts of spermatocytes at the pre-leptotene and leptotene stages in the seminiferous tubule at Stages IX to XIV are considered to decrease at the end of the 2-week treatment in general.[97] In the 2-week dose testis toxicity studies in rats indicating the testis toxicity [see "3.(iii).A.(6).5).(d) Two-week oral dose study in rats" and "3.(iii).A.(6).5).(e) Two-week oral dose study in rats (investigation for the reversibility)"], there were no histopathological findings suggesting spermatogonium cell damage such as the above-mentioned decreased seminiferous epithelium or furthermore degeneration/necrosis or disappearance of the spermatogonium cells. Based on the above, the target cells of favipiravir were considered to be spermatocytes and Sertoli cells but not spermatogonium cells.

The applicant's view on the risk in humans is as follows:
The NOAEL for the testis toxicity in rats decreased with increasing treatment period [see "3.(iii).A.(5).2).(c) Combination study of male fertility and embryo-fetal development toxicity in rats" and "3.(iii).A.(6).5).(c) Single and 1-week oral dose studies in rats" to "3.(iii).A.(6).5).(e) Two-week oral dose study in rats (investigation for the reversibility)"], and thus the testis toxicity in rats depends on the treatment period. Of the testis toxicity studies in rats which are the most sensitive to the testis toxicity of favipiravir, the 1-week dose study [see "3.(iii).A.(6).5).(c) Single and 1-week oral dose studies in rats"] used the treatment duration closest to that in clinical use (5 days). In this study, no testis toxicity was observed at 100 mg/kg/day, at which the exposure (AUC) in rats was 2.5 times the exposure (mean AUC)[98] in humans who received favipiravir in accordance with the proposed dosage regimen and comparable to the maximum exposure (maximum AUC)[99] in humans. In monkeys, no testis toxicity was observed after 2-week treatment at the dose of 300 mg/kg/day and 6-week treatment at the dose of 150 mg/kg/day, which led to the exposure 6.3 times and 1.2 times the maximum exposure[99] in humans, respectively [see "3.(iii).A.(2).3) Two-week oral dose study in monkeys" and "3.(iii).A.(6).5).(h) Six-week oral dose study in monkeys"]. Furthermore, the effects of 2-week favipiravir treatment on the testis in rats were demonstrated to resolve after the withdrawal [see "3.(iii).A.(6).5).(e) Two-week oral dose study in rats (investigation for the reversibility)"]. The testis toxicity of favipiravir is therefore unlikely to raise clinical concerns.

PMDA considers as follows:
The above response is acceptable. The effects on the testis in humans have not raised particular concerns, taking the following findings into account: (1) the use of favipiravir in monkeys for 6 weeks, which is equivalent to the sperm formation period (6 weeks) of the species, did not have any effect on the testis while the proposed treatment duration of favipiravir is 5 days, and in addition, study data in rats suggested that the testis toxicity of favipiravir depends on the treatment duration of favipiravir; (2) the study data suggested that the target cells of favipiravir does not

[96] *Toxicol Pathol.* 2002;30:507-520.
[97] *Toxicol Pathol.* 1997;25:119-131.
[98] 633 μg·hr/mL (Multiple high-dose study in healthy adult Japanese male subjects [Study JP111])
[99] 1593 μg·hr/mL (Multiple high-dose study in healthy adult Japanese male subjects [Study JP111])

include spermatogonium cells and showed that the testis toxicity in rats were reversible; (3) the foreign clinical study (testis safety study [Study US105]) did not suggest the testis toxicity of favipiravir [see "4.(iii).A.(1).17) Testis safety study in healthy adult US subjects"].

3.(iii).B.(5) Deaths in the pharmacology study in monkeys infected with influenza virus

In the pharmacology study [see 4.2.1.1.34] in cynomolgus monkeys infected with highly pathogenic avian influenza A [redacted] (H5N1) virus, no deaths occurred in the control group, while death occurred in 1 of 3 animals each in the favipiravir high-dose group (first dose, 300 mg/kg/day; second and subsequent doses, 150 mg/kg/day) and low-dose group (first dose, 180 mg/kg/day; second and subsequent doses, 90 mg/kg/day). PMDA asked the applicant to explain the relationship of favipiravir with the death.

The applicant responded as follows:

The death occurred only in the favipiravir group, but no serious histopathological changes were observed in the dead animal except for the lungs and the death was considered to be caused by viral pneumonia. In the highly pathogenic avian influenza A (H5N1) virus infection study in cynomolgus monkeys using the same infection method as that in this study, death due to viral infection was also reported.[100] In this study, anesthetics (ketamine, xylazine) were used when favipiravir was administered, and thus a concomitant use toxicity study was conducted to investigate the toxicological interaction of these anesthetics with favipiravir [see "3.(iii).A.(6).7) Toxicity study of concomitant use with anesthetics"]. As a result, the concomitant use of favipiravir with the anesthetics did not clearly aggrevate the toxicity or affect the pharmacokinetics. Furthermore, in the study investigating the effects of favipiravir on the immunity [see "3.(iii).A.(6).1) Immunotoxicity studies"], neither antibody nor cytokine production was affected. In this study, there were no clear differences in blood cytokines (IFN-γ, MCP-1, IL-6, IL-8, TNF-α) between the favipiravir group and control group. Data from the above studies and this pharmacology study showed that the blood concentration of favipiravir in monkeys in the favipiravir group remained below the lower limit of quantitation (<0.1 μg/mL) after the first dose, and after the second and subsequent doses, the concentration remained below the estimated value. Based on the above, the death was considered unrelated to favipiravir. In the favipiravir group, additional anesthesia was more frequently performed than in the other groups, and anesthesia with ketamine has been reported to affect the animal immune status.[101] Based on the above, it was considered that the additional anesthesia may have affected the pathological progression of influenza virus infection, leading to the death.

The applicant considers that it is important to identify the cause of death in monkeys in this study. In addition, favipiravir has a mechanism of action different from those of the existing influenza antiviral drugs and thus is expected to be used in patients with highly pathogenic avian influenza virus infection. To evaluate the efficacy of favipiravir against highly pathogenic avian influenza A (H5N1) virus in not only the mouse infection model but also the cynomolgus monkey infection model, planning of a re-study is underway. The re-study is intended to ensure the integrity of the study; to use the BID regimen for appropriate exposure of favipiravir in consideration that the exposure was not sufficient in this study; and to administer favipiravir without anesthesia so as to avoid excessive procedure-related burden on the monkeys.[102] The pharmacology data in cynomolgus monkeys infected with H5N1 will be provided in the Pharmacology section of the interview form as the reference information.

PMDA considers as follows:

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[100] *Proc Natl Acad Sci USA.* 2009;106:3455-3460.

[101] *Clin Exp Immunol.* 1982;47:457-466.

[102] The final report of the re-study was planned to be completed in [redacted], but this study was not conducted because subsequent investigation found it difficult to conduct the study.

Favipiravir is unlikely to be related to the death, but at present it is difficult to determine the cause of the death only involved in the favipiravir group as viral pneumonia and the relationship of favipiravir with the death cannot be completely ruled out, because no death occurred in the control group in which the lung virus titer was comparable to that in the favipiravir group; and the number of animals investigated was limited (3 animals each per group). Therefore, the relationship of favipiravir with the death in monkeys should be assessed again based on the data from the re-study, and then it is necessary to consider whether or not the relevant information should be further provided to healthcare professionals in clinical practice.

4. Clinical data

4.(i) Summary of biopharmaceutic studies and associated analytical methods

4.(i).A Summary of the submitted data

Biopharmaceutic studies conducted include dissolution studies, food effect studies, and bioequivalence studies. Plasma and urine concentrations of favipiravir and favipiravir hydroxide (M1) were determined by the high performance liquid chromatography (HPLC) assay. Plasma and urine concentrations of concomitant drugs used in drug-drug interaction studies (analytes; theophylline, oseltamivir, and oseltamivir carboxylate) determined by the high performance liquid chromatography/tandem mass spectrometry (LC/MS/MS) assay.

4.(i).A.(1) Dissolution studies (2.7.1.2.1)

The dissolution profiles of the capsule formations used in the clinical trials[103] (30 mg capsule, 100 mg capsule) and the tablet formulations (100 mg tablet,[104] 200 mg tablet[105]) were compared with reference to the Japanese and foreign guidelines.[106] [redacted].

4.(i).A.(2) Food effect

4.(i).A.(2).1 Preliminary food effect study in healthy adult Japanese subjects (5.3.1.1.1, Study JP102 [[redacted] to [redacted]])

A single dose of favipiravir 400 mg (100 mg capsule × 4) was orally administered to 12 healthy adult Japanese male subjects in the fasted state and fed state (30 minutes after the start of a high fat diet) in a two-treatment, two-period, crossover study to investigate the food effect on the pharmacokinetics preliminarily. Following administration of favipiravir in the fasted and fed states, the geometric mean C_{max} (CV) was 15.58 (26.5%) and 7.18 (21.1%) μg/mL, respectively, the geometric mean AUC from time zero to infinity (CV) was 42.11 (36.7%) and 36.64 (31.3%) μg·hr/mL, respectively, and the median t_{max} (minimum, maximum) was 0.5 (0.5, 1) and 2.0 (1.5, 4) hours, respectively. The geometric mean ratios (90% CI) of C_{max} and AUC of favipiravir in the fed state to those in the fasted state were 0.460 (0.397-0.534) and 0.870 (0.808-0.937), respectively, and the 90% CI of the ratio for C_{max} did not fall within the specified range (0.80-1.25).[107]

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[103] Used in the [redacted] clinical pharmacology studies (single dose study [Study JP101], preliminary food effect study [Study JP102], multiple dose study [Study JP103], single dose study in the elderly [Study JP104], single low-dose study [Study US101], single high-dose study [Study US102], and multiple dose study [Study US103]) (30 mg capsules was used only in Study JP101 and Study US101).

[104] Used in dose-response phase II study (Study JP205), supplemental multiple dose study (Study JP106), multiple dose study in the elderly (Study JP107), drug-drug interaction studies (Studies JP108 and JP109), bioequivalence study (Study JP110).

[105] Final formulation (to-be-marketed); used in bioequivalence study (Study JP110), multiple high-dose study (Study JP111), comparative study (Study 312), pharmacokinetic study in patients (Study JP313), food effect study (Study JP114), QT evaluation study (Study JP115), multiple high-dose study (Study US103b), and testis safety study (Study US105).

[106] "Guidelines for Bioequivalence Testing of Generic Drugs (partial revision, PFSB/ELD Notification No. 1124004 dated November 24, 2006)," "Guideline for Bioequivalence Studies for Different Strengths of Oral Solid Dosage Forms (partial revision, PFSB/ELD Notification No. 1124004 dated November 24, 2006)," and "Guidance for Industry Waiver of In Vivo Bioavailability and Bioequivalence Studies for Immediate-Release Solid Oral Dosage Forms Based on a Biopharmaceutics Classification System. FDA/CDER (2002)"

[107] "Guidance for Industry. Food-Effect Bioavailability and Fed Bioequivalence Studies. FDA/CDER (2002)"

4.(i).A.(2).2) Food effect study in healthy adult Japanese subjects (5.3.1.1.2, Study JP114 [[redacted] to [redacted]])

A single dose of favipiravir 1200 mg (200 mg capsule × 6) was orally administered to 16 healthy adult Japanese male subjects in the fasted state and fed state (30 minutes after start of a high fat diet) in a two-treatment, two-period, crossover study to investigate the food effect on the pharmacokinetics. Following administration of favipiravir in the fasted and fed states, the geometric mean C_{max} (CV) was 44.24 (23.7%) and 40.29 (17.1%) μg/mL, respectively, the geometric mean AUC (CV) was 280.95 (59.3%) and 271.58 (53.3%) μg·hr/mL, respectively, and the median t_{max} (minimum, maximum) was 1.0 (0.5, 3) and 2.0 (1, 3) hours, respectively. The geometric mean ratios (90% CI) of C_{max} and AUC_{0-t} of favipiravir in the fed state to those in the fasted state were 0.908 (0.826-0.998) and 0.963 (0.888-1.044), respectively, and the 90% CI of the geometric mean ratios for both parameters fell within the specified range (0.80-1.25).[107]

4.(i).A.(3) Bioequivalence study in healthy adult Japanese subjects (5.3.1.2.1, Study JP110 [[redacted] to [redacted]])

A single dose of favipiravir 400 mg (100 mg tablet × 4, 200 mg tablet × 2) was orally administered to 24 healthy adult Japanese male subjects in the fasted state in a two-treatment and two-period crossover study to compare the pharmacokinetics of the two formulations. The geometric mean C_{max} (CV) following single oral administration of 100 mg tablet × 4 and 200 mg tablet × 2 was 15.98 (14.3%) and 16.22 (19.5%) μg/mL, respectively, and the geometric mean AUC (CV) was 46.67 (26.4%) and 46.39 (24.7%) μg·hr/mL, respectively. The geometric mean ratio (90% CI)[108] of C_{max} and AUC_{0-24} after administration of 200 mg tablet × 2 to those after administration of 100 mg tablet × 4 were 1.017 (0.933-1.108) and 0.996 (0.942-1.053), respectively, and the 90% CI of the geometric mean ratio for both parameters fell within the specified range (0.80-1.25). The formulation of the 100 mg tablet was therefore determined to be biologically equivalent to the final formulation of the 200 mg tablet.

4.(i).B Outline of the review by PMDA

4.(i).*B*.(1) Food effect

In comparison between 2 food effect studies (food effect study [Study JP114], preliminary food effect study [Study JP102]), the C_{max} of favipiravir 400 mg in the fed state decreased by approximately 50% as compared to that in the fasted state, but at 1200 mg, the C_{max} decreased by approximately 10%.

The applicant explained the difference in the results between the 2 studies as follows:
In the preliminary food effect study of favipiravir at 400 mg (100 mg capsule × 4), the metabolic clearance did not decrease, leading to the decrease in C_{max} in the fed state, but in the single dose study of favipiravir at 1200 mg (200 mg tablet × 6) (Study JP114), the metabolic clearance decreased, leading to increased plasma favipiravir concentrations[109] which offset the food effect, resulting in the apparently almost unchanged C_{max}. In addition, in subjects treated with favipiravir in accordance with the proposed dosage regimen, the plasma concentration of favipiravir increase due to irreversible inhibition (mechanism based inhibition [MBI]) against AO as a consequence of the multiple doses of favipiravir [see "4.(ii).A.(1).4).(c) Inhibitory effect against AO" and "4.(ii).A.(2).4) Multiple high-dose study in healthy adult Japanese subjects"], resulting in the reduced food effect on C_{max}; therefore there is no food effect on the drug action.

[108] "Guidelines for Bioequivalence Testing of Generic Drugs (partial revision, PFSB/ELD Notification No. 1124004 dated November 24, 2006)"

[109] The increased plasma concentration due to the decreased metabolic clearance was found following single oral high-dose of favipiravir at ≥800 mg [see "4.(ii).A.(2).1) Single dose study in healthy adult Japanese subjects"].

PMDA asked the applicant to present data on the plasma concentration and efficacy of favipiravir administered in the fed state at the proposed dosage regimen if available as well as simulation data of the plasma concentration of favipiravir in the fasted and fed states at the proposed dosage regimen and then to explain effects of the decreased plasma concentration of favipiravir in the fed state on the drug action.

The applicant responded as follows:
In the dose-response study (Study JP205), pharmacokinetics study in patients (Study JP313), and global phase III study (Study 312) in Japanese patients with influenza virus infection, dosing timing of favipiravir was specified as "favipiravir should be taken at least 30 minutes after a meal when taken in the fed state." There are no data available for comparison of the food effect on the efficacy of favipiravir between in the fasted and fed states (immediately after a meal). In addition, there are no data on plasma concentrations of favipiravir in the fed state (immediately after a meal).

In Study JP102, the plasma kinetics of favipiravir in the fed state was investigated. Food delayed t_{max} by 1.5 hours, decreased C_{max} by approximately 50%, and decreased AUC by approximately 13%. Therefore, the concentration- and the time-dependent MBI-PK model was applied to the plasma concentrations of favipiravir in this study to determine the absorption rate constant (k_a). The results showed that k_a was reduced by food. It was suggested that the absorption of favipiravir was slow in the fed state, resulting in the delayed t_{max} and decreased C_{max}. The (mean) ratio of k_a of favipiravir in the fed state to that of favipiravir in the fasted state was 0.247, and the smallest individual ratio of k_a was 0.043. In the subject with the smallest ratio, AUC values of favipiravir in the fasted and fed states were 71.38 μg·hr/mL and 45.83 μg·hr/mL, respectively, showing an approximately 36% decrease in AUC in the fed state. In the pharmacokinetic simulation of multiple oral doses of 400 mg of favipiravir BID for 5 days, the food-induced decrease in AUC was estimated to be approximately 30% to 35%, indicating that multiple-dose favipiravir will reduce the food effect.

Furthermore, the mean ratio of k_a of favipiravir in the fed state to that of favipiravir in the fasted state calculated from the data obtained in Study JP102 was 0.247. Using this value, the k_a of favipiravir in the fed state was calculated for each subject in the Group 1 in the multiple high-dose study (Study JP111) in which the dosage regimen up to Day 5 were the same as the proposed one. The result was k_a = 0.330 (k_a ratio [0.247] × k_a of favipiravir in the fasted state [1.337]). When the k_a of favipiravir was decreased from that of favipiravir in the fasted state by approximately 20%, the AUC was predicted to decrease by up to 15% from Day 1 to Day 5. Even in this case, the following efficacy criteria for the favipiravir RTP concentration in the human lungs were met: (a) the estimated C_{min} of favipiravir RTP in the lungs at the early stage of the infection is ≥0.3 μmol/kg (in mice infected with influenza A/Osaka/5/70 [H3N2] virus, the inhibition rate against lung virus replication at 48 hours after the infection is ≥90%); and (b) the percentage of the period in which the estimated favipiravir RTP concentration in the lungs is maintained at 0.4 μmol/kg (time above 0.4 μmol/kg) with respect to the treatment period is ≥50% (the survival rate of mice infected with influenza A/Osaka/5/70 [H3N2] virus 21 days after the infection is ≥90%). As described above, the plasma concentration of favipiravir is affected by food, leading to the delayed t_{max}, decreased C_{max}, and slightly decreased AUC, but the favipiravir RTP concentration in the lungs can be maintained at a level considered necessary to be effective.Favipiravir administered in the fed state, therefore, is considered to have only marginal effects on the drug action.

PMDA considers as follows:
The results of the preliminary food effect study (Study JP102) were different from those of the food effect study (Study JP114). Although these studies used different formulations and doses, the difference is understood as a possible consequence of the different metabolic clearance due to

the different doses rather than due to the different formulations in consideration of the dissolution and pharmacokinetic profiles of the 100 mg capsule and 200 mg tablet [see "4.(i).A.(1) Dissolution studies," and "4.(i).A.(3) Bioequivalence study in healthy adult Japanese subjects," as well as "4.(ii).A.(2).1) Single-dose study in healthy adult Japanese subjects"]. Favipiravir is intended to be repeatedly administered to patients with influenza virus infection for 5 days. According to the above simulation results, the food effect on the pharmacokinetics of multiple doses of favipiravir 400 mg is expected to be smaller than that of its single dose, but the efficacy and safety of favipiravir were evaluated in the confirmatory study in which the dosing timing was specified as "favipiravir should be taken at least 30 minutes after a meal when taken in the fed state," and there are no clinical data on favipiravir administered within 30 minutes after a meal. The dosing timing of favipiravir should be, therefore, advised in the package insert after review of the currently available information.

4.(ii) Summary of clinical pharmacology studies

4.(ii).A Summary of the submitted data

The results from the following pharmacokinetic studies of favipiravir were submitted: 1 single-dose study in healthy adult Japanese subjects, 3 multiple dose studies, 2 drug-drug interaction studies, 1 QT/QTc evaluation study, 1 pharmacokinetic study in Japanese patients with influenza virus infection, 2 pharmacokinetic studies in healthy elderly Japanese subjects, and 1 testis safety study in healthy adult US subjects. As the reference data, the results from 2 single-dose studies and 2 multiple dose studies in healthy adult US subjects were submitted.

4.(ii).A.(1) Studies using human biomaterials (5.3.2.1.1 to 5.3.2.1.2, 5.3.2.2.1 to 5.3.2.2.13, 5.3.2.3.1 to 5.3.2.3.6)

4.(ii).A.(1).1) *In vitro* serum protein binding

The *in vitro* protein binding rate of ^{14}C-labeled favipiravir in human serum was almost constant (53.4%-54.4%) in the concentration range examined (0.3-30 μg/mL). The *in vitro* protein binding rate of M1 in human serum was 28.8% to 36.9% in the concentration range examined (0.5-50 μg/mL).

4.(ii).A.(1).2) *In vitro* metabolism

(a) Investigation of favipiravir-metabolizing enzymes

In the *in vitro* metabolism study of ^{14}C-labeled favipiravir (60 μmol/L) using human liver microsome (protein concentration, 1 mg/mL), the percentage (over time) of favipiravir with and without the nicotinamide adenine dinucleotide phosphate (reduced form) (NADPH) generating system was 98.5% to 98.8% and 96.9% to 98.8%, respectively. No NADPH- or time-dependent favipiravir metabolism was observed. On the other hand, in the *in vitro* metabolism study of ^{14}C-labeled favipiravir (60 μmol/L) using human hepatic cytosol (protein concentration, 5 mg/mL), M1 was formed both with and without the NADPH generating system, but the amount of M1 increased with the NADPH generating system, showing that favipiravir is metabolized to M1 mainly by NADPH-independent enzymes and partially by NADPH-dependent enzymes in the human hepatic cytosol.

In the *in vitro* metabolism inhibitory study of ^{14}C-labeled favipiravir (60 μmol/L) using human hepatic cytosol (protein concentration, 5 mg/mL), menadione and isovanillin (AO inhibitors) and allopurinol (XO inhibitor) inhibited the formation of M1 in a concentration-dependent manner (concentrations examined; 1, 10, 100 μmol/L). The inhibition rate at 100 μmol/L was 73.6% for menadione, 52.6% for isovanillin, and 27.3% for allopurinol.

Correlation of the metabolism of favipiravir to M1 with the AO and XO activities was investigated in individual human hepatic cytosol samples (from 8 male subjects and 8 female subjects). As a result, the M1 formation activity is significantly correlated with the AO activity (correlation

coefficient, 0.675; *P* value, 0.004), showing that favipiravir is metabolized to M1 mainly by AO. On the other hand, there was no correlation of the M1 formation activity to the XO activity.

(b) Favipiravir metabolite profile in hepatocytes

The *in vitro* metabolite profile of ^{14}C-labeled favipiravir (30, 300 μmol/L) in humans frozen hepatocytes (1×10^6 cells/mL) was investigated. As a result, favipiravir (unchanged favipiravir) was detected as the most abundant labeled substance followed by favipiravir hydroxide (M1). Two polar metabolites (glucuronide conjugate of favipiravir [M2], UM3, unidentified metabolite) were detected as trace metabolites. These metabolites were not detected in mouse, rat, or dog hepatocytes, but identical with the metabolites detected in the plasma, tissues (lung, liver, kidney, testis), urine, and bile from male rats receiving a single oral dose of ^{14}C-labeled favipiravir at 20 mg/kg and thus considered to be not human-specific.

(c) Metabolism to favipiravir RTP in human peripheral blood mononuclear cells (PBMC)

In the *in vitro* metabolism study of favipiravir (300-1200 μmol/L) using human PBMC (pool of cells from 8 healthy adult male subjects), the results showed that favipiravir RTP was formed in PBMC in a concentration- and time-dependent manner. The $t_{1/2}$ of favipiravir RTP after removal of favipiravir was 2.05 hours.

4.(ii).A.(1).3) *In vivo* metabolism

Metabolite profiles in the plasma and urine from healthy adult subjects were investigated following a single oral dose of favipiravir 1600 mg (Study JP101) and 400 mg (Study US101) and multiple oral doses of favipiravir 400 mg 3 times daily (TID) (Study JP103). Favipiravir, M1, and glucuronide conjugate of favipiravir (M2) were found in the human plasma and urine obtained after single-dose administration, but no human-specific metabolites were detected. There were no differences in plasma or urine metabolite species between multiple and single oral doses.

4.(ii).A.(1).4) *In vitro* drug-drug interaction

(a) Inhibitory effect against human cytochrome P-450 (CYP)

In the *in vitro* CYP inhibition study, the inhibitory effects of favipiravir against major human hepatic CYP isoforms (CYP1A2, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4) activity were investigated in human liver microsome (favipiravir concentrations examined, 8-800 μmol/L). As a result, favipiravir inhibited the CYP2C8 activity in a concentration-dependent manner, with the 50% inhibitory concentration (IC_{50}) of 477 μmol/L (74.9 μg/mL). The metabolic activities of the other CYP isoforms in the presence of favipiravir at the maximum concentration (800 μmol/L [126 μg/mL])[110] were all ≥60% of the control, and IC_{50} values was >800 μmol/L (126 μg/mL) for any isoforms. M1 (concentrations examined, 0.123-270 μmol/L), the major metabolite of favipiravir, decreased the CYP2E1 activity to 72.6% of the control at the maximum concentration (270 μmol/L [46.7 μg/mL]), but hardly inhibited activities of other CYP isoforms with IC_{50} values of >270 μmol/L (46.7 μg/mL) for any isoforms.

(b) Induction action on CYPs

In the *in vitro* CYP induction study, the effects of favipiravir on human hepatic CYP isoforms (CYP1A2, 2C9, 2C19, 3A4) were investigated in fresh human primary hepatocytes. As a result, favipiravir increased the expression of the CYP isoforms up to 1.7 times (mean) in the concentration range examined (8-800 μmol/L), and this induction rate of favipiravir was ≤6.6% of those of the positive controls (omeprazole, rifampicin).

[110] Higher than the highest value (78.9 μg/mL [Study JP111]) of the estimated maximum plasma concentration of favipiravir in the proposed dosage regimen

(c) Inhibitory effect against AO

In the *in vitro* inhibition study, the inhibitory effects of favipiravir against the AO activity were investigated in human hepatic cytosol. As a result, the residual metabolic activity (phthalazone formation activity) of phthalazine, a substrate of AO, decreased favipiravir concentration (20-6000 μmol/L) and preincubation time (0-60 minutes)-dependently, showing MBI of favipiravir against AO.

(d) Inhibitory effect against XO

In the *in vitro* inhibition study, the inhibitory effects of favipiravir against the XO activity were investigated in human hepatic cytosol. As a result, favipiravir did not inhibit the metabolism of 1-methylxanthine, a metabolite of theophylline (substrate of XO), concentration (30-3000 μmol/L) or preincubation time (5 minutes, 60 minutes)-dependently.

(e) Interaction with acetaminophen

In the *in vitro* inhibition study, the inhibitory effects of favipiravir and M1 against acetaminophen metabolism were investigated in human liver S9. As a result, favipiravir did not inhibit the glucuronide conjugation metabolism of acetaminophen in the concentration range examined (30-3000 μmol/L), but inhibited the sulfate conjugation metabolism (IC_{50} = 150 μmol/L [23.6 μg/mL]). M1 did not inhibit glucuronide or sulfate conjugation metabolism of acetaminophen in the concentration range examined (3-300 μmol/L).

(f) Interaction with oseltamivir

In the *in vitro* inhibition study, the inhibitory effects of favipiravir and M1 against oseltamivir metabolism were investigated in human liver S9. As a result, favipiravir inhibited deesterification of oseltamivir in the concentration range examined (30-3000 μmol/L) (residual activity at 3000 μmol/L [471 μg/mL], 71.7%), but IC_{50} values were ≥3000 μmol/L. M1 did not inhibit deesterification of oseltamivir in the concentration range examined (3-300 μmol/L).

(g) P-gp transportation

A membrane fraction from the human MDR1 expressing cells was used to investigate P-gp's substrate recognition. As a result, favipiravir (5-1000 μmol/L) and M1 (1-500 μmol/L) did not increase the adenosinetriphosphatase (ATPase) activity concentration-dependently, suggesting that neither of them will act as a substrate of P-gp. Investigation in LLC-GA5-CoL300 cells[111] showed that favipiravir (5 mmol/L) and M1 (1 mmol/L) decreased the P-gp's transportation activity of the standard substrate to 81.9% and 85.2% (mean) of the control, respectively.[112]

4.(ii).A.(1).5) Others

(a) Human transporters

S2 cells and HEK293 cells were used to investigate non-P-gp transporters' substrate recognition (human organic anion transporters [hOAT1, hOAT2, hOAT3, hOAT4], human organic cation transporters [hOCT1, hOCT2, hOCT3], human organic anion transport polypeptide [hOATP2] human urate transporter [hURAT1]). As a result, favipiravir did not act as the substrate of any of the 9 transporters examined. Favipiravir and M1 inhibited activities of various transporters. Favipiravir inhibited uptake of the standard substrate by hOAT1, hOAT3, and hURAT1 at 800 μmol/L (126 μg/mL), decreasing their uptake activity (mean) to 30.9%, 50.0%, and 65.7% of the control, respectively. M1 inhibited uptake of the standard substrate by hOAT1, hOAT3, and hURAT1 at 300 μmol/L (51.9 μg/mL), decreasing their uptake activity (mean) to 45.4%, 57.7%, and 31.0% of the control, respectively. Furthermore, hURAT1 expressing cells were pre-incubated with favipiravir or M1 followed by their removal for the investigation. As a result,

[111] Human P-gp expressing LLC-PK1 cells (pig renal tubular cell strain)

[112] The concentration in the study was higher than that in the plasma predicted in humans treated in accordance with the proposed dosage regimen.

favipiravir inhibited uric acid uptake by hURAT1 expressing cells in a concentration-dependent manner, while M1 enhanced the uptake in a concentration-dependent manner.

(b) Urinary excretion rate in humans

The urinary excretion rate of M2 was investigated using urine samples collected from 6 healthy adult Japanese subjects who orally received favipiravir at 400 mg as a single dose (Study JP101). As a result, the urinary excretion rate of M2 up to 48 hours after dosing was 2.3% to 4.2%. The urinary excretion rates of favipiravir and M1 in Study JP101 were 0.1% to 0.4% and 82.0% to 92.4%, respectively, and the mean total urinary recovery rate at doses examined was 90.5%.

(c) AO activity evaluation

In 1 subject each in the theophylline coadministration study (Study JP108) and multiple high-dose study (Study JP111), the plasma concentration of favipiravir was higher than that in other subjects, while the plasma concentration of M1 was lower than that in the other subjects. Urine samples were collected from the subjects included in Study JP108 and Study JP111 (Group 1) (10 subjects and 6 subjects excluding those treated with placebo, respectively) to investigate the relationship of the plasma drug concentration with the AO activity. The AO activity was indirectly evaluated using the ratio of pyridone formation (RP) value as the index.[113] As a result, the RP value in the subject with high plasma concentrations of favipiravir (low plasma concentrations of M1) in Study JP108 was 0.470, which was lower than the RP values in the other subjects (0.665-0.881). In the subject with the RP value of 0.470, the ratios of C_{max}, AUC, and C_{12} (plasma concentration at 12 hours after dosing) of M1 to favipiravir were 0.013, 0.102, and 0.020, respectively, which were the lowest among individual values in 10 subjects for the corresponding ratio. On the other hand, the RP value in the subject with the high plasma concentration of favipiravir (low plasma concentration of M1) in Study JP111 was 0.493, which was lower than the RP values in the other 6 subjects (0.645-0.870) except for 1 subject.[114] In the subject with the RP value of 0.493, the ratios of C_{max}, AUC, and C_{12} of M1 to favipiravir were 0.013, 0.025, and 0.017, respectively, which were the lowest among individual values in 6 subjects (treated with favipiravir) for the corresponding ratio.

4.(ii).A.(2) Investigation in healthy adult subjects

4.(ii).A.(2).1) Single dose study in healthy adult Japanese subjects (5.3.3.1.1, Study JP101 [[redacted] to [redacted]])

A single dose of favipiravir 30 to 1600 mg was orally administered to 36 healthy adult Japanese male subjects (included in the pharmacokinetic analysis, aged 20-39 years) in the fasted state to investigate the pharmacokinetics. The results are as shown in the table below.

[113] The AO activity was evaluated by calculation of the RP value, which was based on the metabolic and excretion process of nicotinamide. In this process, the *N*[1]-methylnicotinamide (NMN), a metabolite of nicotinamide, is oxidized by the hepatic AO followed by its degradation into *N*[1]-methyl-2-pyridone-5-carboxamide (2-pyridone form) and *N*[1]-methyl-4-pyridone-3-carboxamide (4-pyridone form), which are then excreted into urine. The RP value is calculated according to the formula, ([2-pyridone form + 4-pyridone form]/[2-pyridone form + 4-pyridone form + NMN]).

[114] Only the NMN concentration in this subject was higher than that in the other subjects, and the high value may have affected the calculation of the RP value. It has been empirically known that the NMN concentration is affected by food or nicotine intake through smoking, and there are cases where the metabolism of favipiravir cannot be explained by the RP value as observed in the subject. The applicant therefore discussed that further investigation should be implemented to identify background factors affecting the RP value, etc.

Pharmacokinetic parameters of favipiravir following single oral dose of favipiravir at 30 to 1600 mg

Pharmacokinetic parameter	30 mg	90 mg	200 mg	400 mg	800 mg	1600 mg
C_{max} [a] (μg/mL)	1.39 (17.9)	4.06 (17.4)	8.39 (11.1)	16.59 (6.0)	33.35 (22.6)	78.61 (26.5)
t_{max} [c] (hr)	0.5 (0.25, 0.5)	0.5 (0.25, 0.75)	0.5 (0.5, 0.5)	0.5 (0.25, 0.75)	0.9 (0.5, 1)	0.6 (0.5, 0.75)
AUC [a] (μg·hr/mL)	2.58 (20.2)	9.23 (12.6)	19.67 (18.2)	39.41 (16.0)	113.15 (26.6)	538.42 (9.7)
$t_{1/2}$ [b] (hr)	1.3 ± 0.1	1.5 ± 0.1	1.5 ± 0.2	1.6 ± 0.2	2.2 ± 0.3	3.9 ± 0.3
CL/F [b] (L/hr)	11.80 ± 1.92	9.81 ± 1.28	10.35 ± 2.24	10.26 ± 1.63	7.31 ± 2.17	2.98 ± 0.30
Vd/F [b] (L)	21.54 ± 1.93	21.44 ± 2.86	22.61 ± 3.04	23.80 ± 3.15	22.45 ± 3.00	16.73 ± 1.55
MRT [b] (hr)	2.0 ± 0.3	2.3 ± 0.2	2.4 ± 0.3	2.5 ± 0.3	3.5 ± 0.7	7.0 ± 0.7
UR [b] [d] (%)	0.0 ± 0.0	0.2 ± 0.2	0.3 ± 0.1	0.2 ± 0.1	0.3 ± 0.0	0.5 ± 0.1

a) Geometric mean (CV%), b) Mean ± SD, c) Median (minimum, maximum)
d) Urinary excretion rate from 0 to 48 hours (calculated from the data in 5 subjects in the 90 mg group, except for those in 1 subject who disposed of the urine)
n = 6 per group

Pharmacokinetic parameters of M1 following single oral dose of favipiravir at 30 to 1600 mg

Pharmacokinetic parameter	30 mg	90 mg	200 mg	400 mg	800 mg	1600 mg
C_{max} [a] (μg/mL)	0.52 (13.8)	1.33 (10.1)	2.77 (7.6)	5.68 (24.2)	10.12 (16.8)	15.28 (22.9)
t_{max} [c] (hr)	0.8 (0.5, 1)	0.8 (0.5, 1.5)	0.8 (0.75, 1)	0.9 (0.5, 1)	1.1 (0.5, 1.5)	1.0 (0.75, 1.5)
AUC [a] (μg·hr/mL)	1.66 (10.4)	4.89 (10.1)	10.31 (18.6)	20.42 (23.4)	44.34 (6.7)	93.70 (7.0)
$t_{1/2}$ [b] (hr)	1.8 ± 0.1	2.1 ± 0.1	2.0 ± 0.3	2.4 ± 0.8	3.0 ± 0.5	5.1 ± 0.4
CL_r [b] [e] (L/hr)	16.41 ± 2.16	19.65 ± 5.50	17.73 ± 3.88	19.04 ± 4.03	16.20 ± 1.68	14.57 ± 1.20
MRT [b] (hr)	3.1 ± 0.3	3.4 ± 0.2	3.4 ± 0.4	3.4 ± 0.2	4.3 ± 0.8	7.3 ± 0.7
UR [b] [d] (%)	81.9 ± 4.2	94.8 ± 16.1	81.4 ± 6.8	86.7 ± 4.3	81.2 ± 4.2	77.3 ± 4.3

a) Geometric mean (CV%), b) Mean ± SD, c) Median (minimum, maximum)
d) Urinary excretion rate from 0 to 48 hours (calculated from the data in 5 subjects in the 90 mg group, excluding data of 1 subject whose urine was disposed
e) Calculated from the data in 5 subjects in the 90 mg group, excluding data of 1 subject whose urine was disposed
n = 6 per group

The C_{max} and AUC values of favipiravir and M1 increased with increasing doses. The C_{max} of favipiravir was linear in the dose range from 30 to 1600 mg, while the AUC values at the dose of ≥800 mg remained higher than the value expected from the dose-proportional relationship. There were no considerable differences in t_{max} of favipiravir or M1 among the doses, but $t_{1/2}$ and MRT prolonged at the high doses of ≥800 mg. The cumulative urinary excretion rate of favipiravir up to 48 hours after dosing was ≤0.5% at any dose, while those of M1 were 81.2% to 94.8% at 30 to 800 mg and 77.3% at 1600 mg.

4.(ii).A.(2).2) Multiple dose study in healthy adult Japanese subjects (5.3.3.1.4, Study JP103 [[redacted] to [redacted]])

Multiple oral doses of favipiravir were administered in accordance with the following dosage regimen to 18 healthy adult Japanese male subjects (included in the pharmacokinetic analysis, aged 20-34 years) in the fasted state[115] to investigate the pharmacokinetics.

Group 1: Favipiravir 400 mg 3 times daily (TID) (BID on Day 1, TID from Day 2 to the morning on Day 8)
Group 2: Favipiravir 400 mg TID (Days 1-2) and 400 mg once daily (QD) (Days 3-7)
Group 3: Favipiravir 600 mg BID (Days 1-2) and 600 mg QD (Days 3-7)

In Group 1 in which favipiravir was administered TID at 400 mg for 7 days (8 days in total), the ratio of the minimum plasma concentration (C_{min}) on Day 8 after multiple dose administration to that on Day 1 (C_{min} ratio) was approximately 130. In Groups 2 and 3 in which the regimen was changed to QD on Day 3, the C_{min} ratio increased on Day 2, but the C_{min} ratio was below 1 in Group 2 on Day 3 and thereafter and in Group 3 on Day 6 and thereafter. Pharmacokinetic parameters of favipiravir and M1 are as shown in the table below.

[115] One hour before a meal

Pharmacokinetic parameters of favipiravir and M1 in Group 1 (400 mg TID for 7 days)

Pharmacokinetic parameter	Favipiravir			M1		
	Day 1	Day 4	Day 8	Day 1	Day 4	Day 8
C_{max} [a] (μg/mL)	17.24 (10.3)	36.15 (28.8)	43.83 (35.5)	4.87 (14.4)	2.40 (15.0)	2.61 (14.2)
t_{max} [c] (hr)	0.5 (0.5, 0.75)	0.6 (0.25, 1)	0.6 (0.5, 0.75)	1.0 (0.75, 1)	0.9 (0.75, 1.5)	1.1 (0.75, 2)
AUC [a] (μg·hr/mL)	50.02 (31.9)	381.57 (96.1)	460.49 (74.3)	22.93 (8.6)	41.12 (32.6)	46.08 (32.6)
$t_{1/2}$ [b] (hr)	2.1 ± 0.5	8.7 ± 5.1	5.2 ± 1.8	2.5 ± 0.4	12.6 ± 3.8	10.5 ± 5.4
UR [b) d)] (%)	0.2 ± 0.1	0.7 ± 0.3	1.1 ± 0.6	75.1 ± 8.5	49.8 ± 8.7	107.6 ± 18.6
CL/F [b] (L/hr)	8.39 ± 2.95	1.23 ± 0.63	0.95 ± 0.34	-	-	-
Vd/F [b] (L)	23.84 ± 3.89	12.21 ± 3.80	6.38 ± 1.33	-	-	-

a) Geometric mean (CV%), b) Mean ± SD, c) Median (minimum, maximum)
d) Day 1 indicates the cumulative urinary excretion rate from 0 to 12 hours, and Days 4 and 8 indicate the urinary excretion rate from 0 to 24 hours on that day.
n = 6

Pharmacokinetic parameters of favipiravir and M1 in Group 2 (400 mg TID from Day 1 to Day 2, 400 mg QD from Day 3 to Day 7)

Pharmacokinetic parameter	Favipiravir		M1	
	Day 1	Day 7	Day 1	Day 7
C_{max} [a] (μg/mL)	18.52 (9.5)	21.88 (12.2)	5.96 (18.1)	4.23 (14.5)
t_{max} [c] (hr)	0.5 (0.5, 0.5)	0.5 (0.5, 0.75)	0.8 (0.5, 1)	0.9 (0.75, 1)
AUC [a] (μg·hr/mL)	43.66 (17.4)	81.87 (11.1)	22.57 (9.6)	23.53 (10.2)
$t_{1/2}$ [b] (hr)	1.8 ± 0.3	2.7 ± 0.2	2.2 ± 0.2	3.5 ± 0.3
UR [b) d)] (%)	0.2 ± 0.1	0.3 ± 0.1	66.7 ± 6.2	81.3 ± 6.2
CL/F [b] (L/hr)	9.29 ± 1.70	4.91 ± 0.54	-	-
Vd/F [b] (L)	23.91 ± 1.89	18.82 ± 1.44	-	-

a) Geometric mean (CV%), b) Mean ± SD, c) Median (minimum, maximum)
d) Day 1 indicates the cumulative urinary excretion rate from 0 to 6 hours, and Day 7 indicates the urinary excretion rate from 0 to 24 hours on that day.
n = 6

Pharmacokinetic parameters of favipiravir and M1 in Group 3 (600 mg BID from Day 1 to Day 2, 600 mg QD from Day 3 to Day 7)

Pharmacokinetic parameter	Favipiravir		M1	
	Day 1	Day 7	Day 1	Day 7
C_{max} [a] (μg/mL)	36.24 (14.6)	36.23 (19.1)	8.08 (19.0)	4.46 (12.5)
t_{max} [c] (hr)	0.5 (0.25, 0.5)	0.5 (0.5, 1)	0.8 (0.75, 0.75)	0.8 (0.5, 1)
AUC [a] (μg·hr/mL)	91.40 (22.0)	215.05 (26.0)	34.08 (8.2)	34.49 (12.3)
$t_{1/2}$ [b] (hr)	2.2 ± 0.4	3.7 ± 0.5	2.6 ± 0.4	5.0 ± 0.9
UR [b) d)] (%)	0.2 ± 0.1	0.6 ± 0.3	82.3 ± 2.7	77.5 ± 10.9
CL/F [b] (L/hr)	6.72 ± 1.68	2.89 ± 0.91	-	-
Vd/F [b] (L)	20.36 ± 1.81	15.00 ± 2.52	-	-

a) Geometric mean (CV%), b) Mean ± SD, c) Median (minimum, maximum)
d) Day 1 indicates the cumulative urinary excretion rate from 0 to 12 hours, and Day 7 indicates the urinary excretion rate from 0 to 24 hours on that day.
n = 6 (5 subjects on Day 7)

The C_{max} and AUC of favipiravir increased with the increasing number of doses. In Groups 2 and 3 in which the regimen was changed to QD on Day 3, the changes due to the multiple dose administration were smaller than those in Group 1. In Group 1, C_{max} of M1 tended to decrease with the increasing number of doses, while AUC remained unchanged on Days 4 and 8. In Groups 2 and 3, the C_{max} of M1 tended to decrease with the increasing number of doses, while the AUC remained unchanged. The cumulative urinary excretion rate of favipiravir up to 48 hours after the final dose was 0.4% to 0.6% in any regimen group, but that of M1 was 60.1% in Group 1 (400 mg TID for 7 days), 73.6% in Group 2 (QD on Day 3 and thereafter), and 76.0% in Group 3 (QD on Day 3 and thereafter).

4.(ii).A.(2).3) Supplemental multiple dose study in healthy adult Japanese subjects (5.3.3.1.6, Study JP106 [[redacted] to [redacted]])

Favipiravir was orally administered between the meals[116] to 12 healthy adult Japanese male subjects (included in the pharmacokinetic analysis, aged 45-57 years) for 5 days in accordance with the following regimens to investigate the pharmacokinetics: Group 1, 600 mg BID (Day 1) and then 600 mg QD (Days 2-5); and Group 2, 400 mg BID (Days 1-4) and then 400 mg QD (Day 5). The results are as shown in the table below.

Pharmacokinetic parameters of favipiravir and M1 in Group 1 (600 mg BID [Day 1] and then 600 mg QD [Day 2-5])

Pharmacokinetic parameter	Favipiravir		M1	
	Day 1	Day 5	Day 1	Day 5
C_{max} [a)] (μg/mL)	23.00 (28.1)	31.88 (15.5)	8.74 (27.1)	5.91 (32.6)
t_{max} [c)] (hr)	0.8 (0.5, 2)	0.5 (0.5, 0.5)	0.9 (0.75, 2)	0.8 (0.75, 1)
AUC [a)] (μg·hr/mL)	74.57 (26.7)	153.07 (40.4)	39.31 (11.7)	38.89 (13.0)
$t_{1/2}$ [b)] (hr)	2.1 ± 0.4	3.1 ± 0.8	2.5 ± 0.3	4.4 ± 1.1
UR [b)] (%)	0.2 ± 0.1	0.4 ± 0.2	66.1 ± 13.0	70.8 ± 6.9
CL/F [b)] (L/hr)	8.29 ± 2.20	4.21 ± 1.70	-	-
Vd/F [b)] (L)	23.66 ± 2.92	17.30 ± 3.32	-	-

a) Geometric mean (CV%), b) Mean ± SD, c) Median (minimum, maximum)
n = 6

Pharmacokinetic parameters of favipiravir and M1 in Group 2 (400 mg BID [Day 1-4] and then 400 mg QD [Day 5])

Pharmacokinetic parameter	Favipiravir		M1	
	Day 1	Day 5	Day 1	Day 5
C_{max} [a)] (μg/mL)	16.97 (18.7)	25.56 (22.0)	6.63 (16.3)	3.43 (28.9)
t_{max} [c)] (hr)	0.5 (0.5, 0.75)	0.5 (0.5, 1)	1.0 (0.75, 1.5)	0.8 (0.75, 1.5)
AUC [a)] (μg·hr/mL)	45.55 (19.7)	151.46 (46.1)	26.94 (13.0)	31.05 (20.7)
$t_{1/2}$ [b)] (hr)	1.8 ± 0.2	3.3 ± 0.7	2.3 ± 0.2	5.0 ± 1.5
UR [b)] (%)	0.2 ± 0.1	0.4 ± 0.2	65.4 ± 12.7	78.4 ± 16.1
CL/F [b)] (L/hr)	8.96 ± 2.10	2.96 ± 1.67	-	-
Vd/F [b)] (L)	22.58 ± 3.82	13.05 ± 4.75	-	-

a) Geometric mean (CV%), b) Mean ± SD, c) Median (minimum, maximum)
n = 6

In Group 1 in which the regimen was changed to 600 mg QD on Day 2, the C_{min} ratios from Day 2 to Day 5 remained below 1 throughout the multiple treatment period, while in Group 2 in which the regimen was changed to 400 mg QD on Day 5, C_{min} increased with the increasing number of doses, and on Day 4, it was approximately 21 times that on Day 1. In both groups, C_{max} of favipiravir on Day 5 was approximately 1.5 times that on Day 1, and AUC on Day 5 was approximately 2 and 3 times that on Day 1 in Group 1 and 2, respectively. The cumulative urinary excretion rate of favipiravir up to 48 hours after the final dose was ≤0.4% in both groups, while that of M1 was 71.7%.

4.(ii).A.(2).4) Multiple high-dose study in healthy adult Japanese subjects (5.3.3.1.8, Study JP111 [[redacted] to [redacted]])

Favipiravir was orally administered between the meals[117] to 12 healthy adult Japanese male subjects (included in the pharmacokinetic analysis, aged 20-33 years) for 7 days in accordance with the following regimens to investigate the pharmacokinetics:[118] Group 1, a single dose of 1200 mg (the first dose) and a single dose of 400 mg (the second dose) on Day 1, 400 mg BID (Days 2-6), and then 400 mg QD (Day 7); and Group 2, a single dose of 1200 mg (first dose) and

[116] Meals should be finished at least 2 hours before dosing, or started at least 1 hour after dosing.
[117] Meals should be finished at least 2 hours before dosing, or started at least 1 hour after dosing.
[118] Each group included 2 subjects to be treated with the placebo.

a single dose of 600 mg (second dose) on Day 1, 600 mg BID (Days 2-6), and then 600 mg QD (Day 7). The results are as shown in the table below.

Pharmacokinetic parameters of favipiravir and M1 in Group 1 (single dose of 1200 mg [first dose] and single dose of 400 mg [second dose] on Day 1, 400 mg BID [Day 2-6], and then 400 mg QD [Day 7])

Pharmacokinetic parameter	Favipiravir		M1	
	Day 1	Day 7	Day 1	Day 7
C_{max} [a)] (μg/mL)	51.46 (22.1)	40.55 (44.4)	7.68 (50.1)	1.86 (31.0)
t_{max} [c)] (hr)	1.5 (1, 2)	1.5 (0.75, 2)	1.5 (1.5, 2)	1.5 (1.5, 2)
AUC [a)] (μg·hr/mL)	475.22 (86.6)	504.87 (97.4)	50.49 (36.8)	38.81 (19.4)
$t_{1/2}$ [b)] (hr)	7.0 ± 4.0	6.7 ± 4.9	4.3 ± 1.3	12.2 ± 11.0
UR [b)] (%)	0.4 ± 0.1	1.4 ± 0.6	47.3 ± 19.9	78.8 ± 24.1
CL/F [b)] (L/hr)	3.01 ± 1.71	1.01 ± 0.71	-	-
Vd/F [b)] (L)	22.78 ± 4.17	7.02 ± 2.64	-	-

a) Geometric mean (CV%), b) Mean ± SD, c) Median (minimum, maximum)
n = 6

Pharmacokinetic parameters of favipiravir and M1 in Group 2 (single dose of 1200 mg [first dose] and single dose of 600 mg [second dose] on Day 1, 600 mg BID [Day 2-6], and then 600 mg QD [Day 7])

Pharmacokinetic parameter	Favipiravir		M1	
	Day 1	Day 7	Day 1	Day 7
C_{max} [a)] (μg/mL)	43.04 (21.4)	61.49 (14.0)	13.01 (14.1)	2.97 (13.3)
t_{max} [c)] (hr)	1.0 (1, 2)	1.0 (0.75, 1.5)	1.5 (1, 2)	1.5 (0.75, 2)
AUC [a)] (μg·hr/mL)	203.87 (20.5)	805.28 (24.0)	66.58 (11.2)	63.64 (8.9)
$t_{1/2}$ [b)] (hr)	3.0 ± 0.7	4.8 ± 0.8	2.9 ± 0.3	9.0 ± 1.2
UR [b)] (%)	0.2 ± 0.1	1.4 ± 0.5	63.8 ± 16.9	86.5 ± 17.5
CL/F [b)] (L/hr)	6.02 ± 1.50	0.77 ± 0.23	-	-
Vd/F [b)] (L)	25.16 ± 1.05	5.18 ± 0.96	-	-

a) Geometric mean (CV%), b) Mean ± SD, c) Median (minimum, maximum)
n = 6 (5 subjects on Day 7)

In Group 1 in which the regimen was changed to 400 mg BID on Day 2, the ratios of C_{min} values from Day 2 to Day 6 to that on Day 1 were 1.0 to 1.2 throughout the multiple treatment period, while in Group 2 in which the regimen was changed to 600 mg BID on Day 2, C_{min} increased with the increasing number of doses, and C_{min} values on Days 2 and 6 were approximately 3 times and 10 times, respectively, that on Day 1.[119] In Group 1, the C_{max} and AUC of favipiravir did not change after the multiple doses, but in Group 2, both parameters on Day 7 were higher than those on Day 1. The cumulative urinary excretion rate of favipiravir up to 48 hours after the final dose was 0.8% in both groups, while that of M1 was 53.1% in Group 1 and 60.3% in Group 2.

The results from the lung concentration simulation of favipiravir RTP, an active metabolite of favipiravir, showed that concentrations of favipiravir RTP in the lung in 5 of 6 subjects in Group 1 and in 4 of 6 subjects in Group 2 met the criteria for 100% survival in the mouse infection model.[120]

[119] In this study, of 6 subjects in Group 1, one subject showed a remarkably high plasma concentration of favipiravir and low plasma concentration of M1, but the exclusion of data from this subject did not considerably change C_{min} on Day 2 to Day 6 (before exclusion, approximately 1.0-1.2; after exclusion, approximately 0.9-1.2) or daily AUC on Day 1 to Day 6 (before exclusion, 545.57-636.80 μg·hr/mL; after exclusion, 443.87-529.78 μg·hr/mL).

[120] Three subjects did not meet the therapeutic criteria in which the lung concentration of favipiravir RTP should be ≥0.3 μmol/kg lung, and in which time above 0.4 μmol/kg lung (the period with the lung concentration of favipiravir RTP of ≥0.4 μmol/kg lung) should be ≥50% of the treatment period. They at least met the criterion for the Time above 0.4 μmol/kg lung, although the lung concentration of favipiravir RTP was found below 0.3 μmol/kg lung at some timepoints.

4.(ii).A.(2).5) Single low-dose study (5.3.3.1.2 [Reference data], Study US101 [[redacted] to [redacted]]) and single high-dose study (5.3.3.1.3 [Reference data], Study US102 [[redacted] to [redacted]]) in healthy adult US subjects

A single dose of favipiravir 30, 90, 200, or 400 mg (Study US101) and 600 mg or 1200 mg (Study US102) was orally administered to 36 healthy adult US male and female subjects (included in the pharmacokinetic analysis, aged 19-58 years) in the fasted state to investigate the pharmacokinetics. The C_{max} and AUC values of favipiravir and M1 increased with the increasing dose. The C_{max} of favipiravir in the dose ranges from 30 to 1200 mg and the AUC in the dose ranges from 30 to 400 mg were linear, while AUC at the dose of ≥600 mg remained higher than the value expected from the dose-proportional relationship. Half life (t_{max}) did not differ considerably among the doses, but the elimination rate constant (ke) and CL/F decreased at the dose of 1200 mg with the extended $t_{1/2}$ and MRT. The cumulative urinary excretion rate of favipiravir up tp 48 hours after dosing was ≤0.27% at any dose level, while that of M1 was 75.10% to 98.26%.

4.(ii).A.(2).6) Multiple dose study in healthy adult US subjects (5.3.3.1.5 [Reference data], Study US103 [[redacted] to [redacted]])

Favipiravir was orally administered 1 hour before a meal to 12 healthy adult US male and female subjects (included in the pharmacokinetic analysis, aged 40-59 years) for 5 days in accordance with the following regimens to investigate the pharmacokinetics: Group 1, 600 mg BID (Days 1-2) and then 600 mg QD (Days 3-5); and Group 2, 800 mg BID (Days 1-2) and then 800 mg QD (Days 3-5). As a result, in Group 1 in which the regimen was changed to 600 mg QD on Day 3, C_{max} did not change after the multiple dose administration, but AUC (geometric mean [CV], 44.11 μg·hr/mL [28.63%] on Day 1 vs. 73.18 μg·hr/mL [37.28%] on Day 5) increased approximately 1.7 times; and in Group 2 in which the regimen was changed to 800 mg QD on Day 3, C_{max} on Day 5 increased approximately 1.2 times that on Day 1 (28.4 μg/mL [33.7%] on Day 1 vs. 34.5 μg/mL [33.7%] on Day 5) and AUC on Day 5 increased approximately 2.3 times that on Day1 (61.19 μg·hr/mL [29.62%] on Day 1 vs. 140.37 μg·hr/mL [43.04%] on Day 5).[121] In any group, t_{max} values of favipiravir and M1 did not change after the multiple dose administration, but $t_{1/2}$ on Day 5 became longer than that on Day 1 with CL/F (calculated only for favipiravir) decreased. In both groups, the Day 2/Day 1 ratios for C_{min} were above 1 for both groups, but the Day 3/Day 1 ratio for C_{min} in Group 1 and the Day 4/Day 1 ratio for C_{min} in Group 2 were ≤1. The cumulative urinary excretion rate of favipiravir up to 48 hours after the final dose was 0.2% in both Groups 1 and 2, while that of M1 was ≥75%.

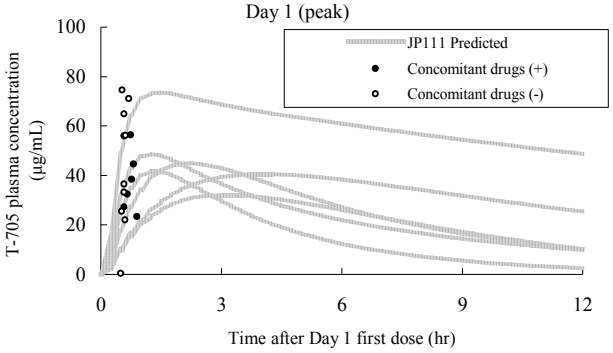
4.(ii).A.(3) Investigations in patients

4.(ii).A.(3).1) Pharmacokinetic study in Japanese patients with influenza virus infection (5.3.4.2.1, Study JP313 [[redacted] to [redacted]])

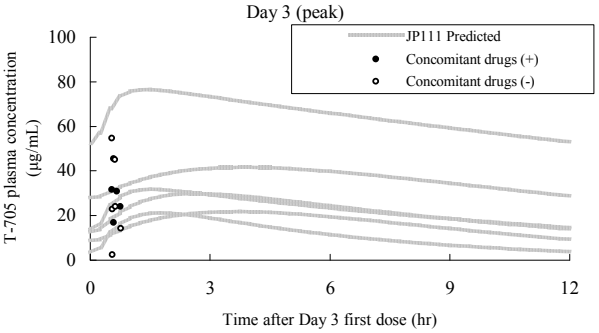
Favipiravir was orally administered to 16 Japanese patients with influenza virus infection (included in the pharmacokinetic analysis, aged 20-74 years) for 5 days[122] in accordance with the following regimen to investigate the pharmacokinetics: 1200 mg (first dose) and 400 mg (second dose) on Day 1, and then 400 mg BID (Day 2-5). The results are as shown in the figures below.

[121] In any dosage regimen, C_{max} of M1 showed a decreasing trend with the increasing number of doses, but no clear changes were observed in AUC.

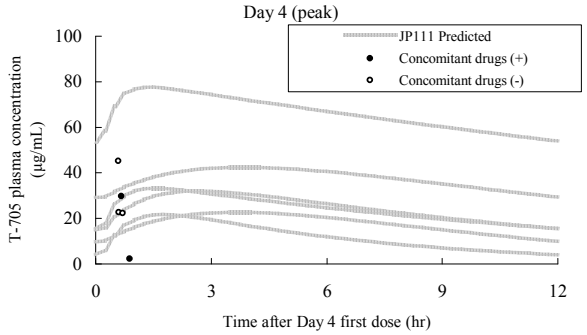
[122] Take the study drug ≥30 minutes after a meal for "postprandial" dosing.



Plasma concentration profile of favipiravir (around the peak on Day 1)



Plasma concentration profile of favipiravir (around the peak on Day 3)



Plasma concentration profile of favipiravir (around the peak on Day 4)

The plasma concentrations of favipiravir and M1 in patients with influenza virus infection (peak values on Day 1, Day 3, and Day 4) mostly fell within the range of the plasma concentrations observed in healthy adult subjects (Study JP111), and the plasma concentrations of favipiravir and M1 on Day 15 were below the quantitation limit in all patients. There were no clear differences in trough values between patients and healthy adult subjects, and the concomitant drugs[123] did not tend to change the plasma concentrations of favipiravir and M1.

Based on data on the RP value[113] (baseline, 0.482-0.905), an indirect indicator of the AO activity, and the plasma concentrations, a relationship was identified between the RP value and the ratio

[123] Acetaminophen, glucose, rebamipide, lactomin formulation, indomethacin, furosemide, calcium lactate, diclofenac sodium, alfacalcidol, carvedilol, alendronate sodium hydrate, telmisartan. Of 16 subjects, 2 subjects used concomitant drugs (excluding antipyretic analgesics and therapeutic drugs for adverse events) at the baseline.

of the peak plasma concentrations (M1/favipiravir) on Day 1 (relative contribution = 0.6159). There were no clear correlations of the trough plasma concentration value of favipiravir on Day 3 or Day 4 with any of the age, body weight, BMI, and creatinine clearance (CL_{cr}), but the relative contribution of the age, body weight, BMI, and CL_{cr} with respect to the trough plasma concentration value of M1 were 0.2848, 0.6849, 0.4303, and 0.6923, respectively. The trough plasma concentration value of M1 on Day 3 or Day 4 tended to increase with decreasing body weight, BMI, and CL_{cr}.[124]

4.(ii).A.(4) Intrinsic factors

4.(ii).A.(4).1) Elderly single dose study in healthy elderly Japanese subjects (5.3.3.3.1, Study JP104 [[redacted] to [redacted]])

A single dose of favipiravir 400 or 800 mg was orally administered to 12 healthy elderly Japanese subjects (included in the pharmacokinetic analysis, aged 65-77 years) in the fasted state (at least 10 hours after a meal) to investigate the pharmacokinetics. The results are as shown in the table below.

Pharmacokinetic parameters of favipiravir and M1 following single dose of 400 mg or 800 mg of favipiravir

Pharmacokinetic parameter	Favipiravir		M1	
	400 mg	800 mg	400 mg	800 mg
C_{max} [a] (μg/mL)	22.14 (20.9)	47.29 (12.4)	6.57 (13.3)	13.43 (19.7)
t_{max} [c] (hr)	0.5 (0.5, 1)	0.5 (0.5, 0.5)	0.8 (0.5, 1.5)	0.8 (0.75, 1)
AUC [a] (μg·hr/mL)	58.63 (25.5)	149.93 (23.4)	30.28 (7.7)	64.83 (12.3)
$t_{1/2}$ [b] (hr)	1.9 ± 0.4	2.4 ± 0.5	2.5 ± 0.5	3.1 ± 0.6
CL/F [b] (L/hr)	7.01 ± 1.75	5.50 ± 1.56	-	-
Vd/F [b] (L)	18.95 ± 2.62	18.32 ± 2.93	-	-
MRT [b] (hr)	2.9 ± 0.5	3.6 ± 0.7	4.1 ± 0.4	4.6 ± 0.7

a) Geometric mean (CV%), b) Mean ± SD, c) Median (minimum, maximum)
n = 6

C_{max} and AUC of favipiravir and M1 increased with the increasing dose; t_{max} did not differ among the doses; CL/F slightly decreased at 800 mg, and $t_{1/2}$ and MRT extended.[125] The cumulative urinary excretion rate of favipiravir up to 48 hours after dosing was ≤0.3% at any dose, while that of M1 was 81.7% at the doses of 400 mg and 74.1% at the dose of 800 mg.

4.(ii).A.(4).2) Multiple dose study in healthy elderly Japanese subjects (5.3.3.3.2, Study JP107 [[redacted] to [redacted]])

Favipiravir was orally administered between the meals[126] to 12 Japanese healthy elderly subjects (included in the pharmacokinetic analysis, aged 65-72 years) for 5 days in accordance with the following regimens to investigate the pharmacokinetics: Group 1, 600 mg BID (Day 1) and then 600 mg QD (Day 2-5); and Group 2, 400 mg BID (Day 1-4) and then 400 mg QD (Day 5). The results are as shown in the table below.

[124] The plasma concentrations of favipiravir and M1 in the patient with the minimum body weight and BMI (body weight, 41.5 kg; BMI, 17.3 kg/m^2) were within the range of those in other patients. The patient with the minimum CL_{cr} (42.4 mL/min) was elderly. In this patient, the plasma concentration of favipiravir was within the range of that in other patients, but the plasma concentration of M1 was 2.23 μg/mL at the Day-3 test on Day 4, on which the concentration was expected to be around the trough value, and 2.16 μg/mL at the Day-8 test on Day 6. These values were 0.40 to 2.119 μg/mL and 0.68 to 2.16 μg/mL higher, respectively, than those in the other patients. The applicant, however, claimed that the differences were slight, and the concentrations would not be of a level that causes issues.

[125] Compared with the data from healthy adult Japanese male subjects (Study JP101) treated with favipiravir 400 mg or 800 mg, the C_{max} and AUC values of favipiravir and M1 in this study tended to be high, but these parameters did not clearly correlate with the body weight.

[126] Meals should be finished at least 2 hours before dosing, or started at least 1 hour after dosing.

Pharmacokinetic parameters of favipiravir and M1 in Group 1 (600 mg BID [Day 1] and then 600 mg QD [Day 2-5])

Pharmacokinetic parameter	Favipiravir		M1	
	Day 1	Day 5	Day 1	Day 5
C_{max} [a] (μg/mL)	21.92 (28.2)	28.76 (20.0)	9.95 (13.8)	4.86 (21.3)
t_{max} [c] (hr)	1.1 (0.5, 2)	1.5 (1, 4)	1.5 (0.75, 2)	2.0 (2, 4)
AUC [a] (μg·hr/mL)	79.80 (22.4)	218.26 (34.8)	50.06 (10.9)	47.46 (12.0)
$t_{1/2}$ [b] (hr)	2.0 ± 0.3	3.6 ± 0.6	2.4 ± 0.3	5.3 ± 1.0
UR [b] (%)	0.2 ± 0.1	0.5 ± 0.4	79.9 ± 2.8	71.8 ± 3.5
CL/F [b] (L/hr)	7.66 ± 1.58	2.89 ± 0.99	-	-
Vd/F [b] (L)	21.18 ± 2.69	14.44 ± 2.51	-	-

a) Geometric mean (CV%), b) Mean ± SD, c) Median (minimum, maximum)
n = 6

Pharmacokinetic parameters of favipiravir and M1 in Group 2 (400 mg BID [Day 1-4] and then 400 mg QD (Day 5)

Pharmacokinetic parameter	Favipiravir		M1	
	Day 1	Day 5	Day 1	Day 5
C_{max} [a] (μg/mL)	16.05 (9.4)	33.84 (22.5)	7.13 (13.1)	3.47 (21.6)
t_{max} [c] (hr)	1.5 (1, 2)	1.5 (0.75, 1.5)	1.8 (1, 2)	2.0 (1.5, 2)
AUC [a] (μg·hr/mL)	56.12 (20.8)	277.36 (42.5)	35.33 (16.1)	46.56 (15.0)
$t_{1/2}$ [b] (hr)	1.9 ± 0.3	4.1 ± 0.8	2.3 ± 0.4	6.5 ± 1.4
UR [b] (%)	0.2 ± 0.1	0.8 ± 0.5	76.5 ± 9.7	91.4 ± 6.8
CL/F [b] (L/hr)	7.28 ± 1.72	1.59 ± 0.82	-	-
Vd/F [b] (L)	19.23 ± 1.48	8.66 ± 2.32	-	-

a) Geometric mean (CV%), b) Mean ± SD, c) Median (minimum, maximum)
n = 6

In Group 1 in which the regimen was changed to 600 mg QD on Day 2, the C_{max} and AUC values of favipiravir on Day 5 increased to approximately 1.3 times and 2.2 times those on Day 1, respectively, while in Group 2 in which the regimen was changed to 400 mg QD on Day 5, C_{max} on Day 5 increased to approximately 2.1 times that on Day 1 and AUC on Day 5 increased to approximately 3.8 times that on Day 1.[127] In any group, t_{max} of favipiravir and M1 did not change after the multiple dose administration, but $t_{1/2}$ on Day 5 became longer than that on Day 1 with CL/F (calculated only for favipiravir) decreased. In Group 1, the ratios of C_{min} on each day to that on Day 1 decreased on Day 3 (the following day of the regimen change to QD) and thereafter, while in Group 2, the C_{min} ratio reached approximately 35 on Day 4 (the previous day of the regimen change to QD). The cumulative urinary excretion rate of favipiravir up to 48 hours after the final dose was ≤0.4% in both Groups 1 and 2, while that of M1 was approximately 74%.

4.(ii).A.(4).3) Multiple high-dose study in healthy adult US subjects (5.3.3.1.7 [Reference data], Study US103b [[redacted] to [redacted]])

Favipiravir was orally administered 1 hour before a meal to 12 healthy adult US male and female subjects (included in the pharmacokinetic analysis, aged 34-58 years) and to 12 healthy elderly male and female subjects (included in the pharmacokinetic analysis, aged 66-80 years) for 5 days in accordance with the following regimens to investigate the pharmacokinetics: Groups 1 (non-elderly) and 2 (elderly), 1200 mg BID (Day 1) and then 600 mg BID (Days 2-5); and Groups 3 (non-elderly) and 4 (elderly), 1200 mg BID (Day 1) and then 800 mg BID (Days 2-5). The results on pharmacokinetic parameters of favipiravir showed that in both Groups 1 (non-elderly) and 2 (elderly) in which the regimen was changed to 600 mg BID on Day 2, C_{max} on Day 5 reduced to approximately 0.7 to 0.8 times that on Day 1, but AUC on Day 5 increased to approximately 1.2 times that on Day 1. In Groups 3 (non-elderly) and 4 (elderly) in which the regimen was changed to 800 mg BID on Day 2, C_{max} on Day 5 increased to approximately 1.3 times that on Day 1 and AUC on Day 5 increased to approximately 3.1 times that on Day 1 in the non-elderly subjects,

[127] In any dosage regimen, C_{max} and AUC of M1 decreased with the increasing number of doses.

while in the elderly subjects, C_{max} on Day 5 remained unchanged following the multiple dose administration, but AUC on Day 5 increased to approximately 2.5 times that on Day 1.[128] In any group, $t_{1/2}$ values of favipiravir and M1 in the non-elderly and elderly subjects on Day 5 were longer than that on Day 1, and CL/F (calculated only for favipiravir) decreased.

There was no difference in distribution of the individual RP values among groups, and the inter-individual variations were small (minimum to maximum, 0.755-0.891). In the subjects treated with favipiravir in accordance with the same dosage regimen, the AUC ratio (ratio of AUC of M1 to that of favipiravir) positively correlated to the RP value, but there were no clear correlations of the genetic polymorphism of AO (aldehyde oxidase 1 [AOX1] mutant)[129] with the AUC ratio, the C_{max} ratio (ratio of C_{max} of M1 with respect to that of favipiravir), or RP value on Day 5.

4.(ii).A.(5) Drug-drug interaction

4.(ii).A.(5).1) Drug interaction study of favipiravir in combination with theophylline in healthy adult Japanese subjects (5.3.3.4.1, Study JP108 [[redacted] to [redacted]])

Favipiravir and/or theophylline were administered to 10 healthy adult Japanese male subjects (included in the pharmacokinetic analysis, aged 46-61 years) in the following regimen to investigate the pharmacokinetics of favipiravir in combination with theophylline[130] for 5 days by the add-on method. For combination therapy with theophylline, subjects received favipiravir 600 mg BID (Day 6) and 600 mg QD (Days 7-10) and theophylline 200 mg BID (Days 1-9) and 200 mg QD (Day 10); and for favipiravir monotherapy, subjects received favipiravir 600 mg BID (Day 24) and 600 mg QD (Day 25). Both favipiravir and theophylline were administered between the meals.[131] The results are as shown in the table below.

[128] In any dosage regimen, C_{max} and AUC of M1 decreased with the increasing number of doses.
[129] Of 4 AOX1 mutants characterized, 3 mutants were identified in the limited number of the subjects as heterozygotes.
[130] Theophylline is metabolized mainly by CYP1A2, and its metabolite, 1-methylxanthine, is then metabolized by XO (partially involved in the metabolism of favipiravir to M1). In this study, XO-mediated interaction potential between favipiravir and theophylline was investigated.
[131] Meals should be finished at least 2 hours before dosing, orl started at least 1 hour after dosing.

C_{max} and AUC ratios (concomitant use/monotherapy) of favipiravir, M1, and theophylline and their 90% CI

	Pharmacokinetic parameter	Dosing schedule	Geometric mean	Ratio of the geometric mean[a)] 90% CI
Favipiravir	C_{max} (μg/mL)	Theophylline + favipiravir (Day 1 of combination therapy)	28.70	1.327
		Favipiravir (Day 1 of monotherapy)	21.63	1.192, 1.477
		Theophylline + favipiravir Day 2 of combination therapy)	34.72	1.029
		Favipiravir (Day 2 of monotherapy)	33.74	0.918, 1.153
	AUC_{0-12} (μg·hr/mL)	Theophylline + favipiravir (Day 1 of combination therapy)	100.30	1.270
		Favipiravir (Day 1 of monotherapy)	78.98	1.151, 1.401
		Theophylline + favipiravir (Day 2 of combination therapy)	214.99	1.167
		Favipiravir (Day 2 of monotherapy)	184.18	1.039, 1.311
M1	C_{max} (μg/mL)	Theophylline + favipiravir (Day 1 of combination therapy)	6.49	1.107
		Favipiravir (Day 1 of monotherapy)	5.86	0.948, 1.293
		Theophylline + favipiravir (Day 2 of combination therapy)	3.77	1.001
		Favipiravir (Day 2 of monotherapy)	3.77	0.886, 1.130
	AUC_{0-12} (μg·hr/mL)	Theophylline + favipiravir (Day 1 of combination therapy)	33.76	1.163
		Favipiravir (Day 1 of monotherapy)	29.02	1.056, 1.281
		Theophylline + favipiravir (Day 2 of combination therapy)	28.46	1.065
		Favipiravir (Day 2 of monotherapy)	26.72	0.959, 1.184
Theophylline	C_{max} (μg/mL)	Theophylline + favipiravir (Day 2) of combination therapy	7.94	0.925
		Theophylline (Day 5 of monotherapy)	8.59	0.850, 1.007
		Theophylline + favipiravir (Day 5 of combination therapy)	8.46	0.985
		Theophylline (Day 5 of monotherapy)	8.59	0.937, 1.035
	AUC_{0-12} (μg·hr/mL)	Theophylline + favipiravir (Day 2 of combination therapy)	83.90	0.915
		Theophylline (Day 5 of monotherapy)	91.66	0.865, 0.969
		Theophylline + favipiravir (Day 5 of combination therapy)	88.56	0.966
		Theophylline (Day 5 of monotherapy)	91.66	0.908, 1.028

a) Favipiravir and M1, Theophylline + favipiravir/favipiravir; Theophylline, Theophylline + favipiravir/theophylline

The 90% CI of the ratio of the geometric mean C_{max} and AUC_{0-12} of favipiravir and M1 (combination therapy/monotherapy) was outside of the specified range from 0.80 to 1.25 except for the C_{max} ratio for favipiravir on Day 2, and the C_{max} and AUC_{0-12} ratios for M1 on Day 2, indicating that the combination therapy with theophylline affected the pharmacokinetics of favipiravir and M1. On the other hand, both parameter ratios of theophylline fell within the above range.

4.(ii).A.(5).2) Drug-interuction study of favipiravir in combination with oseltamivir in healthy Japanese adult subjects (5.3.3.4.2, Study JP109 [[redacted] to [redacted]])

Favipiravir and/or oseltamivir phosphate were administered to 10 healthy adult Japanese male subjects (included in the pharmacokinetic analysis, aged 46-62 years) in the following regimen to investigate the pharmacokinetics of favipiravir in combination with oseltamivir phosphate[132] for 2 days by the add-on method. For favipiravir monotherapy, subjects received favipiravir was administered 600 mg BID (Day 1) and 600 mg QD (Day 2); and for combination therapy with

[132] Favipiravir and oseltamivir phosphate are metabolized into M1 and oseltamivir carboxylate, respectively, which are excreted into urine. Oseltamivir carboxylate undergoes tubular secretion through OAT1, but non-clinical data have demonstrated that favipiravir and M1 inhibit OAT1. In this study, potential interaction between favipiravir (and M1) and oseltamivir carboxylate in the excretion process was investigated.

oseltamivir phosphate, subjects received favipiravir 600 mg BID (Day 16) and 600 mg QD (Day 17) and oseltamivir phosphate 75 mg BID (Days 12-16) and 75 mg QD (Day 17). Both favipiravir and oseltamivir phosphate were administered between the meals. The results are as shown in the table below.

C_{max} and AUC ratios (combination therapy/monotherapy) of favipiravir and oseltamivir carboxylate and their 90% CI

	Pharmacokinetic parameter	Dosing schedule	Geometric mean	Ratio of the geometric mean[a] 90% CI
Favipiravir	C_{max} (μg/mL)	Oseltamivir phosphate + favipiravir (Day 2 of combination therapy)	35.43	0.977
		Favipiravir (Day 2 of monotherapy)	36.28	0.866, 1.101
	AUC_{0-t} [b] (μg·hr/mL)	Oseltamivir phosphate + favipiravir (Day 2 of combination therapy)	185.49	1.005
		Favipiravir Day 2 of monotherapy)	184.56	0.908, 1.113
Oseltamivir carboxylate	C_{max} (ng/mL)	Oseltamivir phosphate + favipiravir (Day 2 of combination therapy)	502.11	1.104
		Oseltamivir phosphate (Day 4 of monotherapy)	454.82	1.064, 1.146
	AUC_{0-12} (ng·hr/mL)	Oseltamivir phosphate + favipiravir (Day 2 of combination therapy)	4359.00	1.138
		Oseltamivir phosphate (Day 4 of monotherapy)	3830.69	1.102, 1.175

a) Favipiravir: Oseltamivir phosphate + favipiravir/favipiravir,
Oseltamivir carboxylate: Oseltamivir phosphate + favipiravir/oseltamivir phosphate
b) t: Final plasma concentration measurable timepoint

The 90% CI of the ratio (combination therapy/monotherapy) of the geometric mean C_{max} and AUC of favipiravir and oseltamivir carboxylate fell within the specified range from 0.80 to 1.25. There were no significant differences in the cumulative urinary excretion rate or CL_r of M1 and oseltamivir carboxylate up to 12 hours after dosing between the monotherapy and combination therapy.

4.(ii).A.(6) Pharmacodynamics

4.(ii).A.(6).1) QT/QTc evaluation study in healthy adult Japanese male and female subjects (5.3.4.1.1, Study JP115 [[redacted] to [redacted]])

A single dose of favipiravir 1200 mg or 2400 mg,[133] placebo, or moxifloxacin (MFLX) 400 mg (positive control) was orally administered to 56 healthy adult Japanese male and female subjects (included in the pharmacokinetic analysis) in the fasted state to investigate the effects on QT interval or corrected QT (QTc) interval and the pharmacokinetics in a four-treatment, four-period crossover design. In this study, the pharmacokinetics and tolerability following single oral dose of favipiravir 2000 mg or 2400 mg were evaluated before the QT/QTc interval evaluation in a four-treatment, four-period crossover design.

Regarding the pharmacokinetics, the geometric mean C_{max} and AUC (CV) of favipiravir were 83.62 (19.3%) μg/mL and 1093.62 (40.9%) μg·hr/mL, respectively, for favipiravir 2000 mg and 92.17 (12.6%) μg/mL and 1297.56 (31.4%) μg·hr/mL, respectively, for favipiravir 2400 mg. The geometric mean C_{max} and AUC (CV) of M1 were 16.21 (14.1%) μg/mL and 127.25 (12.0%) μg·hr/mL, respectively, forfavipiravir 2000 mg and 16.15 (19.2%) μg/mL and 139.01 (11.3%) μg·hr/mL, respectively, forfavipiravir 2400 mg. There were no considerable differences in CL_r or $t_{1/2}$ values of favipiravir and M1 between the doses.

[133] Simulation in the MBI-PK model suggests that C_{max} of favipiravir 2000 mg in subjects with the average AO activity would reach a level (approximately 75 μg/mL) around C_{max} of favipiravir 1200 mg in subjects with low AO activity, and C_{max} of favipiravir 2400 mg would reach a plasma concentration level (approximately 100 μg/mL) expected as a consequence of inhibition against XO-mediated alternative metabolic pathway in subjects with low AO activity.

Regarding the effects on QT/QTc interval, the changes in QTcF (QT interval corrected according to Fridericia's formula) from the baseline (ΔQTcF) in subjects treated with favipiravir 1200 mg and 2400 mg were similar to those in subjects treated with the placebo, while in subjects treated with MFLX, the changes remained approximately 5 to 15 msec higher than those with the placebo. The estimated difference in ΔQTcF in subjects treated with either drug from that in subjects treated with the placebo (ΔΔQTcF) reached the maximum (one-sided 95% CI) at 3 hours after administration of favipiravir 1200 mg (0.83 [-1.33, 3.00] msec) and 6 hours after administration of favipiravir 2400 mg (0.50 [-1.88, 2.88] msec), and the upper limit of the one-sided 95% CI was <4 msec at any measurement timepoint. On the other hand, in subjects treated with MFLX, the lower limit of the one-sided 95% CI of ΔΔQTcF was greater than 0 msec, and that of the maximum ΔΔQTcF was greater than 5 msec, suggesting that the analytical sensitivity of MFLX as the positive control was ensured.

Regarding the relationship of the plasma drug concentration with ΔQTcF and ΔΔQTcF, the relative contributions of ΔQTcF and ΔΔQTcF to the plasma concentration of favipiravir were 0.0012 and 0.0019, respectively, and the relative contributions to the plasma concentration of M1 were 0.0011 and 0.0030, respectively, while the relative contributions to the plasma concentration of MFLX were 0.2280 and 0.1326, respectively, indicating that the ΔQTcF and ΔΔQTcF tended to increase with the increasing plasma concentration of MFLX.

4.(ii).A.(6).2) Testis safety study in healthy adult US male subjects (5.3.4.1.2, Study US105 [[redacted] to [redacted]])

Favipiravir was orally administered 1200 mg BID (Day 1) and 800 mg BID (Day 2-5) to 116 healthy adult US male subjects[134] (included in seminal test analysis population, aged 19-45 years) in the fasted state to investigate its safety and pharmacokinetic profiles in the testis.

Regarding the pharmacokinetics, the geometric mean (CV) C_{max} and AUC_{0-24} of favipiravir were 35.9 μg/mL (15.4%) and 346 μg·hr/mL (44%) on Day 1, respectively, and 57.6 μg/mL (30.9%) and 957 μg·hr/mL (41%) on Day 5, respectively; both parameters slightly increased with increasing number of doses. There were no changes in t_{max}. The concentrations of favipiravir in the seminal fluid at 29 days after the end of the treatment were below the lower limit of quantitation (0.0200 μg/mL) in all subjects, while M1 was detected in 31 subjects[135] at 29 days after the end of the treatment and then in 6 subjects at 60 days after the end of the treatment, but its concentrations were below the lower limit of quantitation (0.0500 μg/mL) 90 days after the end of the treatment.

At the seminal test, the mean results on the seminal fluid parameters (seminal fluid volume, sperm concentration, sperm motility rate, sperm viability, progressive motility rate, sperm count, sperm normal form rate, total motile sperm count) at 60 days and 90 days after the end of the favipiravir treatment fell within the specified range, and no trend changing to abnormal values were observed after the favipiravir treatment. The changes in these parameters from the baseline and their change rates in subjects treated with favipiravir were almost comparable to those in subjects treated with the placebo.

4.(ii).A.(7) Others

4.(ii).A.(7).1) Comparison of pharmacokinetics between Japanese and US subjects

The pharmacokinetics in the dose range in which the pharmacokinetic profiles were linear were compared between healthy adult subjects in Japan and the US. Following a single oral dose of 400 mg of favipiravir to subjects, the C_{max} and AUC of favipiravir were higher in healthy adult

[134] A total of 58 subjects were included in the pharmacokinetic analysis population.
[135] The concentration was 6 μg/mL in 2 subjects, but the plasma concentration profiles of M1 in these subjects were comparable to those in the other subjects.

Japanese subjects than in healthy adult US subjects, while CL/F and Vd/F were lower in Japanese subjects than US subjects. When the doses were normalized on the basis of a body weight of 60 kg; however, all of the parameters in Japanese subjects was almost comparable to the corresponding values in US subjects.

Pharmacokinetic parameters of single oral dose of 400 mg of favipiravir (before/after normalization to 60 kg body weight)

Pharmacokinetic parameter	Before normalization to 60 kg body weight			After normalization to 60 kg body weight		
	Japanese subjects[a)]	US subjects[b)]	US/Japanese	Japanese subjects[a)]	US subjects[b)]	US/Japanese
C_{max}[c), e)] (μg/mL)	16.59 (6.0)	12.17 (20.4)	0.733	17.95 (11.8)	17.69 (14.4)	0.985
t_{max}[f)] (hr)	0.5	0.6	1.250	-	-	-
AUC[c), e)] (μg·hr/mL)	39.41 (16.0)	26.74 (18.2)	0.679	42.64 (13.4)	38.86 (13.9)	0.911
$t_{1/2}$[g)] (hr)	1.6 ± 0.2	1.4 ± 0.1	0.835	-	-	-
CL/F[d), g)] (L/hr)	10.26 ± 1.63	15.19 ± 3.05	1.481	9.45 ± 1.25	10.38 ± 1.50	1.099
Vd/F[d), g)] (L)	23.80 ± 3.15	29.55 ± 5.55	1.242	22.01 ± 3.16	20.16 ± 2.35	0.916
MRT[g)] (hr)	2.5 ± 0.3	2.2 ± 0.2	0.887	-	-	-

a) Single dose study (Study JP101), n = 6; b) Single low-dose study (Study US101), n = 6
c) C_{max} or AUC × body weight (kg)/60, after normalization to 60 kg body weight
d) CL/F or Vd/F × 60/body weight (kg), after normalization to 60 kg body weight
e) Geometric mean (CV%); f) Median
g) Mean ± SD

In the dose range in which the pharmacokinetic parameter profiles were not linear, the pharmacokinetics of multiple oral doses of favipiravir 600 mg BID (Days 1-2) and then 600 mg QD (Days 3-7) in healthy adult Japanese subjects were compared with those of multiple oral doses of favipiravir 600 mg BID (Days 1-2) and then 600 mg QD (Days 3-5) in healthy adult US subjects. On Day 1, C_{max} and AUC in Japanese subjects were higher than those in the US subjects, while CL/F in Japanese subjects was lower than that in the US subjects. When the body weight was normalized to 60 kg, these differences were reduced. On Day 7 or Day 5, the days of the final dose, C_{max} and AUC in Japanese subjects were higher than those in the US subjects, while CL/F and Vd/F in Japanese subject were lower than those in the US subjects as observed on Day 1. The normalization of the body weight to 60 kg reduced these differences, but AUC was higher, CL/F was lower, and Vd/F was slightly lower in Japanese subjects than in the US subjects. The AUC ratio of M1 to favipravir was lower in Japanese subjects than in the US subjets. The decrease in the AUC ratio after the final dose was also greater in Japanese subjects than in the US subjects.

Pharmacokinetic parameters of multiple doses of favipiravir in healthy adult Japanese and US subjects

Pharmacokinetic parameter	First dose			Final dose		
	Japanese subjects[a)]	US subjects[b)]	US/Japanese	Japanese subjects[a)]	US subjects[b)]	US/Japanese
	Day 1	Day 1	-	Day 7	Day 5	-
C_{max}[d)] (μg/mL)	36.24 (14.6)	22.01 (19.0)	0.607	36.23 (19.1)	23.94 (22.9)	0.661
t_{max}[e)] (hr)	0.5	0.5	1.003	0.5	0.6	1.250
AUC[d)] (μg·hr/mL)	91.40 (22.0)	44.11 (28.6)	0.483	215.05 (26.0)	73.27 (37.3)	0.341
AUC ratio[c), f)]	0.381 ± 0.091	0.820 ± 0.206	-	0.162 ± 0.030	0.508 ± 0.192	-
$t_{1/2}$[f)] (hr)	2.2 ± 0.4	1.4 ± 0.2	0.638	3.7 ± 0.5	1.9 ± 0.5	0.519
CL/F[f)] (L/hr)	6.72 ± 1.68	14.16 ± 4.49	2.106	2.89 ± 0.91	8.73 ± 3.41	3.022
Vd/F[f)] (L)	20.36 ± 1.81	27.25 ± 5.39	1.338	15.00 ± 2.52	22.55 ± 4.72	1.504
MRT[f)] (hr)	3.1 ± 0.5	2.1 ± 0.5	0.680	5.7 ± 0.7	3.0 ± 0.7	0.523

a) Multiple dose study (Study JP103), n = 6; b) Multiple dose study (Study US103), n = 6; c) M1/favipiravir; d) Geometric mean (CV%); e) Median; f) Mean ± SD

Pharmacokinetic parameters following multiple dose administration of favipiravir in healthy adult Japanese and US subjects (after normalization to 60 kg body weight)

Pharmacokinetic parameter	First dose			Final dose		
	Japanese subjects[a)]	US subjects[b)]	US/Japanese	Japanese subjects[a)]	US subjects[b)]	US/Japanese
	Day 1	Day 1	-	Day 7	Day 5	-
C_{max}[c), e)] (μg/mL)	38.11 (14.6)	29.47 (8.4)	0.773	38.32 (15.6)	32.06 (9.3)	0.837
AUC[c), e)] (μg·hr/mL)	96.12 (21.4)	59.07 (27.9)	0.615	227.47 (20.6)	98.11 (36.4)	0.431
CL/F[d), f)] (L/hr)	6.40 ± 1.67	10.49 ± 2.86	1.639	2.69 ± 0.59	6.42 ± 2.03	2.388
Vd/F[d), f)] (L)	19.33 ± 1.30	20.31 ± 3.60	1.050	14.07 ± 1.17	16.62 ± 1.80	1.181

a) Multiple dose study (Study JP103), n = 6; b) Multiple dose study (Study US103), n = 6
c) C_{max} or AUC × body weight (kg)/60, after normalization to 60 kg body weigh
d) CL/F or Vd/F × 60/ body weight (kg), after normalization to 60 kg body weight; e) Geometric mean (CV%);
f) Mean ± SD

The minimum plasma concentration (C_{min}) of favipiravir was compared between healthy adult Japanese subjects who received favipiravir 600 mg BID (Days 1-2) and then 600 mg QD (Day 3-7) and healthy adult US subjects who received favipiravir 800 mg BID (Days 1-2) and then 800 mg QD (Days 3-5), because the dose per kg body weight in the Japanese subjects was comparable to that in the US subjects (Japanese subjects, 9.53 mg/kg; US subjects, 10.14 mg/kg). As a result, in Japanese subjects, C_{min} reached a peak (11.83 μg/mL) after the second dose on Day 2and then decreased to ≤1 μg/mL (0.66 μg/mL) on Day 5. On the other hand, in the US subjects, C_{min} also reached a peak (3.18 μg/mL) after the second dose on Day 2 and decreased to ≤1 μg/mL (0.24 μg/mL) on Day 3, indicating rapid elimination of favipiravir from the plasma. In the dose range in which the pharmacokinetic parameter profiles were not linear, C_{min} decreased more rapidly in the US subjects than in Japanese subjects even when the dose per kg body weight was almost the same, suggesting that recovery of the AO activity may differ between Japanese and US populations. The applicant therefore consisered that the pharmacokinetics of multiple oral administration of favipiravir may differ among the races.[136]

4.(ii).B Outline of the review by PMDA

4.(ii).B.(1) Plasma concentration levels of favipiravir at the proposed dosage regimen

PMDA asked the applicant to explain the expected plasma concentrations and safety risk of favipiravir at the proposed dosage regimen in consideration that favipiravir irreversibly inhibits AO, its metabolic enzyme, in a concentration- and time-dependent manner [see "4.(ii).A.(1).4).(c) Inhibitory effect against AO"]; and the AO activity[137] differs among individuals [see "4.(ii).A.(1).5).(c) AO activity evaluation"].

The applicant responded as follows:
The clinical studies included 2 subjects who were likely to have little AO activity (subjects in which the RP value, an indirect indicator of the AO activity, was lower than in other subjects) [see "4.(ii).A.(1).5).(c) AO activity evaluation"]. In 1 subject who was included in the drug-interaction study of favipiravir in combination with theophylline (Study JP108), the AUC (555.23 μg·hr/mL) of favipiravir administered as the first dose of the monotherapy was approximately 7.5 times higher than the geometric mean AUC (73.91 μg·hr/mL) in other 9 subjects. In the other subject who was included in Group 1 in the multiple high-dose study (Study JP111), the AUC (1623.54 μg·hr/mL) of favipiravir administered as the first dose was approximately 6.0 times higher than the geometric mean AUC (267.86 μg·hr/mL) in other 11 subjects. Neither subject showed any changes in the plasma concentration profile even after receiving the multiple doses. On the assumption that favipiravir is administered to these 2 subjects in accordance with the proposed dosage regimen, the plasma concentration, daily AUC, and C_{max} of favipiravir were simulated. The C_{max} and daily AUC in the subject of Study JP108 were estimated to be 52.58 to

[136] As of July 5, 2011, there are no published literature reporting ethnic differences of the AO activity.
[137] As of July 5, 2011, there are no published literature reporting proportion of individuals with low AO activity.

59.71 μg/mL and 1077.84 to 1222.25 μg·hr/mL, respectively, which fell within the range of the corresponding individual values in Study JP111 (C_{max}, 73.47-77.72 μg/mL; daily AUC 1452.73-1592.52 μg·hr/mL). The plasma concentration of favipiravir at the proposed dosage regimen is considered to increase up to the level noted in the subject of Study JP111 who was likely to have little AO activity.

Concerning the safety, the only adverse event observed in the subject of Study JP111 who were likely to have little AO activity was blood uric acid increased, which was also observed in other subjects. The parameter was returned to the baseline at 7 days after the end of the favipiravir treatment. In the subjects in whom blood uric acid increased in clinical studies other than Study JP111, the blood uric acid level was decreased to below the upper limit of the institutional reference value by 1 week after the end of the treatment. Blood uric acid increased that occurred after treatment with favipiravir is considered to be transient. Blood uric acid increased after treatment with favipiravir is considered unlikely to cause gout attacks, but the finding that the plasma concentration of favipiravir is high in patients with decreased AO activity is important information regarding pharmacokinetics. The following information therefore will be provided in the package insert: (1) the metabolic enzyme of favipiravir is AO; (2) AO activity differs among individuals; (3) the plasma concentration of favipiravir in patients with decreased AO activity is higher than that in patients without decreased AO activity according to the pharmacokinetic parameters (AUC, etc.) in the subject of Study JP111 who is considered to have little AO activity.

PMDA has accepted the following applicant's view: the plasma pharmacokinetics of favipiravir at the proposed dosage regimen are expected to differ among individuals due to inter-individual differences in AO activity, and the plasma concentrations of favipiravir may increase in patients considered to have little AO activity, but the currently available clinical data shows that there have been no adverse events associated with the increased plasma favipiravir concentrations other than blood uric acid increased. In Japan, however, the percentage of individuals with decreased AO activity remains unknown, and clinical studies included several subjects in whom plasma favipiravir concentrations increased due to decreased AO activity. The safety of favipiravir administered to the target population including these individuals in accordance with the proposed dosage regimen should be thoroughly discussed in "4.(iii).B.(2) Safety," and then it is necessary to examine how to alert the medical practice.

4.(ii).B.(2) Effect of hepatic impairment on pharmacokinetics of favipiravir and M1

PMDA asked the applicant to explain the possibility of effects of hepatic impairment on the pharmacokinetics of favipiravir and M1.

The applicant responded as follows:

Favipiravir is mainly metabolized to M1, which is then excreted into urine. Clearance of favipiravir thus depends on the metabolism. If metabolism decreases due to hepatic impairment, the plasma concentration of favipiravir may increase. Information on the plasma concentration of favipiravir administered to subjects with underlying medical conditions of hepatobiliary disorders in clinical studies in Japan are available only from 1 subject in the pharmacokinetic study in patients (Study JP313). In this subject, no adverse event occurred. The currently available information is not sufficient for discussion about the relationship between the plasma concentration and hepatic impairment. The applicant thus decided to investigate the relationship between the RP value, an indirect indicator of AO activity, and hepatic impairment.

The relationship between the Child-Pugh score[138] and RP value from Study JP313 and the global phase III study (Study 312) was investigated. This analysis included a total of 774 patients, consisting of 16 patients from Study JP313 and 758 patients from Study 312 (all of the patients

[138] Guidance for treatment of chronic hepatitis (2008). Bunkodo Co., Ltd.; 2007:62-69.

were included in the safety analysis population). Of the 774 patients, 5 patients were classified into Child-Pugh Class B (Child-Pugh score was 7 for all), and the remaining patients were classified into Child-Pugh Class A. Since the RP value in these patients did not vary depending on the class, it is considered that hepatic impairment may not affect the AO activity and thus is unlikely to change the pharmacokinetics of favipiravir, if any. Underlying medical conditions of hepatobiliary disorders were found in 1 patient in Study JP313 and in 18 patients in Study 312, and all of them were classified into Child-Pugh Class A. Of the patients classified into Child-Pugh Class B, 1 patient in the favipiravir group experienced adverse events of white blood cell count decreased and neutrophil count decreased, but these events also occurred in Child-Pugh Class A patients treated with favipiravir. There were no adverse events specific to Child-Pugh Class B patients treated with favipiravir. Based on the above results, the applicant considers that there is no relationship between Child-Pugh score and RP value in patients classified into Child-Pugh Class A and Class B, and hepatic impairment is unlikely to decrease metabolism of favipiravir, or to affect plasma concentrations of favipiravir and M1. The dose-adjustment in response to hepatic impairment is therefore considered unnecessary.

In the US, a pharmacokinetic study will be conducted in patients with hepatic impairment (mild to severe hepatic impairment according to Child-Pugh classification). This study is planned to investigate the safety and pharmacokinetics in patients with mild and moderate hepatic impairment from [redacted], and then, investigation in patients with severe hepatic impairment will be started in [redacted].

PMDA considers as follows:
At present, no pharmacokinetic studies in patients with hepatic impairment have been conducted, and thus there is no information on the relationship between the severity of hepatic impairment and plasma favipiravir concentrations. Based on the pharmacokinetic profile of favipiravir, it cannot be ruled out that plasma concentrations of favipiravir may increase due to hepatic impairment. The package insert should include precautions stating that plasma concentrations of favipiravir may increase in patients with hepatic impairment, and the relationship between the severity of hepatic impairment and the plasma concentration has not been investigated. It is important to collect information on the pharmacokinetics and safety of favipiravir in patients with hepatic impairment. Therefore, the applicant should conduct the planned pharmacokinetic study in the concerned patients in the US promptly so as to obtain pharmacokinetic data in patients with hepatic impairment, and then should review the use of favipiravir in those patients including the necessity of the dose adjustment when new findings become available. The obtained information should be appropriately provided to healthcare providers in clinical practice.

4.(ii).B.(3) Effect of renal impairment on pharmacokinetics of M1
Favipiravir is eliminated mainly by renal excretion as M1 after oral administration. PMDA asked the applicant to explain the possibility of changes in pharmacokinetics of M1 due to renal impairment and the safety risk.

The applicant responded as follows:
In the global phase III study (Study 312) and pharmacokinetic study in patients (Study JP313), none of the patients were found to have severe renal impairment (CL_{cr} <30 mL/min), while 1 patient in Study JP313 (female, aged 7[redacted] old, [redacted] kg, CL_{cr} [redacted] mL/min) was found to have moderate renal impairment (30≤ CL_{cr} <50 mL/min), and 30 patients were found to have mild renal impairment (50≤ CL_{cr} <80 mL/min). Both trough plasma concentrations of favipiravir and M1 in patients with moderate renal impairment on Day 3 were 1.46 times and 2.55 times higher, respectively, than the corresponding mean in the other 15 patients in Study JP313. The relative contribution of CL_{cr} to the trough value of M1 was 0.6923, indicating that the trough value of M1 increased with decreasing CL_{cr}, but no correlation between the trough value of favipiravir and CL_{cr} was observed.

From the pharmacokinetic data of the subject in whom the peak plasma concentration of M1 was the highest among those in Group 1 in the multiple high-dose study (Study JP111) using the same dosage regimen up to Day 5 as that in Study JP313, the AUC and C_{max} values of M1 from Day 1 to Day 5 were estimated on the assumption that the renal function of the above subject was decreased.[139] Both parameters reached a peak on Day 1. The daily AUC and C_{max} on Day 1 were estimated to be 80.07 μg·hr/mL and 14.50 μg/mL, respectively, in patients with normal renal function, 159.34 μg·hr/mL and 23.6 μg/mL, respectively, in patients with moderate renal impairment, and 237.45μg·hr/mL and 30.0 μg/mL, respectively, in patients with severe renal impairment. As described above, in patients with renal impairment, the daily AUC and C_{max} of M1 in plasma were estimated to increase approximately 3 times and 2 times, respectively, those in patients with normal renal function, due to decreased CL_r of M1. Adverse events noted in patients with moderate renal impairment in Study JP313 were only plasma uric acid increased, and its severity was mild.

The safety risk associated with increased exposure to M1 resulting from renal impairment was discussed based on the non-clinical data. The no observed adverse effect levels (NOAELs) in rabbits and cynomolgus monkeys in 2-week repeated oral dose toxicity studies of favipiravir were 200 and 100 mg/kg/day, respectively. C_{max} and $AUC_{0\text{-}t}$ of M1 at the NOAEL were 81.3 to 101 μg/mL and 163 to 260 μg·hr/mL, respectively, in rabbits and 29.6 to 67.8 μg/mL and 173 to 273 μg·hr/mL, respectively, in cynomolgus monkeys. The estimated C_{max} (30.0 μg/mL) and daily AUC (237.45 μg·hr/mL) in patients with severe renal impairment were equivalent to or less than the exposure to M1 at the NOAEL in rabbits and cynomolgus monkeys. Serious adverse events attributable to M1 are therefore considered unlikely to occur.

Based on the above, although no clinical data in patients with severe renal impairment are available, the currently available study data suggest that serious adverse events attributable to M1 are unlikely to occur in patients with mild to moderate renal impairment if favipiravir is administered in accordance with the proposed dosage regimen.

PMDA considers as follows:
The following applicant's view is understandable: non-clinical toxicity data suggest that serious adverse events are unlikely to occur in patients with mild to moderate renal impairment even when the plasma concentration of M1 is high. The information on the pharmacokinetics and adverse events in patients with renal impairment available at present, however, only includes data from 1 patient. Thus, the package insert should include a precaution stating that the information on the safety in patients with renal impairment is not sufficiently obtained. In addition, when new findings about the pharmacokinetics in patients with renal impairment (including data from the planned US pharmacokinetics study) become available, information on the findings should be appropriately provided to alert healthcare providers in clinical practice.

4.(ii).B.(4) Drug interaction

4.(ii).B.(4).1) Possibility of interaction with concomitant drugs through the tubular secretion

Favipiravir is mainly excreted in urine as M1, and the involvement of renal excretion of M1 in the tubular secretion is suggested. PMDA therefore asked the applicant to explain the possibility that favipiravir may interact with concomitant drugs through the tubular secretion.

The applicant responded as follows:

[139] The elimination rate constant in subjects with normal renal function was set at ke × 1; the elimination rate constant in subjects with decreased renal function was set at ke × 0.5 for moderate renal impairment and ke × 0.33 for severe renal impairment on the assumption that the ke would reduce with decreasing renal function as M1 is mainly excreted in urine.

At the development stage of favipiravir, M1 was confirmed not to act as a substrate of P-gp [see "4.(ii).A.(1).4).(g) P-gp transportation"], but whether or not M1 can be recognized as a substrate of the transporters other than P-gp has not been investigated. To evaluate the risk of pharmacokinetic drug-drug interactions of M1 with drugs excreted through the tubular secretion, inhibitory effects of M1 against hOAT1 and hOAT3 were investigated, although the relative contribution of M1 to the tubular secretion was unknown. As a result, M1 inhibited uptake of standard substrates of hOAT1 and hOAT3 by 54.6% and 42.3%, respectively, at 300 μmol/L (51.9 μg/mL) [see "4.(ii).A.(1).5).(a) Human transporters"]. Based on the concentration of M1 in human plasma (C_{max} [geometric mean] of M1 on Day 1 in Study JP111, 7.68 μg/mL; calculated C_{max} of non-binding form, 5.14 μg/mL), the clinical risk of interactions with drugs that can act as a substrate of hOAT1 and hOAT3 is considered low. In fact, when favipiravir was concomitantly used with oseltamivir phosphate, of which the active form acts as a substrate of hOAT1 and hOAT3, favipiravir did not affect the plasma concentration and CL_r of the active form (oseltamivir carboxylate) [see "4.(ii).A.(5).2) Drug-interaction study of favipiravir in combination with oseltamivir in healthy adult Japanese subjects"]. On the other hand, C_{max} and AUC_{0-t} of M1 following the concomitant use were 6.66 μg/mL and 46.81 μg·hr/mL, respectively, which were slightly higher than those following the monotherapy (C_{max}, 5.86 μg/mL; AUC_{0-t}, 42.91 μg·hr/mL). CL_r (11.01 L/hr) after the concomitant use was almost comparable to that following the monotherapy (11.71 L/hr), but the former value was slightly lower than the latter value. This finding suggests that competitive inhibition of oseltamivir carboxylate against hOAT1 and hOAT3 inhibited the tubular secretion of M1, resulting in increased plasma concentrations of M1.

In the dose-response phase II study (Study JP205), global phase III study (Study 312), and pharmacokinetic study in patients (Study JP313), adverse events in patients treated concomitantly with drugs that can act as a substrate of hOAT1, hOAT3 or both were investigated. All of the adverse events in the patients also occurred in those treated with favipiravir alone. Of 8 patients concomitantly treated with drugs that can act as a substrate of hOAT1 or hOAT3, 3 patients experienced an adverse event of blood uric acid increased, but some of the patients without the concomitant drugs also experienced blood uric acid increased or hyperuricaemia as an adverse event. There were no considerable differences in the blood uric acid profile between the patients concomitantly treated with drugs that can act as a substrate of hOAT1 or hOAT3 and those without the concomitant drugs.

PMDA considers as follows:
Although the currently available non-clinical data show that M1 inhibits hOAT1 and hOAT3, it is not highly necessary to provide special precautions about concomitant use of favipiravir with drugs involved in the tubular secretion (hOAT1, hOAT3) at present for the following reasons: (1) given the plasma concentration in humans, clinically significant drug interaction is unlikely to occur; (2) in the study of favipiravir in combination with oseltamivir phosphate, a substrate of hOAT1 and hOAT3, favipiravir had no effects on the plasma concentration of oseltamivir carboxylate; and (3) in the same study, the plasma concentration of M1 following the concomitant use of the drugs was slightly higher than that following the monotherapy, but in the previous clinical studies, concomitant use of favipiravir with drugs that can act as a substrate of hOAT1 and hOAT3 have not raised particular safety concerns. When any new relevant finding becomes available after marketing of favipiravir; however, it is necessary to provide the information to healthcare providers in clinical practice appropriately.

4.(ii).B.(4).2) Possibility of interaction with concomitant drugs mediated by AO

PMDA asked the applicant to explain the possibility of interaction with concomitant drugs mediated by AO, a major metabolic enzyme of favipiravir, and the necessity of providing precautions.

The applicant responded as follows:

(a) Concomitant use with AO inhibitors

When favipiravir is administered concomitantly with an AO inhibitor, the metabolic clearance of favipiravir may decrease, resulting in increased plasma concentrations of favipiravir. Also, the increased plasma concentrations of favipiravir intensify the irreversible inhibition against AO, which may result in a more rapid increase in plasma favipiravir concentrations than that without the concomitant AO inhibitor. On the other hand, favipiravir is also metabolized through a different pathway involving non-AO enzymes (XO, aldehyde dehydrogenase, etc.) [see "4.(ii).A.(1).2).(a) Investigation of favipiravir-metabolizing enzymes"], and in subjects with little AO activity, the plasma favipiravir concentration will be hardly affected by AO inhibitor. The plasma favipiravir concentration after concomitant use of favipiravir with an AO inhibitor will not considerably exceed the maximum exposure (AUC, 1623.54 μg·hr/mL) in subjects with little AO activity identified in the clinical studies. At present, there have been no reports of irreversible inhibition by AO inhibitors. The inhibitory effect against AO is therefore considered to decrease with decreasing blood concentrations of the AO inhibitor. In the subject of Study JP111 in whom the plasma concentration of favipiravir was remarkably high, there were no clinically-related findings or changes in laboratory parameters including testis-related endocrine results other than blood uric acid increased. Even in patients in whom the plasma concentration of favipiravir is increased due to concomitant use with an AO inhibitor, the safety risk will not remarkably increase. In the US, an interaction study with an AO inhibitor (raloxifene hydrochloride) is planned to be conducted.

(b) Concomitant use with AO substrate drugs

Although concomitant use of favipiravir with an AO substrate drug may lead to increased plasma concentrations of favipiravir and the AO substrate drug, favipiravir can also be metabolized through a different pathway with non-AO metabolic enzymes. Thus, the exposure to favipiravir in combination with such an AO substrate drug may not considerably exceed the maximum favipiravir exposure (AUC, 1623.54 μg·hr/mL) observed in the study subject who was considered to have little AO activity. In contrast, the effects of favipiravir on plasma concentrations of AO substrate drugs were investigated. Based on the information included in the package inserts, etc., drugs that are commercially available in Japan and reported to be metabolized by AO were classified into 3 classes of (a) substrate drugs of which blood concentration may remarkably increase, (b) substrate drugs of which blood concentration may increase but the changes are considered to be slight, and (c) substrate drugs of which metabolism to their active forms may be inhibited, resulting in their reduced effects, and the risk of concomitant use of the AO substrate drugs with favipiravir was evaluated for each class. Since hydralazine (hydralazine hydrochloride) classified as (a) has a hypotensive effect, it cannot be ruled out that its concomitant use with favipiravir in a drug interaction study may excessively decrease the blood pressure. In view of the risk in subjects, it is therefore inappropriate to conduct the drug interaction study. The effects of drugs classified as (c) can decrease when these drugs are used concomitantly with favipiravir, but their drug interaction studies have not been conducted taking into account that there is an unclear correlation between decreased plasma concentrations of the active form of these substrate drugs and a decrease in the efficacy, and it would be difficult to conduct a clinical study for confirmation of the decreased efficacy in patients. Drugs classified as (a) and (c), however, are to be listed in the "Precautions for concomitant use" section in the package insert, because it cannot be ruled out that their concomitant use with favipiravir may pose a risk affecting the safety or efficacy.

AO inhibitors (chlorpromazine, hydralazine, raloxifene hydrochloride, estradiol, cimetidine, etc.) and AO substrate drugs (methotrexate, pyrazinamide, allopurinol, etc.) were listed in the precautions for concomitant use in the protocols in the global phase III study (Study 312) and pharmacokinetic study in patients (Study JP313). Differences in the safety between patients treated with favipiravir alone and those treated with favipiravir in combination with any of such inhibitors and substrate drugs were evaluated, although the number of the latter patients was

limited. As a result, none of the patients used AO substrate drugs concomitantly, but 13 patients used AO inhibitors concomitantly. Of these, adverse events were reported in 5 patients (7 events) (rhinitis, dysgeusia, duodenal ulcer, enteritis infectious, urticaria, blood uric acid increased, and blood potassium decreased [1 event each]). The risk ratio (95% CI) of adverse events in patients treated with favipiravir in combination with AO inhibitors with respect to those in patients treated with favipiravir alone was 1.263 (0.625, 2.554). The concomitant use did not considerably change the risk.

PMDA considers as follows:
The proposed dosage regimen of favipiravir is designed in consideration of the irreversible inhibition of favipiravir against AO so that favipiravir can balance the inhibition and restoration of the AO activity, thereby preventing the remarkable increase of its plasma concentration[see "4.(ii).A.(2).4) Multiple high-dose study in healthy adult Japanese subjects"]. Balancing is also important in maintaining the plasma concentration of favipiravir at an intended level. The effects of the concomitant use of favipiravir with an AO inhibitor or a substrate drug on the pharmacokinetics remain unknown because the relevant interaction studies have not been conducted. It should be advised that no information on the effects of the concomitant use with an AO inhibitor or substrate drug on the plasma concentration is available at present. The interaction data from the concomitant use of favipiravir with these drugs can serve as important information for the clinical use and the relevant interaction studies should be conducted immediately. When they become available, the results should be reviewed including necessity of the dose adjustment, and the obtained information should be appropriately provided to healthcare providers in clinical practice.

4.(ii).B.(4).3) Other drug interactions

The results from the *in vitro* drug interaction study using human biomaterials have raised concerns about the effect of concomitant use of favipiravir with acetaminophen or CYP2C8 substrate drugs [see "4.(ii).A.(1).4).(a) Inhibitory effect against human cytochrome P-450 (CYP)" and "4.(ii).A.(1).4).(e) Interaction with acetaminophen"], as a clinical effect of drug interaction other than the above 1) and 2).

The applicant explained the clinical effect of the drug interaction following the concomitant use with CYP2C8 substrate drugs and acetaminophen as follows:
The IC_{50} value of favipiravir against CYP2C8 was 477 μmol/L (74.9 μg/mL), which was almost comparable to the highest value of the expected maximum plasma concentration followingtreatment with favipiravir in accordance with the proposed dosage regimen (78.9 μg/mL[140]), suggesting possibility of the pharmacokinetic interaction. Paclitaxel is one of the CYP2C8 substrate drugs commercially available in Japan and known to have a narrow safety margin. The drug interaction study of CYP2C8 substrate drugs is planned to be conducted in the US and the safety of their concomitant use with favipiravir has not been established, thus, at present, such drug is to be listed in the "Precautions for concomitant use" section in the package insert. The IC_{50} value of favipiravir against sulfate conjugation metabolism of acetaminophen was 150 μmol/L (23.6 μg/mL), which was 0.30 times the highest value of the expected maximum plasma concentration of favipiravir (78.9 μg/mL, Study JP111) following treatment with favipiravir in accordance with the proposed dosage regimen. The plasma concentration of acetaminophen in combination with favipiravir may increase, but the expected increase in AUC of acetaminophen administered concomitantly with favipiravir, which is 1.79 times the AUC of

[140] The maximum plasma concentration (Study JP111) in the subject in which the RP value, an indirect indicator of the AO activity, was lower than that in the other subjects. The applicant explained that according to the currently available study data, the maximum plasma concentration of the drug at the proposed dosage regimen would be around the level observed in this subject in Study JP111 [see "4.(ii).B.(1) Plasma concentration levels of favipiravir at the proposed dosage regimen"].

acetaminophen administered alone,[141] is considered to produce a very low risk of poisoning symptoms (hepatic disorder). This is based on the background data that following oral administration of acetaminophen 400 mg to humans, the maximum plasma concentration was 9.1 μg/mL, the poisoning symptoms (hepatic disorder) are reported to develop when the plasma acetaminophen concentration reaches ≥300 μg/mL at 4 hours after dosing, and at the plasma acetaminophen concentration of ≤120 μg/mL, the risk of the poisoning symptoms is low.[142] The drug interaction study with acetaminophen was conducted in the US from [redacted] to [redacted], and the currently available draft data are as shown below.

To 28 healthy adult US male and female subjects (included in the pharmacokinetic analysis), favipiravir was administered at 1200 mg BID on Day 2, at 800 mg BID from Day 3 to Day 5, and at 800 mg QD on Day 6,[143] and acetaminophen was concomitantly administered at 650 mg QD on Day 1, Day 2, and Day 6[144] (both administered in the fasted state[145]) to investigate the pharmacokinetics. The results are as shown below.

Combination therapy/monotherapy ratios for C_{max} and AUC of acetaminophen and their 90% CI (draft data)

	C_{max}		AUC	
	Day 2/Day 1 ratio	Day 6/Day 1 ratio	Day 2/Day 1 ratio	Day 6/Day 1 ratio
Geometric mean	1.03	1.08	1.17	1.14
90% CI	0.93, 1.14	0.96, 1.22	1.09, 1.26	1.04, 1.26

Number of subjects, n = 28

Pyrazinamide, an antituberculous drug, is also considered to interact with favipiravir. This drug is reported to increase blood uric acid level through a urate transporter (hURAT1) as that associated with the adverse event following administration of favipiravir[146] and gout is listed as its adverse drug reaction, although its frequency is unknown.[147] In consideration of the above, it cannot be ruled out that pyrazinamide and favipiravir, when administered concomitantly, may increase the blood uric acid level synergistically through the same URAT1, although there is no experience with their concomitant use, and thus this drug is to be listed in the ”Precautions for the concomitant use” section in the package insert. A drug interaction study is to be conducted in Japan from the end of [redacted] to the early [redacted].

PMDA considers as follows:
The drug interaction studies conducted in the process for development of the drug product until the regulatory application only covered the studies of favipiravir in combination with theophylline (Study JP108) and oseltamivir (Study JP109), and the available information on the clinical drug interactions are limited. Based on the above applicant’s explanation, concomitant use of favipiravir with CYP2C8 substrate drugs is expected to affect the plasma concentrations of these concomitant drugs clinically. It should be, therefore, sufficiently advised that their concomitant use with favipiravir is expected to cause interaction clinically. Also, favipiravir is expected to be concomitantly used with acetaminophen in the treatment of influenza infection in many patients. The results from this study can serve as important information for clinical use of favipiravir and therefore should be included in the package insert for information provision. When the results are

[141] Analysis results according to Note 4 of the “Investigation method of drug interactions” (PMSB/ELD Notification No. 813 dated June 4, 2001)
[142] Calonal Tab. 200/Calonal Tab. 300 Pharmaceutical interview form. Showa Yakuhin Kako Co., Ltd.; 2008: Version 5
[143] Dosage regimen in which the exposure in US subjects is expected to be comparable to that in Japanese subjects (dosage regimen proposed in Japan)
[144] The dose is within the range of the ordinary dose in the US (1.3 times 500 mg, the dose usually used in Japan).
[145] In the morning, the drug is administered ≥10 hours after a meal, and in the evening, the drug is administered 4 to 5 hours after a meal.
[146] *Gout and Nuclei Acid Metabolism.* 2004;28:1-5.
[147] Package insert of Pyramide powder (revised in June 2009 [version 8])

obtained from other interaction studies ongoing or to be conducted in Japan and overseas, relevant information should be provided to healthcare providers in clinical practice appropriately.

4.(ii).B.(5) Differences in pharmacokinetics between Japanese and US subjects

The exposure (C_{max}, AUC) after multiple oral doses of favipiravir was higher in Japanese subjects than in the US subjects. Concerning the difference in pharmacokinetics between Japanese and US subjects, the applicant considered that apart from body weight, the difference in restoration of the AO activity between Japanese and US subjects led to this difference[see "4.(ii).A.(7).1) Comparison of pharmacokinetics between Japanese and US subjects"].

PMDA asked the applicant to present the information on AO activity restoration-time profile and to discuss the background factors leading to the difference in pharmacokinetics between Japanese and US subjects other than the restoration of this activity and body weight.

The applicant responded as follows:

1) AO restoration

In the normal body, degradation of the enzyme is in equilibrium with its biosynthesis, and the degradation rate constant (k_{deg}) is thus considered to be equivalent to the biosynthesis rate constant.[148] The k_{deg} of AO was calculated for each subject according to the method of Venkatakrishnan, et. al,[149] as it was not available in published literature. As a result, the k_{deg} values of AO in both Japanese and US subjects showed large individual differences, but k_{deg} (0.001720 min^{-1}) in the US subjects was approximately 3.3 times that in Japanese subjects (0.000517 min^{-1}). The result suggests that AO is biosynthesized more rapidly in the US subjects than in Japanese subjects. Under the condition in which the exposure in Japanese subjects was comparable to that in the US subjects (geometric mean AUC_{0-12} after the final dose in Group 1 in Study JP111, 315.82 μg·hr/mL; geometric mean AUC_{0-12} after the final dose in Group 3 in Study US103b, 362.19 μg·hr/mL), k_{deg} in the US subjects (0.002059 min^{-1}) was higher than that in Japanese subjects (0.000629 min^{-1}). Thus, k_{deg} is unlikely to be dependent on the exposure. The difference in restoration of the AO activity between Japanese and US subjects possibly led to the difference in pharmacokinetics. Time (estimated) to restore ≥98% of the AO activity after the final dose was approximately 13 days in Japanese subjects.

2) Distribution of RP value

Investigation of the distribution of the RP values in 582 Japanese subjects (healthy subjects, patients with influenza virus infection) and 32 US subjects (healthy subjects) indicated that many of the Japanese subjects had an RP value ≥0.65 and the highest number of Japanese subjects had an RP value ranging from 0.85 to 0.90. In the US, the highest number of US subjects had an RP value ranging from 0.80 to 0.85, which was not largely different from the result in Japanese subjects.

3) Pharmacokinetic data for comparison

In comparison of the pharmacokinetics between Japanese and foreign subjects [see "4.(ii).A.(7).1) Comparison of pharmacokinetics between Japanese and US subjects"], the pharmacokinetic parameters on Day 7 in Study JP103 were compared with those on Day 5 in Study US103. The dosing day was different, but in Study JP103, the daily AUC on Day 5 (geometric mean, 240.18 μg·hr/mL) was comparable to that on Day 7 (geometric mean, 220.58 μg·hr/mL). Although there were more blood sampling timepoints in Study JP103 than in Study US103, C_{max}, AUC, CL/F, and Vd/F on both Days 1 and 7 were not different between the studies except for the timepoints at 1.5 and 3 hours.

[148] *Drug Metab Dispos.* 2003;31:945-954.
[149] *Drug Metab Dispos.* 2005;33:845-852.

4) Intrinsic factors

Study JP103 included male subjects only, but Study US103 included 1 female subject. The plasma concentration profile and pharmacokinetic parameters of favipiravir in male subjects were comparable to those in the female subject, and sex differences is therefore unlikely to affect the pharmacokinetics of favipiravir. The subjects in Study US103 were generally older than those in Study JP103, but data from Study JP103 and Study JP106 did not show large differences in plasma concentration profile and pharmacokinetic parameters of favipiravir between young subjects (aged 20-39 years) and non-elderly subjects (aged 45-64 years), and the difference in age distribution is unlikely to affect the pharmacokinetics of favipiravir. On the other hand, the height in the subjects in Study US103 was comparable to that in Study JP103, but the body weight and BMI in Study US103 were greater than those in Study JP103. As the results from Study JP101 and Study US101 demonstrated the relationship of the body weight with C_{max} and AUC of favipiravir, the difference in body weight between these studies is considered to have affected the pharmacokinetics.

5) Extrinsic factors

Extrinsic factors were compared between Study JP103 and Study US103. As a result, all of the conditions about the concomitant drugs, smoking, and alcohol drinking were the same, and favipiravir was administered in the fasted state in both studies. There were no differences in extrinsic factors between these studies.

As described above, the difference in pharmacokinetics between Japanese and US subjects is likely to be attributable to the differences in restoration of the AO activity and body weight, and unlikely to be attributable to other factors. Whether or not any relationship exist between k_{deg}, an indicator of restoration of the AO activity, and body weight was investigated, but no relationship between k_{deg} and body weight was found. Results suggest that k_{deg} and body weight may affect the pharmacokinetics independently.

PMDA considers as follows:

The ethnic difference in restoration of the AO activity may possibly have affected the pharmacokinetics, as explained by the applicant, because the difference in pharmacokinetics noted between Japanese and US subjects in the clinical studies cannot be attributed only to the difference in body weight. At present, however, the ethnic difference in the AO activity has not been reported in published literature, and it is unknown whether the difference in biosynthesis rate constant of AO calculated from the clinical study data (difference in restoration of the AO activity) is due to the ethnic difference or is a secondary consequence due to other factors. There is only weak evidence supporting the applicant's consideration that the difference in pharmacokinetics between Japanese and US subjects were caused by the ethnic differences in body weight and restoration of the AO activity. When new findings about the differences in pharmacokinetics of favipiravir between Japanese and foreign subjects become available, the newly obtained data should be compared with the existing data and their effects on the results should be reviewed continuously.

4.(iii) Summary of clinical efficacy and safety

4.(iii).A Summary of the submitted data

The results from a total of 16 studies were submitted as evalutation data in this regulatory application, including 12 Japanese phase I studies in healthy adult Japanese subjects or elderly subjects, 1 Japanese pharmacokinetic study in patients with influenza infection, 1 foreign phase I study in healthy adult foreign male subjects, 1 Japanese phase II study in patients with influenza infection, and 1 global phase III study in patients with influenza infection. In addition, the results from 4 foreign phase I studies were submitted as the reference data. Clinical studies are listed in the table below.

List of clinical studies

Study Location	Study number	Study population	Number of treated subjects	Dosage regimen	Primary endpoint
Evaluation data					
Japan	JP101	Healthy adult male subjects	48	Single oral dose of favipiravir 30, 90 (30 mg capsule), 200, 400, 800, and 1600 mg (100 mg capsule) or placebo in the fasted state	Pharmacokinetics, safety
Japan	JP102	Healthy adult male subjects	12	Single oral dose of favipiravir 400 mg (100 mg capsule) in the fasted state or 30 minutes after start of a high fat diet (protein 150 kcal, carbohydrate 250 kcal, fat 500-600 kcal) (two-treatment, two-period crossover)	Pharmacokinetics, safety
Japan	JP103	Healthy adult male subjects	24	Group 1: Favipiravir 400 mg TID (BID on Day 1, TID from Day 2 to morning on Day 8) or placebo Group 2: Favipiravir 400 mg TID (Days 1-2) and 400 mg QD (Days 3-7) or placebo Group 3: Favipiravir 600 mg BID (Days 1-2) and 600 mg QD (Days 3-7) or placebo 1 hour before a meal Treatment duration: 7 days (Group 1, 8 days in total) *Favipiravir, 100 mg capsule	Pharmacokinetics, safety
Japan	JP104	Healthy elderly male and female subjects	16	Single oral dose of favipiravir 100 mg capsule at 400 mg, 800 mg (100 mg capsule) or placebo in the fasted state	Pharmacokinetics, safety
Japan	JP106	Healthy adult male subjects	16	Group 1: Favipiravir 600 mg BID (Day 1) and 600 mg QD (Days 2-5) or placebo Group 2: Favipiravir 400 mg BID (Days 1-4) and 400 mg QD (Day 5) or placebo Administered between meals (meals should be finished at least 2 hours before dosing, and started at least 1 hour after dosing), Treatment duration: 5 days *Favipiravir, 100 mg tablet	Pharmacokinetics, safety
Japan	JP107	Healthy elderly male and female subjects	16	Group 1: Favipiravir 600 mg BID (Day 1) and 600 mg QD (Days 2-5) or placebo Group 2: Favipiravir 400 mg BID (Days 1-4) and 400 mg QD (Day 5) or placebo Administered between meals (meals should be finished at least 2 hours before dosing, and started at least 1 hour after dosing), Treatment druation: 5 days *Favipiravir, 100 mg tablet	Pharmacokinetics, safety
Japan	JP108	Healthy adult male subjects	10	Favipiravir 600 mg BID (Day 6, Day 24) and 600 mg QD (Days 7-10, Day 25) Theophylline 200 mg BID (Days 1-9) and 200 mg QD (Day 10) Administered between meals (meals should be finished at least 2 hours before dosing and, started at least 1 hour after dosing), Treatment druation: Favipiravir 7 days, theophylline 10 days *Favipiravir, 100 mg tablet	Pharmacokinetics, safety
Japan	JP109	Healthy adult male subjects	10	Favipiravir 600 mg BID (Day 1, Day 16) and 600 mg QD (Day 2, Day 17) Oseltamivir phosphate 75mg BID (Days 12-16) and 75 mg QD (Day 17) Administered between meals (meals should be finished at least 2 hours before dosing and started at least 1 hour after dosing), Treatment duration: Favipiravir, 4 days; oseltamivir phosphate, 6 days *Favipiravir, 100 mg tablet	Pharmacokinetics, safety
Japan	JP110	Healthy adult male subjects	24	Single oral dose of favipiravir 400 mg (100 mg tablet and the drug product [200 mg tablet]) in the fasted state (two-treatment, two-period crossover)	Pharmacokinetics, safety

Study Location	Study number	Study population	Number of treated subjects	Dosage regimen	Primary endpoint
Japan	JP111	Healthy adult male subjects	16	Group 1: Single doses of favipiravir 1200 mg (first dose) and 400 mg (second dose) on Day 1, 400 mg BID (Days 2-6) and then 400 mg QD (Day 7) or placebo Group 2: Single doses of favipiravir 1200 mg (first dose) and 600 mg (second dose) on Day 1, 600 mg BID (Days 2-6), and then 600 mg QD (Day 7) or placebo Administered between meals (meals should be finished at least 2 hours before dosing, and started at least 1 hour after dosing), Treatment duration: 7 days	Pharmacokinetics, safety
Japan	JP114	Healthy adult male subjects	16	A single oral dose of favipiravir 1200 mg in the fasted state or 30 minutes after the start of a high fat diet (protein 150 kcal, carbohydrate 250 kcal, fat 500 kcal) (two-treatment, two-period crossover)	Pharmacokinetics, safety
Japan	JP115	Healthy adult male and female subjects	68	Part A: Single oral dose of favipiravir 2000 mg or 2400 mg in the fasted state Part B: Single oral dose of favipiravir 1200 mg, 2400 mg, MFLX 400 mg, or placebo in the fasted state (four-treatment, four-period crossover)	Pharmacokinetics, safety, QT/QTc
Japan	JP313	Patients with influenza infection	16	Single doses of favipiravir 1200 mg (first dose) and 400 mg (second dose) on Day 1, 400 mg BID (Days 2-5) Administered at least 30 minutes after a meal for administration in the fed state Treatment duration: 5 days	Pharmacokinetics, safety, efficacy
US	US105	Healthy adult male subjects	116	Favipiravir 1200 mg BID (Day 1) and 800 mg BID (Days 2-5) or placebo Administered 1 hour before a meal Treatment duration: 5 days	Testis safety, other safety, pharmacokinetics
Japan	JP205	Patients with influenza infection	160	Favipiravir high-dose group: Favipiravir 600 mg BID (Day 1) and 600 mg QD (Day 2-5) Favipiravir low-dose group: Favipiravir 400 mg BID (Day 1-2) and 400 mg QD (Day 3-5) Oseltamivir phosphate 75 mg BID (Day 1-5) Avoid immediately before or after a meal, administered at least 30 minutes after a meal, Treatment duration: 5 days *Favipiravir, 100 mg tablet	Efficacy, safety
Japan, Korea, and Taiwan	312	Patients with influenza infection	762	Single doses of favipiravir 1200 mg (first dose) and 400 mg (second dose) on Day 1, and 400 mg BID (Days 2-5) Oseltamivir phosphate 75mg BID (Days 1-5) Administered at least 30 minutes after a meal for administration in the fed state Treatment duration: 5 days	Efficacy, safety
Reference data					
US	US101	Healthy adult male and female subjects	32	Single oral doses of favipiravir 30 mg and 90 mg (30 mg capsule), 200 mg and 400 mg (100 mg capsule) or placebo in the fasted state	Pharmacokinetics, safety
US	US102	Healthy adult male and female subjects	16	Single oral doses of favipiravir 600 mg and 1200 mg (100 mg capsule) or placebo in the fasted state	Pharmacokinetics, safety
US	US103	Healthy adult male and female subjects	16	Group 1: Favipiravir 600 mg BID (Days 1-2) and 600 mg QD (Days 3-5) or placebo Group 2: Favipiravir 800 mg BID (Days 1-2) and 800 mg QD (Days 3-5) or placebo Administered 1 hour before meal, Treatment duration: 5 days *Favipiravir, 100 mg capsule	Pharmacokinetics, safety

Study Location	Study number	Study population	Number of treated subjects	Dosage regimen	Primary endpoint
US	US103b	Healthy adult male and female subjects Healthy elderly male and female subjects	32	Groups 1 (non-elderly) and 2 (elderly): Favipiravir 1200 mg BID (Day 1) and 600 mg BID (Days 2-5) or placebo Groups 3 (non-elderly) and 4 (elderly): Favipiravir 1200 mg BID (Day 1) and 800 mg BID (Days 2-5) or placebo Administered 1 hour before meal, Treatment duration: 5 days	Pharmacokinetics, safety

QD: Once daily, BID: 2 times daily, TID: 3 times daily

4.(iii).A.(1) Clinical pharmacology studies

4.(iii).A.(1).1) Preliminary food effect study in healthy adult Japanese subjects (5.3.1.1.1, Study JP102 [[redacted] to [redacted]])

A two-treatment, two-period, randomized crossover study was conducted at 1 site in Japan to investigate food effects on the pharmacokinetics of favipiravir in healthy adult Japanese male subjects (target sample size, 12 subjects [n = 6 per group]).

Favipiravir 400 mg (100 mg capsule × 4) was orally administered as a single dose in the fasted state and fed state (30 minutes after the start of a high fat diet), and Period 1 and Period 2 was separated by a wash-out period of 7 days.

All of the 12 subjects enrolled in this study were included in the safety analysis population.

One adverse event (blood bilirubin increased) occurred in 1 subject treated with favipiravir in the fasted state, and the causal relationship with the study drug could not be ruled out. No adverse events occurred in the fed state.

No adverse events leading to discontinuation of the treatment, deaths, or serious adverse events occurred.

Findings in laboratory parameters included increasing trends of lymphocytes, total bilirubin, and triglyceride on Day 2 in both Period 1 and Period 2, but no findings potentially causing clinical issues were reported for vital sign[150] or 12-lead electrocardiogram (ECG).

4.(iii).A.(1).2) Food effect study in healthy adult Japanese subjects (5.3.1.1.2, Study JP114 [[redacted] to [redacted]])

A two-treatment, two-period, randomized crossover study was conducted at 1 site in Japan to investigate food effect on pharmacokinetics of favipiravir in healthy adult Japanese male subjects (target sample size, 16 subjects [n = 8 per group]).

Favipiravir 1200 mg (200 mg tablet × 6) was t orally administered as a single dose in the fasted state and fed state (30 minutes after the start of a high fat diet), and Period 1 and Period 2 was separated by a wash-out period of 14 days.

All of the 16 subjects enrolled in this study were included in the safety analysis population.

Six adverse events occurred in 1 subject (gastroenteritis norovirus, lymphocyte count decreased, neutrophil count increased, bilirubin conjugated increased, blood bilirubin increased, and protein

[150] Systolic pressure at 80 to 90 mmHg was found in 1 subject, who did not complain of symptoms associated with this event. The investigator therefore determined that it was not an adverse event.

urine present [1 event each]) after the fasted administration, and 2 adverse events occurred in 1 subject (pruritus and rash [1 event each]) after the fed administration. A causal relationship with the study drug could not be ruled out for pruritus and rash (mild for both) observed after fed administration.

Adverse events leading to discontinuation of the treatment were reported by 1 subject (2 events) (pruritus and rash [1 event each]) after fed administration, but neither deaths nor serious adverse events occurred.

Findings in laboratory parameters included a decreasing trend of creatine phosphokinase (CPK) on Day 3 in both Period 1 and Period 2, but no noteworthy findings in vital sign[151] or ECG[152] were reported.

4.(iii).A.(1).3) Bioequivalence study in healthy adult Japanese subjects (5.3.1.2.1, Study JP110 [[redacted] to [redacted]])

A two-treatment, two-period, randomized crossover study was conducted at 1 site in Japan to investigate bioequivalence of the 100 mg tablet and the 200 mg tablet of favipiravir at 400 mg (100 mg tablet × 4, 200 mg tablet × 2) in healthy adult Japanese male subjects (target sample size, 24 subjects [n = 12 per group]).

Favipiravir was orally administered as a single dose at 400 mg (100 mg tablet × 4, 200 mg tablet × 2) in the fasted state.

All of the 24 subjects enrolled into this study were included in the safety analysis population.

Nine adverse events occurred in 6 subjects following use of 100 mg tablets (blood bilirubin increased [4 events], dysphoria, nausea, pyrexia, blood pressure decreased, and activated partial thromboplastin time prolonged [1 event each]), and 4 events occurred in 3 subjects following use of 200 mg tablets (blood bilirubin increased [2 events], pruritus and joint sprain [1 event each]). A causal relationships with the study drug could not be ruled out for blood bilirubin increased (4 events in 4 subjects), and dysphoria, blood pressure decreased, and activated partial thromboplastin time prolonged (1 event in 1 subject, each) following use of 100 mg tablets, and blood bilirubin increased (2 events in 2 subjects) following use of 200 mg tablets.

An adverse event leading to discontinuation of the treatment was pyrexia, which occurred in 1 subject receiving 100 mg tablets, but neither deaths nor serious adverse events occurred.

Laboratory parameters showed an increase in bilirubin total in 9 subjects at the end of treatment in Period 1 and in 7 subjects at the end of treatment in Period 2. Other than the subjects with adverse events for which a causal relationship with the study drug could not be ruled out (blood bilirubin increased), all of the remaining changes were assessed not to be clinically relevant by the investigator. Other than activated partial thromboplastin time prolonged in 1 subject, no special findings were reported, and there were no findings causing clinical issues in vital sign[153] or ECG.[154]

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[151] The subject who experienced a body temperature of 38.4°C on Day 2 in Period 1 (administration in the fasted state) due to pyrexia associated with gastroenteritis norovirus was excluded.

[152] There were no subjects with a change in QTc (Fridericia) from the baseline (ΔQTc [Fridericia]) >30 msec. Although 1 subject experienced a change of 33 msec in QTc (Bazett) from the baseline (ΔQTc [Bazett]) before dosing on Day 1 in Period 2, the medical expert judged that the event was not clinically relevant.

[153] One subject with blood pressure decreased was excluded.

[154] Although there were 2 subjects with ΔQTc (Fridericia) of >30 msec, the event was assessed not to be clinically relevant.

4.(iii).A.(1).4) Single dose study in healthy adult Japanese subjects (5.3.3.1.1, Study JP101 [[redacted] to [redacted]])

A placebo controlled, randomized, double-blind study was conducted at 1 site in Japan to investigate the pharmacokinetics, tolerability, and safety of favipiravir in healthy adult Japanese male subjects (target sample size, 48 subjects [n = 8 per group (6 subjects in the favipiravir group, 2 subjects in the placebo group)]).

Favipiravir (30 mg, 90 mg, 200 mg, 400 mg, 800 mg, or 1600 mg) or placebo was orally administered as a single dose in the fasted state.

All of the 48 subjects enrolled in this study were included in the safety analysis population.

Adverse events reported in this study included 2 events in 1 subject in the favipiravir 30 mg group (ALT increased and AST increased in 1 event each), 2 events in 1 subject in the favipiravir 200 mg group (blood CPK increased and AST increased [1 event each]), 3 events in 2 subjects in the favipiravir 800 mg group (pharyngolaryngeal pain, C-reactive protein [CRP] increased, and blood triglycerides increased [1 event each]), 4 events in 1 subject in the favipiravir 1600 mg group (cough, pyrexia, monocyte count increased, and CRP increased [1 event each]), and 2 events in 2 subjects in the placebo group (nausea and blood potassium increased in 1 event each). Adverse events for which causal relationships with the study drug could not be ruled out (adverse drug reactions) included 2 events in 1 subject in the favipiravir 30 mg group (ALT increased and AST increased [1 event each]) and 2 events in 2 subjects in the placebo group (nausea and blood potassium increased [1 event each]).

No adverse events leading to discontinuation of the treatment, deaths, or serious adverse events occurred.

Laboratory parameters found throughout the study period included an increasing trend of triglyceride and a decreasing trend of creatine kinase (CK), but both trends were resolving on Day 6, and no findings causing clinical issues were reported in vital sign[155] or ECG.

4.(iii).A.(1).5) Multiple dose study in healthy adult Japanese subjects (5.3.3.1.4, Study JP103 [[redacted] to [redacted]])

A placebo controlled, randomized, double-blind study was conducted at 1 site in Japan to investigate the pharmacokinetics, tolerability, and safety of favipiravir in healthy adult Japanese male subjects (target sample size, 24 subjects [n = 8 per group (6 subjects in the favipiravir group, 2 subjects in the placebo group)]).

Favipiravir or placebo was orally administered 1 hour before a meal for 7 days (Group 1, 8 days in total).[156]

Group 1: Favipiravir 400 mg TID (BID on Day 1, TID from Day 2 to morning on Day 8)
Group 2: Favipiravir 400 mg TID (Days 1-2) and 400 mg QD (Days 3-7)
Group 3: Favipiravir 600 mg BID (Days 1-2) and 600 mg QD (Days 3-7)

All of the 24 subjects enrolled in this study were included in the safety analysis population.

Adverse events reported in this study included 2 events in 2 subjects (blood uric acid increased [2 events]) in Group 1, 2 events in 1 subject (headache and pharyngolaryngeal pain [1 event each])

[155] There were no subjects with abnormal values during the observation period. Pyrexia occurred in 1 subject treated with favipiravir at 1600 mg after discharge on Day 3, but this event was judged to be a change associated with incidental acute upper respiratory tract inflammation, and its causal relationship with the study drug was ruled out.
[156] Each group included 2 subjects to be treated with the placebo.

in Group 3, and 1 event in 1 subject (ALT increased in 1 event) in the placebo group.[157] No adverse events occurred in Group 2. Adverse drug reactions included 2 events in 2 subjects (blood uric acid increased [2 events]) in Group 1 and 1 event in 1 subject (ALT increased [1 event]) in the placebo group.

No adverse events leading to discontinuation of the treatment, deaths, or serious adverse events occurred.

Laboratory parameters found throughout the study period included increasing trends of blood uric acid level (only in the favipiravir group) and triglyceride and a decreasing trend of CK, but no findings affecting vital sign or ECG were reported.

4.(iii).A.(1).6) Supplemental multiple dose study in healthy adult Japanese subjects (5.3.3.1.6, Study JP106 [[redacted] to [redacted]])

A placebo controlled, randomized, double-blind study was conducted at 1 site in Japan to investigate the pharmacokinetics and safety of favipiravir including effects on the testis in healthy adult Japanese male subjects (target sample size, 16 subjects [n = 8 per group (6 subjects in the favipiravir group, 2 subjects in the placebo group)]).

Favipiravir was orally administered between meals[158] for 5 days in accordance with the following dosage regimen[159]: in Group 1, favipiravir 600 mg BID (Day 1) and then 600 mg QD (Days 2-5); and in Group 2, favipiravir 400 mg BID (Days 1-4) and then 400 mg QD (Day 5).[160]

All of the 16 subjects enrolled in this study were included in the safety analysis population.

Adverse events reported in this study included 8 events in 6 subjects (β-N-acetyl D-glucosaminidase increased [6 events], diarrhoea [2 events]) in Group 1 and 16 events in 6 subjects (β-N-acetyl D-glucosaminidase increased [6 events], feeling hot [4 events], headache [3 events], eczema, blood uric acid increased and blood urine present [1 event each]) in Group 2. No adverse events occurred in the placebo group. Adverse drug reactions included 1 event in 1 subject (diarrhoea) in Group 1 and 7 events in 1 subject (headache [3 events], feeling hot [3 events], blood uric acid increased [1 event]) in Group 2.

No adverse events leading to discontinuation of the treatment, deaths, or serious adverse events occurred.

Laboratory parameters found throughout the study period included an increasing trend of blood uric acid level (only in the favipiravir group), but no findings affecting vital sign and ECG were reported. In either group, no constant changes associated with sperm formation disorder were reported in concentration-time profiles of inhibin B, follicle-stimulating hormone (FSH), free testosterone, or luteinizing hormone (LH).

4.(iii).A.(1).7) Multiple high-dose study in healthy adult Japanese subjects (5.3.3.1.8, Study JP111 [[redacted] to [redacted]])

A placebo controlled, randomized, double-blind study was conducted at 1 site in Japan to investigate the pharmacokinetics, tolerability, and safety of favipiravir in healthy adult Japanese

[157] Except for 1 event of blood uric acid increased rated as Grade 4 (the level exceeded 10 mg/dL on Day 7, but no symptoms were associated, and the severity was thus mild), all of the adverse events were mild and at Grade 1.
[158] Meals should be finished at least 2 hours before dosing, or started at least 1 hour after dosing.
[159] The dosage regimen set in this study to investigate the pharmacokinetics of favipiravir at the dosage regimen in the dose-response phase II study (Study JP205) was as follows: the same dosage regimen as that in the high dose group in the dose-response study (Study JP205) was used in Group 1; and the same dosage regimen as that in the low dose group in Study JP205 was used until the morning on Day 3 in Group 2.
[160] Each group included 2 subjects to be treated with the placebo.

male subjects (target sample size, 16 subjects [n = 8 per group (6 subjects in the favipiravir group, 2 subjects in the placebo group)]).

Favipiravir was orally administered between the meals[161] for 7 days in accordance with the following regimens: Group 1, a single dose of favipiravir 1200 mg (first dose) and a single dose of 400 mg (second dose) on Day 1, 400 mg BID (Days 2-6), and then 400 mg QD (Day 7); and Group 2, a single dose of favipiravir 1200 mg (first dose) and a single dose of 600 mg (second dose) on Day 1, 600 mg BID (Days 2-6), and then 600 mg QD (Day 7).[162]

All of the 16 subjects enrolled in this study were included in the safety analysis population.

Adverse events reported in this study included 4 events in 4 subjects (blood uric acid increased [3 events], diarrhoea [1 event]) in Group 1, 7 events in 5 subjects (blood uric acid increased [5 events], rash and musculoskeletal stiffness [1 event each]) in Group 2, and 3 events in 3 subjects (syncope, diarrhoea, and blood bilirubin increased [1 event each]) in the placebo group. Moderate adverse events included 1 event of rash in 1 subject in Group 2 and 1 event of syncope in 1 subject in the placebo group, and all of the other adverse events were mild. For adverse events in the placebo group other than syncope, causal relationships with the study drug could not be ruled out.

As an adverse event leading to discontinuation of the treatment, 1 event of rash occurred in 1 subject in Group 2. Neither deaths nor serious adverse events occurred.

Laboratory parameters found throughout the study period included an increasing trend of blood uric acid level (only in the favipiravir group) and a decreasing trend of protein total, but no noteworthy findings were reported in vital signs.[163] In either group, no constant changes associated with sperm formation disorder were observed in inhibin B, total testosterone, FSH, or LH. In terms of ECG findings, ΔQTc (Fridericia) ≥30 msec was not reported in any subject, but ΔQTc (Bazett) ≥30 msec was reported in 1 subject in Group 1.[164]

4.(iii).A.(1).8) Single dose study in healthy elderly Japanese subjects (5.3.3.3.1, Study JP104 [[redacted] to [redacted]])

A placebo controlled, randomized, double-blind study was conducted at 1 site in Japan to investigate the pharmacokinetics, tolerability, and safety of favipiravir in healthy elderly Japanese subjects (target sample size, 16 subjects [n = 8 per group (6 subjects in the favipiravir group, 2 subjects in the placebo group)]).

Favipiravir 400 mg (Group 1) or 800 mg (Group 2) or placebo was orally administered as a single dose in the fasted state at least 10 hours after a meal.

All of the 16 subjects enrolled in this study were included in the safety analysis population.

Adverse events reported in this study included 1 event in 1 subject (beta 2 microglobulin urine increased) in Group 1 and 1 event in 1 subject (β-N-acetyl D-glucosaminidase increased) in Group 2, and a causal relationship of these events with the study drug could not be ruled out. No adverse events occurred in the placebo group.

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[161] Meals should be finished at least 2 hours before dosing, or started at least 1 hour after dosing.
[162] Each group included 2 subjects to be treated with the placebo.
[163] In 5 subjects including 1 subject treated with the placebo, systolic pressure of 80 to 90 mmHg was observed, but the change was not significant compared with the baseline. The investigator and medical expert therefore determined that the event was not clinically relevant abnormality.
[164] Although in this subject, the ΔQTc (Bazett) was 41 msec before dosing in the morning on Day 3, the QTc remained normal throughout the study period. The investigator and medical expert therefore determined that it was not clinically relevant abnormality.

No adverse events leading to discontinuation of the treatment, deaths, or serious adverse events occurred.

Laboratory parameters found throughout the study period included an increasing trend of triglyceride and a decreasing trend of CK, but no findings affecting vital sign or ECG were reported.

4.(iii).A.(1).9) Multiple dose study in healthy elderly Japanese subjects (5.3.3.3.2, Study JP107 [[redacted] to [redacted]])

A placebo controlled, randomized, double-blind study was conducted at 1 site in Japan to investigate the pharmacokinetics, tolerability, and safety of favipiravir in healthy elderly Japanese subjects (target sample size, 16 subjects).

Favipiravir was to be orally administered between meals[165] for 5 days in accordance with the following dosage regimen: in Group 1, favipiravir 600 mg BID (Day 1) and then 600 mg QD (Days 2-5); and in Group 2, favipiravir 400 mg BID (Days 1-4) and then 400 mg QD (Day 5).[166]

All of the 16 subjects enrolled in this study were included in the safety analysis population.

Adverse events reported in this study included 3 events in 2 subjects (wound, blood fibrinogen increased, and CRP increased [1 event each]) in Group 2 and 1 event in 1 subject (CRP increased) in the placebo group. No adverse events occurred in Group 1. Of adverse events in Group 2 other than a wound, causal relationships with the study drug could not be ruled out.

No adverse events leading to discontinuation of the treatment, deaths, or serious adverse events occurred.

Laboratory parameters found throughout the study period included a decreasing trend of serum albumin value, but no findings affecting vital sign were reported. No constant changes associated with sperm formation disorder were reported in inhibin B, free testosterone, FSH, or LH. ECG findings included QTc (Fridericia) ≥450 msec in 1 subject in Group 2 and ΔQTc (Fridericia) ≥30 msec in 1 subject in the placebo group.[167]

4.(iii).A.(1).10) Drug-interaction study of favipiravir in combination with theophylline in healthy adult Japanese subjects (5.3.3.4.1, Study JP108 [[redacted] to [redacted]])

An open-label, add-on study was conducted at 1 site in Japan to investigate the pharmacokinetics, tolerability, and safety of favipiravir in healthy adult Japanese male subjects (target sample size, 10 subjects).

Favipiravir and/or theophylline[168] were to be administered for 5 days in the following dosage regimen: for combination therapy with favipiravir and theophylline, favipiravir was administered at 600 mg BID (Day 6) and at 600 mg QD (Days 7-10), and theophylline was administered at 200 mg BID (Days 1-9) and at 200 mg QD (Day 10); and for favipiravir monotherapy, favipiravir was administered at 600 mg BID (Day 24) and at 600 mg QD (Day 25). Both favipiravir and

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[165] Meals should be finished at least 2 hours before dosing, or started at least 1 hour after dosing.

[166] Each group included 2 subjects to be treated with the placebo.

[167] In these subjects, the QTc was 460 msec, 30 minutes after dosing in the morning on Day 2, and ΔQTc was 39 msec, 1 hour after dosing in the morning on Day 5. These numerical values were not relevant. The investigator and medical expert therefore determined that they were not clinically relevant abnormalities.

[168] Theophylline is metabolized mainly by CYP1A2, and its metabolite, 1-methylxanthine, is then metabolized by XO (partially involved in the metabolism of favipiravir into M1). In this study, XO-mediated interaction potential between favipiravir and theophylline was investigated.

theophylline were administered between the meals,[169] and the study included a wash-out period of 14 days.

All of the 10 subjects enrolled in this study were included in the safety analysis population.

Adverse events reported in this study included 21 events in 8 subjects (blood uric acid increased [8 events; 4 events after coadministration of favipiravir with theophylline, 2 events after the theophylline monotherapy, and 2 events after the favipiravir monotherapy], urine uric acid decreased [4 events after coadministration of favipiravir with theophylline], β-N-acetyl D-glucosaminidase increased [2 events; during the wash-out period and posterior examination] and blood fibrinogen increased [2 events; during the wash-out period and posterior examination], nasopharyngitis [at the posterior examination], diarrhoea [after the favipiravir monotherapy], white blood cell count increased [after coadministration of favipiravir with theophylline], blood triglycerides increased [1 event at the posterior examination], and CRP increased [1 event during the wash-out period]). Adverse drug reactions included blood uric acid increased in 6 subjects (8 events) and urine uric acid decreased in 4 subjects (4 events).[170]

No adverse events leading to discontinuation of the treatment, deaths, or serious adverse events occurred.

Laboratory parameters found throughout the study period included increased blood uric acid level and decreased urine uric acid level. In terms of vital sign, 1 subject[171] experienced temporary hypothermia with the body temperature at 34.7°C on Day 3 of theophylline monotherapy, but no changes causing clinical issues including this event were found. In terms of ECG, ΔQTc (Fridericia) >60 msec was not reported in any subject, and no noteworthy findings were reported except for ΔQTc (Bazett) of 459 msec[172] in 1 subject.

4.(iii).A.(1).11) Drug-interaction study of favipiravir in combination with oseltamivir in healthy adult Japanese subjects (5.3.3.4.2, Study JP109 [[redacted] to [redacted]])

An open-label, add-on study was conducted at 1 site in Japan to investigate the pharmacokinetics, tolerability, and safety of favipiravir in healthy adult Japanese male subjects (target sample size, 10 subjects).

For favipiravir monotherapy, favipiravir was administered at 600 mg BID on Day 1 and at 600 mg QD on Day 2. Favipiravir and oseltamivir phosphate[173] were concomitantly administered for 2 days and favipiravir was administered at 600 mg BID on Day 16 and then at 600 mg QD on Day 17, and oseltamivir phosphate was administered at 75 mg BID from Day 12 to Day 16 and then at 75 mg QD on Day 17. Both favipiravir and oseltamivir phosphate were administered between the meals, and the study included a wash-out period of 14 days.

All of the 10 subjects enrolled in this study were included in the safety analysis population.

Adverse events reported in this study included 1 event in 1 subject (blood fibrinogen increased [9 days after the end of the favipiravir monotherapy]), and its causal relationship with the study drug

[169] Meals should be finished at least 2 hours before dosing, or started at least 1 hour after dosing.
[170] All of these subjects also experienced blood uric acid increased.
[171] This subject had low body temperature throughout the study period. The investigator therefore determined that the change was not relevant.
[172] It was obtained at the posterior examination. The investigator therefore determined that it was not attributable to the study drug.
[173] Favipiravir and oseltamivir phosphate are metabolized into M1 and oseltamivir carboxylate, respectively, which are excreted into urine. Oseltamivir carboxylate undergoes tubular secretion through OAT1, but non-clinical data have demonstrated that favipiravir and M1 inhibit OAT1. In this study, potential interaction between favipiravir (and M1) and oseltamivir carboxylate in the excretion process was investigated.

was ruled out.

No adverse events leading to discontinuation of the treatment, deaths, or serious adverse events occurred.

No special changes in laboratory parameters, except for blood fibrinogen increased, were observed throughout the study period. Although a decrease in systolic blood pressure (80-90 mmHg) occurred in 2 subjects and increased body temperature (37.2°C) in 1 subject,[174] no other special changes in vital sign were reported. No changes causing clinical issues were found in ECG.

4.(iii).A.(1).12) QT/QTc evaluation study in healthy adult Japanese subjects (5.3.4.1.1, Study JP115 [[redacted] to [redacted]])

A single dose blind study (Part A) and a blind, randomized, four-treatment, four-period crossover study (Part B) were conducted at 1 site in Japan to investigate the effects of favipiravir on QT/QTc interval in Japanese healthy adult male subjects (target sample size, 68 subjects [12 subjects in Part A, 56 subjects in Part B]).

In Part A, subjects orally received favipiravir at 2000 or 2400 mg as a single dose in the fasted state. In Part B, subjects were ramdomly allocated to one of 4 treatment groups to receive a sequence of favipiravir 1200, favipiravir 2400 mg, MFLX 400 mg and placebo as a single dose in the fasted state. The treatments were administered to each group in a different sequence in Periods 1 to 4 and the sequences were determined by the assignment manager. The treatment periods were separated by a wash-out period of 14 days.

All of the 68 subjects enrolled in this study (12 subjects in Part A, 56 subjects in Part B) were included in the safety analysis. Of 56 subjects in Part B, 55 subjects were included in the QT/QTc analysis, excluding 1 subject who discontinued the study due to rash.[175]

Adverse events reported in this study included 1 event in 1 subject in the favipiravir 2000 mg group (faeces hard) and 3 events in 2 subjects in the 2400 mg group (diarrhoea, faeces hard, and blood uric acid increased [1 event each]) in Part A; and 24 events in 15 subjects in the favipiravir 1200 mg group (headache [4 events]; activated partial thromboplastin time prolonged and faeces hard [3 events each]; nasopharyngitis [2 events]; gastroenteritis, tonsillitis, vessel puncture site pain, visual impairment, abdominal pain lower, abdominal pain upper, diarrhoea, nausea, arthralgia, back pain, feeling hot, and ALT increased [1 event each]), 30 events in 18 subjects in the 2400 mg group (blood uric acid increased [6 events]; diarrhoea [4 events]; faeces hard, erythema, rash, ALT increased, and AST increased [2 events each]; gastroenteritis, nasopharyngitis, headache, abdominal pain lower, eczema, dysmenorrhoea, blood CK increased, blood triglycerides increased, blood urine present, and body temperature increased [1 event each]), 35 events in 18 subjects in the MFLX group (diarrhoea [5 events]; nasopharyngitis [4 events]; headache, nausea, vomiting, and electrocardiogram QT prolonged [3 events each]; abdominal discomfort and faeces hard [2 events each]; dizziness, presyncope, pruritus, rash, neck pain, feeling hot, malaise, ALT increased, AST increased, and blood bilirubin increased [1 event each]), and 22 events in 18 subjects in the placebo group (nasopharyngitis [4 events], diarrhoea [2 events], headache, somnolence, oropharyngeal pain, enterocolitis, faeces hard, nausea, erythema, pruritus, neck pain, dysmenorrhoea, lymphocyte count decreased, neutrophil count increased, blood bilirubin increased, blood triglycerides increased, blood uric acid increased, and blood urine present [1 event each]) in Part B. Adverse drug reactions included 1 event in 1 subject in the

[174] None of the events were associated with symptoms. The investigator therefore determined that they were not clinically relevant.
[175] For the effect on the QT/QTc interval, see "4.(ii).A. 6).1) QT/QTc evaluation study in healthy adult Japanese male and female subjects."

favipiravir 2000 mg group (faeces hard) and 3 events in 2 subjects in the 2400 mg group (diarrhoea, faeces hard, and blood uric acid increased [1 event each]) in Part A; and 17 events in 13 subjects in the favipiravir 1200 mg group (headache [4 events]; activated partial thromboplastin time prolonged [3 events]; faeces hard [2 events]; visual impairment, abdominal pain lower, abdominal pain upper, diarrhoea, nausea, arthralgia, back pain, and feeling hot [1 event each]), 17 events in 13 subjects in the 2400 mg group (blood uric acid increased [6 events]; diarrhoea [4 events]; faeces hard [2 events]; headache, abdominal pain lower, eczema, blood triglycerides increased, and body temperature increased [1 event each]), 26 events in 18 subjects in the MFLX group (diarrhoea [5 events]; headache, nausea, and electrocardiogram QT prolonged [3 events each]; abdominal discomfort, faeces hard, and vomiting [2 events each]; dizziness, presyncope, rash, feeling hot, malaise, and blood bilirubin increased [1 event each]), and 7 events in 6 subjects in the placebo group (diarrhoea, headache, somnolence, faeces hard, nausea, blood bilirubin increased, and blood uric acid increased [1 event each]) in Part B.

Neither deaths nor serious adverse events occurred.

An adverse event leading to discontinuation of the treatment occurred in 1 subject (rash) treated with moxifloxacin, and its causal relationship with the study drug could not be ruled out, but it resolved later.

4.(iii).A.(1).13) Single low-dose study (5.3.3.1.2 [Reference data], Study US101 [[redacted] to [redacted]]) and single high-dose study (5.3.3.1.3 [Reference data], Study US102 [[redacted] to [redacted]]) in healthy adult US subjects

A placebo controlled, randomized, double-blind study was conducted at 1 site in the US to investigate the pharmacokinetics, tolerability, and safety of favipiravir in healthy adult US male and female subjects (target sample size, 48 subjects[176] [n = 8 per group (6 subjects in the favipiravir group, 2 subjects in the placebo group)]).

Favipiravir was orally administered as a single dose at 30 mg, 90 mg, 200 mg, 400 mg (Study US101), 600 mg, or 1200 mg (Study US102) in the fasted state.[177]

All of the 48 subjects enrolled in this study were included in the safety analysis.

Adverse events reported in this study included 21 events in 4 subjects in the favipiravir 30 mg group (diarrhoea and headache [3 events each]; pharyngolaryngeal pain and feeling hot [2 events each]; abdominal pain upper, nausea, fatigue, anorexia, musculoskeletal pain, neck pain, paraesthesia, rhinorrhoea, sinus congestion, excoriation, and scab [1 event each]), 8 events in 2 subjects in the favipiravir 90 mg group (headache, pharyngolaryngeal pain, and nail discolouration [2 events each]; yellow skin and sinus congestion [1 event each]), 15 events in 5 subjects in the favipiravir 200 mg group (nausea, vomiting, and headache [2 events each]; asthenia, fatigue, feeling hot, pain, back pain, musculoskeletal pain, pain in extremity, sinus headache, and rhinorrhoea [1 event each]), 11 events in 5 subjects in the favipiravir 400 mg group (myalgia [2 events]; lymph node pain, dry mouth, chills, musculoskeletal stiffness, headache, pharyngolaryngeal pain, cold sweat, dry skin, and dizziness [1 event each]), 17 events in 4 subjects in the favipiravir 600 mg group (pruritus and rash erythematous [4 events each]; pyrexia [2 events]; headache, cough, nasal congestion, respiratory tract congestion, rhinorrhoea, sinus congestion, and pruritus generalised [1 event each]), 5 events in 1 subject in the favipiravir 1200 mg group (diarrhoea [3 events], nausea and discomfort [1 event each]), and 10 events in 5 subjects in the placebo group (Study US101, 9 events in 4 subjects [dermatitis contact (4 events); fatigue (2 events); ear pain, headache, and pharyngolaryngeal pain (1 event each)]; Study US102,

[176] A total of 32 subjects in Study US101 and 16 subjects in Study US102
[177] Each group included 2 subjects to be treated with the placebo.

1 event in 1 subject [headache]). Adverse drug reactions included 6 events in 2 subjects in the favipiravir 30 mg group (headache [2 events]; abdominal pain upper, nausea, feeling hot, and anorexia [1 event each]), 4 events in 2 subjects in the favipiravir 90 mg group (nail discolouration [2 events], yellow skin and headache [1 event each]), 6 events in 2 subjects in the favipiravir 200 mg group (headache [2 events]; fatigue, back pain, musculoskeletal pain, and pain in extremity [1 event each]), 6 events in 3 subjects in the favipiravir 400 mg group (myalgia [2 events]; dry mouth, headache, cold sweat, and dizziness [1 event each]), 9 events in 2 subjects in the favipiravir 600 mg group (pruritus and rash erythematous [4 events each], pruritus generalised [1 event]), 5 events in 1 subject in the favipiravir 1200 mg group (diarrhoea [3 events], nausea and discomfort [1 event each]), and 2 events in 2 subjects in the placebo group (Study US101, 1 event in 1 subject [fatigue]; Study US102, 1 event in 1 subject [headache]).

No adverse events leading to discontinuation of the treatment, deaths, or serious adverse events occurred.

Laboratory parameters found throughout the study period included high CK value (1 subject in the 30 mg group), high AST value (1 subject in the 30 mg group), and high reticulocyte count (1 subject in the 600 mg group, 4 subjects in the 1200 mg group), but no findings affecting vital sign or ECG were reported. No findings causing clinical issues were reported at skin and nail coloration examination and seminal test. As for clinical findings, rash erythematous and pruritus occurred in 1 subject in the favipiravir 600 mg group at 4 hours after the dosing, and the causal relationship of the findings with the study drug could not be ruled out.

4.(iii).A.(1).14) Multiple dose study in healthy adult US subjects (5.3.3.1.5 [Reference data], Study US103 [[redacted] to [redacted]])

A placebo controlled, randomized, double-blind study was conducted at 1 site in the US to investigate the pharmacokinetics, tolerability, and safety of favipiravir in healthy adult US male and female subjects (target sample size, 16 subjects [n = 8 per group (6 subjects in the favipiravir group, 2 subjects in the placebo group)]).

Favipiravir was orally administered 1 hour before a meal for 5 days in accordance with the following dosage regimen: in Group 1, favipiravir 600 mg BID (Days 1-2) and then 600 mg QD (Days 3-5); and in Group 2, favipiravir 800 mg BID (Days 1-2) and then 800 mg QD (Days 3-5).[178]

All of the 16 subjects enrolled in this study were included in the safety analysis.

Adverse events reported in this study included 6 events in 4 subjects (pain [2 events], diarrhoea, lower extremity mass, dizziness, and pruritus [1 event each]) in Group 1, 6 events in 4 subjects (headache [2 events], abnormal faeces, mucous stools, panic attack, and urine odour abnormal [1 event each]) in Group 2, and 6 events in 3 subjects (fatigue, headache, poor quality sleep, abnormal dreams, pruritus, and rash erythematous [1 event each]) in the placebo group. Adverse drug reactions included 4 events in 3 subjects (diarrhoea, pruritus, pain) in Group 1, 5 events in 3 subjects (headache, abnormal faeces, mucous stools, urine odour abnormal) in Group 2, and 6 events in 3 subjects (abnormal dreams, headache, poor quality sleep, pruritus, rash erythematous, and fatigue [1 event each]) in the placebo group.

No adverse events leading to discontinuation of the treatment, deaths, or serious adverse events occurred.

[178] Each group included 2 subjects to be treated with the placebo.

Laboratory parameters found throughout the study period included increased reticulocyte count (1 subject in Group 1, 5 subjects in Group 2, 1 subject in the placebo group), but the highest value was 3.2%, and its increase was small compared to the reference range (0.4%-2.2%). No findings causing clinical issues were reported in vital sign, ECG, skin or nails in terms of coloration, or general condition. In any group, no constant changes associated with sperm formation disorder were found in inhibin B, FSH, or LH, but decrease in total testosterone was reported in Group 2 on Day 13 and thereafter and in the placebo group on Day 6 and thereafter.

4.(iii).A.(1).15) Multiple high-dose study in healthy adult US subjects (5.3.3.1.7 [Reference data], Study US103b [[redacted] to [redacted]])

A placebo controlled, randomized, double-blind study was conducted at 2 sites in the US to investigate the pharmacokinetics, tolerability, and safety of favipiravir in healthy adult US male and female subjects (target sample size, 32 subjects [n = 8 per group (6 subjects in the favipiravir group, 2 subjects in the placebo group)]).

Favipiravir was orally administered 1 hour before meal for 5 days in accordance with the following dosage regimen: in Groups 1 (non-elderly) and 2 (elderly), favipiravir 1200 mg BID on Day 1 and then 600 mg BID from Day 2 to Day 5; and in Groups 3 (non-elderly) and 4 (elderly), favipiravir 1200 mg BID on Day 1 and then 800 mg BID from Day 2 to Day 5.[179]

All of the 32 subjects enrolled in this study were included in the safety analysis.

Adverse events reported in this study included 5 events in 4 non-elderly subjects (sinusitis, headache, taste disturbance, nasal congestion, and back pain [1 event each]) and 1 event in 1 elderly subject (blood pressure increased) in Groups 1 and 2; and 4 events in 3 non-elderly subjects (headache [4 events]) and 3 events in 2 elderly subjects (ocular hyperaemia, constipation, and arthralgia [1 event each]) in Groups 3 and 4; and 6 events in 3 non-elderly subjects (headache [4 events], nasal congestion [2 events]) and 8 events in 3 elderly subjects (constipation [3 events]; upper respiratory tract infection, insomnia, abdominal pain, dyspepsia, and back pain [1 event each]) in the placebo group. Adverse drug reactions included 4 events in 3 non-elderly subjects (headache, taste disturbance, nasal congestion, and back pain [1 event each]) and 1 event in 1 elderly subject (blood pressure increased) in Groups 1 and 2; and 4 events in 3 non-elderly subjects (headache [4 events]) and 3 events in 2 elderly subjects (ocular hyperaemia, constipation, and arthralgia [1 event each]) in Groups 3 and 4; and 6 events in 3 non-elderly subjects (headache [4 events], nasal congestion [2 events]) and 7 events in 3 elderly subjects (constipation [3 events]; insomnia, abdominal pain, dyspepsia, and back pain [1 event each]) in the placebo group.

No adverse events leading to discontinuation of the treatment, deaths, or serious adverse events occurred.

Laboratory parameters found throughout the study period included increased blood uric acid level and decreased urine uric acid level, but no findings causing clinical issues were reported in vital sign, ECG, skin or nail in terms of coloration, or general condition. In any group, no constant changes associated with sperm formation disorder potentially causing clinical issues were reported in inhibin B, total testosterone, FSH, or LH.

4.(iii).A.(1).16) Pharmacokinetic study in patients with influenza virus infection (5.3.4.2.1, Study JP313 [[redacted] to [redacted]])

An open-label, multicenter study was conducted at 16 sites in Japan to investigate the pharmacokinetics and safety of favipiravir in Japanese patients with influenza virus infection

[179] Each group included 2 subjects to be treated with the placebo.

(target sample size, 12 subjects [16 subjects included]; aged 20-74 years).

Favipiravir was orally administered for 5 days in accordance with the following dosage regimen: a single dose of 1200 mg (the first dose) and a single dose of 400 mg (the second dose) on Day 1, and then 400 mg BID from Day 2 to Day 5.[180]

All of the 16 subjects enrolled in this study were included in the safety analysis population.

Adverse events reported in this study included 5 events in 4 subjects (hyperuricaemia, diarrhoea, blood uric acid increased, ALT increased, and AST increased [1 event each]). All of the events were mild in severity, which eventually resolved or improved. Causal relationships between the study drug and all adverse events except diarrhea cannot be ruled out.

No adverse events leading to discontinuation of the treatment, deaths, or serious adverse events occurred.

Laboratory parameters found throughout the study period included an increasing trend of blood uric acid level, but no findings affecting vital sign were reported. No constant changes associated with sperm formation disorder were reported in total testosterone, FSH, or LH. In terms of ECG findings, ΔQTc (Fridericia) of >30 msec and ≤60 msec was reported observed in 3 subjects.[181]

4.(iii).A.(1).17) Testis safety study in healthy adult US male subjects (5.3.4.1.2, Study US105 [[redacted] to [redacted]])

A placebo controlled, randomized, double-blind study was conducted at 2 sites in the US to investigate the effects of favipiravir on the testis in healthy adult US male subjects (target sample size, 116 [58 subjects per group]).

Favipiravir or placebo was orally administered 1 hour before a meal for 5 days in accordance with the following dosage regimen: 1200 mg BID on Day 1 and 800 mg BID from Day 2 to Day 5.

All of the 116 subjects (58 subjects per group) enrolled in the study were included in the seminal test analysis and safety analysis population.

Based on the seminal test data, subjects in which the sperm concentration decreased by ≥50% from the baseline (mean of values measured at 3 timepoints [1 at the screening and 2 during hospitalization]) to 90 days after the end of the treatment were identified. The table below shows 95% CI of the difference in percentage of the identified subjects in the group (reaction rate) between the favipiravir and placebo groups.

Reaction rate 90 days after the end of the treatment

Seminal test parameter	Favipiravir n = 57[a)]	Placebo n = 54[b)]	Total	Difference[c)]	95% CI of the difference
Sperm concentration	1 (1.75)	1 (1.85)	2 (1.80)	-0.10%	-6.86, 6.66

Number of responders (%)
a) Excluding 1 subject who did not complete the test (due to no visit for test)
b) Excluding 4 subjects who did not complete the test (2 subjects due to no visit for test and 2 subjects due to inability of study continuation)
c) Difference in reaction rate between the favipiravir and placebo groups (favipiravir group - placebo group)

[180] Take the study drug ≥30 minutes after a meal when dosing in the fed state is necessary.
[181] For these 3 patients and the 2 patients with "abnormality suspected" by ECG automatic analysis, ECG profiles were re-examined by the ECG examiner. As a result, none of these changes were determined to be clinically relevant.

It has been recommended that the non-inferiority of favipiravir to placebo is established when the upper limit of the 95% is <20%. The non-inferiority of favipiravir to the placebo was hereby demonstrated.

The table below shows the mean values (mean of values measured at 3 timepoints, i.e., test days) of the seminal fluid parameters (seminal fluid volume, sperm concentration, sperm motility rate, sperm viability, progressive motility, sperm count, sperm normal form rate, total motile sperm count) 60 days and 90 days after the end of the treatment in the favipiravir group and placebo group.

Comparison of changes in seminal fluid parameters from the baseline by analysis of covariance

Seminal test parameter	Test day	Least squares mean		Difference[a)]	95% CI of the difference
		Favipiravir group	Placebo group		
Sperm concentration (106/mL)	60	10.26 (57)	17.91 (55)	-7.65	-41.83, 26.53
	90	47.38 (57)	28.03 (54)	19.35	-14.93, 53.63
Sperm motility rate (%)	60	-1.72 (57)	-1.13 (55)	-0.59	-4.02, 2.84
	90	-2.65 (57)	-3.12 (54)	0.48	-2.97, 3.92
Sperm normal form rate (%)	60	-0.44 (57)	-0.26 (55)	-0.17	-1.17, 0.83
	90	-1.86 (57)	-1.89 (54)	0.02	-0.98, 1.03
Total sperm count (106/mL)	60	-14.83 (57)	-46.96 (55)	32.13	-73.19, 137.44
	90	44.61 (57)	36.76 (54)	7.85	-97.75, 113.44
Total motile sperm count (106/mL)	60	-18.18 (57)	-49.32 (55)	31.15	-55.55, 117.84
	90	35.67 (57)	7.07 (54)	28.60	-58.31, 115.52

Total sperm count = sperm count in seminal fluid specimen + urine sperm count after ejaculation
Figure in ( ) indicates the number of subjects.
Test day indicates the number of days after the end of the treatment.
a) Difference of least squares mean between the favipiravir group and placebo group (favipiravir group - placebo group)

Adverse events reported in this study included 73 events in 27 subjects in the favipiravir group and 79 events in 28 subjects in the placebo group. Adverse events reported by ≥2 subjects in the favipiravir group and the placebo group included headache (7 subjects and 18 subjects, respectively), palpitations (3 subjects and 0 subjects, respectively), nasal congestion (3 subjects and 0 subjects, respectively), abdominal pain lower (3 subjects and 1 subject, respectively), back pain (0 subjects and 3 subjects, respectively), insomnia (2 subjects and 1 subject, respectively), nausea (2 subjects and 1 subject, respectively), pruritus generalized (2 subjects and 2 subjects, respectively), sperm count decreased (2 subjects and 0 subjects, respectively), spermatozoa progressive motility decreased (2 subjects and 1 subject, respectively), somnolence (1 subject and 2 subjects, respectively), eye pruritus (1 subject and 2 subjects, respectively), rash macular (1 subject and 2 subjects, respectively), dizziness (2 subjects and 1 subject, respectively), and diarrhoea (1 subject and 2 subjects, respectively). Adverse drug reactions included 54 events in 21 subjects in the favipiravir group and 52 events in 21 subjects in the placebo group. Adverse drug reactions reported by ≥2 subjects in either group included headache (5 subjects and 15 subjects, respectively), palpitations (3 subjects and 0 subjects, respectively), abdominal pain lower (3 subjects and 0 subjects, respectively), back pain (0 subjects and 2 subjects, respectively), insomnia (2 subjects and 0 subjects, respectively), nausea (2 subjects and 1 subject, respectively), pruritus generalized (2 subjects and 2 subjects, respectively), sperm count decreased (2 subjects and 0 subjects, respectively), spermatozoa progressive motility decreased (2 subjects and 1 subject, respectively), somnolence (1 subject and 2 subjects, respectively), rash macular (1 subject and 2 subjects, respectively), dizziness (1 subject and 2 subjects, respectively), and diarrhoea (1 subject and 2 subjects, respectively).

No deaths, serious adverse events, or adverse events leading to discontinuation of the treatment occurred.

4.(iii).A.(2) Phase II studies

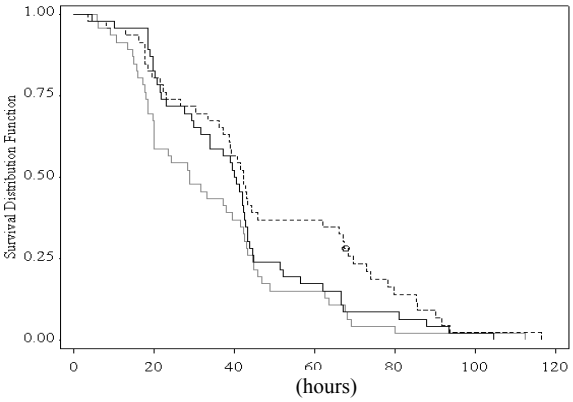
4.(iii).A.(2).1) Japanese phase II study in patients with seasonal influenza virus infection (5.3.5.1.1, Study JP205 [[redacted] to [redacted]])

An active-controlled, double-blind, parallel-group study was conducted at 75 sites in Japan to investigate the efficacy and safety of favipiravir in Japanese patients with seasonal influenza virus infection (target sample size, 144 subjects [n = 40 per group]; aged 45-64 years).

Favipiravir was orally administered for 5 days in accordance with the following dosage regimen: in the high-dose group, 600 mg BID on Day 1 and then 600 mg QD from Day 2 to Day 5; and in the low-dose group, 400 mg BID on Day 1 and Day 2 and then 400 mg QD from Day 3 to Day 5.[182] In the oseltamivir phosphate group, oseltamivir was to be orally administered at 75 mg BID for 5 days.

All of the 160 subjects (55 subjects in the high-dose group, 52 subjects in the low-dose group, and 53 subjects in the oseltamivir phosphate group) enrolled in the study were included in the safety analysis. Of the subjects included in the safety analysis, 155 subjects (54 subjects in the high-dose group, 50 subjects in the low-dose group, and 51 subjects in the oseltamivir phosphate group) were included in the Full Analysis Set (FAS), and 5 subjects with a disease other than influenza were excluded. Of the FAS, 138 subjects (46 subjects in the high-dose group, 46 subjects in the low-dose group, 46 subjects in the oseltamivir phosphate group) were included in the Per Protocol Set (PPS), and 17 subjects were excluded (13 subjects [violation of dosage regimen], 1 subject [inability of primary endpoint evaluation], 1 subject [violation of prohibited concomitant drug use], 2 subjects [who were ineligibilie for efficacy evaluation]). The PPS was defined as the efficacy analysis set.

The median (95% CI) of the pyrexia duration, primary endpoint for the efficacy, was 40.2 hours (31.5, 42.8) in the high-dose group, 42.2 hours (37.3, 62.1) in the low-dose group, and 28.8 hours (19.8, 41.5) in the oseltamivir phosphate group. The pyrexia duration in each dose group is as shown in the figure below. The difference (95% CI) of the mean in the high-dose group and low-dose group from that in the oseltamivir phosphate group was -6.6 hours (-15.7, 2.5) and -13.2 hours (-23.5, -2.9), respectively. The lower limit of the 95% CI of the difference of the mean in both the high-dose group and the low-dose group from that in the oseltamivir phosphate group remained above the predetermined threshold (-28.9 hours).



—: High-dose group, ---: Low-dose group, —: Oseltamivir phosphate group
○: Censoring (low-dose group)

Pyrexia duration (PPS)

[182] Avoid just before or after a meal, take the study drug ≥ 30 minutes after a meal.

Adverse events occurred in 22 of 55 subjects (40.0%) of the high-dose group, 20 of 52 subjects (38.5%) of the low-dose group, and 23 of 53 subjects (43.4%) of the oseltamivir phosphate group. Adverse drug reactions occurred in 14 of 55 subjects (25.5%) in the high-dose group, 8 of 52 subjects (15.4%) in the low-dose group, and 13 of 53 subjects (24.5%) in the oseltamivir phosphate group. Adverse events and/or adverse drug reactions reported by ≥2% of the subjects in any group are shown in the table below.

Adverse events and/or adverse drug reactions reported by ≥2% of subjects in any group

System organ class	Preferred term	Adverse events			Adverse drug reactions		
		High-dose group (n = 55)	Low-dose group (n = 52)	Oseltamivir phosphate group (n = 53)	High-dose group (n = 55)	Low-dose group (n = 52)	Oseltamivir phosphate group (n = 53)
Gastrointestinal disorders	Diarrhoea	8 (14.5)	4 (7.7)	6 (11.3)	5 (9.1)	3 (5.8)	4 (7.5)
	Abdominal pain upper	2 (3.6)	1 (1.9)	2 (3.8)	2 (3.6)	0 (0.0)	1 (1.9)
	Vomiting	1 (1.8)	2 (3.8)	0 (0.0)	1 (1.8)	1 (1.9)	0 (0.0)
	Nausea	1 (1.8)	0 (0.0)	4 (7.5)	0 (0.0)	0 (0.0)	3 (5.7)
	Stomach discomfort	0 (0.0)	1 (1.9)	2 (3.8)	0 (0.0)	1 (1.9)	2 (3.8)
Infections and infestations	Bronchitis	1 (1.8)	1 (1.9)	2 (3.8)	0 (0.0)	0 (0.0)	0 (0.0)
Investigations	Neutrophil count decreased	3 (5.5)	4 (7.7)	2 (3.8)	3 (5.5)	1 (1.9)	0 (0.0)
	AST increased	2 (3.6)	0 (0.0)	1 (1.9)	2 (3.6)	0 (0.0)	1 (1.9)

Number of subjects with the event/reaction (%)

Adverse events leading to discontinuation of the treatment included 2 events in 2 subjects in the high-dose group (haematochezia, vertigo), 1 event in 1 subject in the low-dose group (pneumonia), and 2 events in 2 subjects in the oseltamivir phosphate group (gastroenteritis, urticaria). Causal relationships of all the events except for pneumonia with the study drug could not be ruled out, but they eventually improved or resolved.

No deaths occurred. Two adverse events in 2 subjects were classified into serious adverse events due to their hospitalization (1 subject in the high-dose group was hospitalized due to haematochezia, 1 subject in the low-dose group was hospitalized due to pneumonia).

4.(iii).A.(3) Phase III studies

4.(iii).A.(3).1) Global phase III study in patients with influenza virus infection (5.3.5.1.2, Study 312 [[redacted] to [redacted]])

An active-controlled, double-blind, parallel-group comparative study was conducted at 153 sites in Japan and overseas (132 sites in Japan, 10 sites in Taiwan, 11 sites in Korea) to investigate the efficacy and safety of favipiravir in patients with influenza virus infection (target sample size, 750 subjects [660 subjects eligible for evaluation, 330 subjects per group]; aged 20-74 years).

Favipiravir was orally administered for 5 days in accordance with the following dosage regimen: at a dose of 1200 mg (the first dose) and at a dose of 400 mg (the second dose) on Day 1, and then at 400 mg BID from Day 2 to Day 5.[183] In the oseltamivir phosphate group, oseltamivir was to be orally administered at 75 mg BID for 5 days.

Of 762 subjects (540 Japanese subjects, 140 Taiwanese subjects, 82 Korean subjects) enrolled in this study, 758 subjects were included in the safety analysis population (378 subjects in the favipiravir group, 380 subjects in the oseltamivir phosphate group), and excluded were 4 subjects

[183] Take the study drug ≥30 minutes after a meal when dosing after a meal.

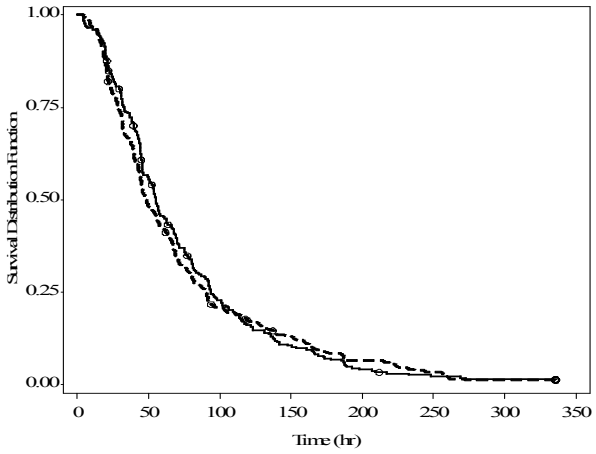
who did not take the study drug. Of the safety analysis population, 683 subjects (330 subjects in the favipiravir group, 353 subjects in the oseltamivir phosphate group) were included in the FAS, and 75 subjects were excluded (74 subjects with a disease other than influenza, 1 subject who violated the inclusion criteria). Of the FAS, 640 subjects (306 subjects in the favipiravir group, 334 subjects in the oseltamivir phosphate group) were included in the PPS, and 43 subjects were excluded (29 subjects who used prohibited concomitant drugs, 7 subjects who violated dosage regimen, 7 subjects who violated exclusion criteria). The PPS was defined as the primary efficacy analysis set.

The median time to alleviation of major influenza symptoms[184] (95% CI), the primary efficacy endpoint, was 55.4 (50.4, 62.5) hours in the favipiravir group and 47.8 (44.4, 55.8) hours in the oseltamivir phosphate group. The Kaplan-Meier curve of the time to alleviation of major influenza symptoms for each group is shown in the figure below. The difference (95% CI) of the median between the favipiravir group and oseltamivir phosphate group was 7.7 (-2.2, 15.3) hours. The hazard ratio (95% CI) of the time to alleviation of major influenza symptoms in the favipiravir group to that in the oseltamivir phosphate group by the Cox proportional hazard model on the drug effect only was 0.955 (0.815, 1.118), and the lower limit of the 95% CI of the hazard ratio was above the predetermined non-inferiority margin.

Based on the results from a placebo-controlled study conducted for development of oseltamivir phosphate and from Study JP205, the non-inferiority margin was set at a hazard ratio of 0.784 for the distribution of time to alleviation of major influenza symptoms including the median time to alleviation of major influenza symptoms (70 hours) of the oseltamivir phosphate group and additional tolerance (19 hours). The tolerance was set for the following reasons.

- Below the lower limit (19.5 hours) of the 95% CI of the difference (34.3 hours) from the placebo, obtained from the results of pooled analysis of multiple studies
- Below the difference (23.3 hours) from the minimum value in the placebo group in all studies
- Below half of the difference (42.5 hours) from the maximum value in the placebo group in all studies

[184] Time to "alleviation" of all of the 7 major influenza symptoms (cough, pharyngolaryngeal pain, headache, nasal congestion, feeling hot, myalgia, general malaise) from the start of the study treatment (when all scores decrease to ≤"1"). The influenza symptoms were scored by the investigator or sub-investigator based on the patient diary. "Alleviated condition" is defined as a condition in which the scores for the influenza symptoms have remained ≤"1" for at least 21.5 hours. The symptom score rated within 4 hours after use of antipyretic analgesics should be excluded from assessment of "alleviated condition." Symptom score (0: None, 1: Mild [hardly bothersome symptoms, daily activity possible], 2: Moderate [bothersome symptoms, daily activity slightly interfered], 3: Severe [intolerable symptoms, daily activity impossible])



— Favipiravir group --- Oseltamivir phosphate group
○ Censoring (favipiravir group, oseltamivir phosphate group)

Kaplan-Meier curve of the major influenza symptomatic duration (PPS)

Adverse events occurred in 120 of 378 subjects (31.7%) in the favipiravir group and in 96 of 380 subjects (25.3%) in the oseltamivir phosphate group. Adverse drug reactions occurred in 75 of 378 subjects (19.8%) in the favipiravir group and in 57 of 380 subjects (15.0%) in the oseltamivir phosphate group. Adverse events and/or adverse drug reactions reported by ≥2% of the subjects in either group are shown in the table below.

Adverse events and/or adverse drug reactions reported by ≥2% of subjects in either group

System organ class	Preferred term	Adverse events		Adverse drug reactions	
		Favipiravir group (n = 378)	Oseltamivir phosphate group (n = 380)	Favipiravir group (n = 378)	Oseltamivir phosphate group (n = 380)
Gastrointestinal disorders	Diarrhoea	24 (6.3)	23 (6.1)	16 (4.2)	20 (5.3)
	Vomiting	2 (0.5)	10 (2.6)	1 (0.3)	7 (1.8)
	Nausea	3 (0.8)	9 (2.4)	3 (0.8)	8 (2.1)
Investigations	Blood triglycerides increased	7 (1.9)	8 (2.1)	7 (1.9)	7 (1.8)
	Blood uric acid increased	21 (5.6)	1 (0.3)	21 (5.6)	1 (0.3)

Number of subjects with the event/reaction (%)

Adverse events leading to discontinuation of the treatment included 2 events (eczema, enteritis infectious) in 2 subjects in the favipiravir group and 6 events in 4 subjects (eczema, gastroenteritis, vomiting, pruritus, rash, herpes simplex) in the oseltamivir phosphate group. Causal relationships of these events except for enteritis infectious and herpes simplex with the study drug could not be ruled out, but all of them were improving or resolved.

Serious adverse events included 1 event in 1 subject (cellulitis) in the favipiravir group and 1 event in 1 subject (abortion spontaneous) in the oseltamivir phosphate group, and causal relationships of both events with the study drug were ruled out, and both were improving or resolved.

No deaths occurred.

4.(iii).B. Outline of the review by PMDA

4.(iii).B.(1) Efficacy

PMDA evaluated the efficacy of favipiravir mainly based on the data from the Japanese dose-response phase II study (Study JP205) and global phase III study (Study 312).

4.(iii).B.(1).1) Efficacy evaluation method

(a) Appropriateness of non-inferiority margin

PMDA's view on the appropriateness of the non-inferiority margin in Study 312 is as follows:
The median time to alleviation of major influenza symptoms in the oseltamivir phosphate group in Study 312 was 47.8 hours, which was shorter than 70 hours expected on the basis of the rationale for setting the non-inferiority margin [see "4.(iii).A.(3).1) Global phase III study in patients with influenza virus infection"] and the results[185] (70-90 hours) from the placebo-controlled study conducted for development of oseltamivir phosphate. It is therefore necessary to examine if application of the predetermined non-inferiority margin to interpretation of the results would cause any issue. On the other hand, in patients with pandemic influenza infection, who accounted for most of the subjects in Study 312, the difference in the median time to alleviation of major influenza symptoms between oseltamivir phosphate and placebo was unknown. It is thus difficult to discuss the appropriateness of the non-inferiority margin from a viewpoint of whether or not demonstration of non-inferiority to oseltamivir phosphate would have led to demonstration of the superiority of favipiravir to placebo if favipiravir and placebo had been compared. To investigate the size of the non-inferiority margin as done at the stage of planning, the non-inferiority margin expressed as the hazard ratio was converted into a difference in the median time to alleviation of major influenza symptoms. The difference in the median was 13.2 hours, which was considered to be not unacceptably large non-inferiority margin from the viewpoint of the clinical significance. It was also acceptable to assume that the tolerable hazard ratio should be consistent irrespective of the length of the median time to alleviation of major influenza symptoms in the oseltamivir phosphate group. Based on the above, the efficacy evaluation based on the predetermined non-inferiority margin would not cause particular issues.

(b) Primary endpoint

In Study 312, the Influenza Intensity and Impact Questionnaire (Flu-iiQ) was used as an assessment measure of the influenza symptoms to uniformly assess the time to alleviation of major influenza symptoms as the primary endpoint.

On the other hand, in clinical studies of approved influenza antiviral drugs, the Influenza Symptom Severity scale (ISS) was used as an assessment measure of influenza symptoms. PMDA therefore asked the applicant to explain the reason why the Flu-iiQ was used but not the ISS and to justify its use.

The applicant responded as follows:
As Study 312 was conducted in 3 countries of Japan, Korea, and Taiwan, the applicant considered it necessary to use a unified measure to assess the primary endpoint (time to alleviation of major influenza symptoms), which may often be assessed subjectively, in order to reduce variations among these countries. The ISS, a global standard influenza assessment scale, was used in global clinical studies of oseltamivir phosphate and zanamivir hydrate, both of which are approved influenza antiviral drugs. In Study 312, the ISS was also planned to be used initially, but actually Flu-iiQ was used, because at the start of Study 312, the Flu-iiQ had been developed as the revised ISS to be more specific to influenza symptoms, and its validity had been justified.[186] Both ISS and Flu-iiQ still use the same method to assess 7 symptoms for the time to alleviation of major influenza symptoms (the primary endpoint), including the use of a 4-point scale rating. The

[185] Summary of initial product application of oseltamivir phosphate ("Tamiflu Capsule 75" Summary of product applications)
[186] Development and Validation of the Influenza intensity and Impact Questionnaire (Flu-iiQ). *VALUE IN HEALTH*. In press. 2011.

applicant therefore considered that the outcomes of the time to alleviation of major influenza symptoms assessed based on the ISS can be compared with those assessed based on the Flu-iiQ.

In order to ensure consistency between the Japanese or Korean version and the original English Flu-iiQ, the development of the translated versions involved not only translators but also healthcare professionals (medical experts and coordinating investigators) and the sponsor who reviewed and discussed the translations. The translated versions of the Flu-iiQ were considered sufficiently consistent and therefore used in this study.

In the protocol of Study 312, the primary endpoint allowed the investigator or sub-investigator to review the influenza symptoms score based on the patient diary, while in clinical studies of other drugs of the same class, alleviation of the symptoms was assessed based on patient-rated scores in the patient diary.

PMDA asked the applicant to explain the reason why the protocol of Study 312 specified that the investigator or sub-investigator give scores based on the patient diary.

The applicant explained as follows:
In Study JP205 conducted before Study 312, patient-rated scores on the influenza symptoms in the patient diary were used for the assessment. However, it could not be ruled out that different scores were given to the symptoms in a similar severity because the perception of the symptoms varies among individuals. To minimize the variations due to subjective assessment and to evaluate effects of the influenza antiviral drug based on influenza symptoms alone, the protocol of Study 312 specified that patient-rated scores in the patient diary should be reviewed by the investigator at the site, because it was considered difficult for the patient to distinguish the influenza symptoms from the symptoms caused by other factors (for example, secondary complications to influenza infection). To ensure objective assessment, the medical decisions by physicians were incorporated. The protocol, therefore, specified that "the investigator or sub-investigator should give scores based on the influenza symptoms scores rated by the patient in the patient diary." The scores on the influenza symptoms was not only based on the self-rated scores in the patient diary but also ensured by the medical decision of the attending investigator or sub-investigator. The scores have not been changed by inquiries of a third-party (e.g., case review committee) after the end of the study.

The self-rated scores in the patient diary were changed in 46 of 762 patients (6.0%). Of these 46 patients, 29 were due to "the findings from physical examinations and interviews by the attending physician," 10 were due to "symptoms assessed to be adverse events," and 2 were due to "symptoms assessed to be unrelated to influenza."

PMDA considers as follows:
The use of the Flu-iiQ for the primary endpoint is acceptable for the following reasons: the Flu-iiQ is a revised version of the ISS, which has been used conventionally; it was developed as a Patient Reported Outcomes (PRO) measure applicable to the primary endpoint in clinical studies in patients with influenza virus infection; and the validity of the questionnaire has been justified.

The applicant's explanation about the physician's review of the symptom scores is understandable in that the patients are allowed to rate their symptom scores at their discretion, and thus it cannot be ruled out that the assessment is affected by subjective symptoms due to factors unrelated to influenza virus infection.

The Flu-iiQ itself, however, was developed as a PRO measure to assess the patient's condition directly described by him or her without a physician's interpretation of the clinical response, and it is thus inappropriate for the investigator or sub-investigator to review the patient-rated scores

because such assessment would deviate from the concept of the outcome measurement intended by the questionnaire. The Flu-iiQ is a questionnaire justified as a PRO measure through the validation studies, etc. so that it can be used as the primary endpoint in clinical studies. Thus, the intended use of it is different from some of other PRO measures developed for the score assessment on the assumption of the physician's involvement and the Flu-iiQ scores reviewed by the investigator or sub-investigator cannot be justified.

In addition, it is difficult to clearly distinguish the influenza symptoms from those caused by non-influenza factors in general. Even if symptoms are distinguishable, it would be difficult to correct the score appropriately on a particular symptom based on the relative contribution of influenza to this symptom. Furthermore, it cannot be ruled out that such a correction may have introduced a bias into the analysis of differences between groups.

Based on the above, PMDA has concluded that the influenza symptoms should be assessed based on the Flu-iiQ scores rated by the patients, which are not reviewed by the physician; and the data from Study 312 should be re-assessed based on the Flu-iiQ scores rated by the patients for the time to alleviation of major influenza symptoms, the primary endpoint, and then, re-analysed. The results of the re-analysis will be discussed in "4.(iii).B.(1).2) Efficacy in the global phase III study."

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

(c) Efficacy analysis set

The efficacy analysis set in the global phase III study (Study 312) is defined as shown below. The FAS and PPS proposed by the applicant are as shown in the figure below. In Study 312, the "per-protocol set (PPS)" was used for the primary analysis [see "4.(iii).A.(3).1) Global phase III study in patients with influenza virus infection"].

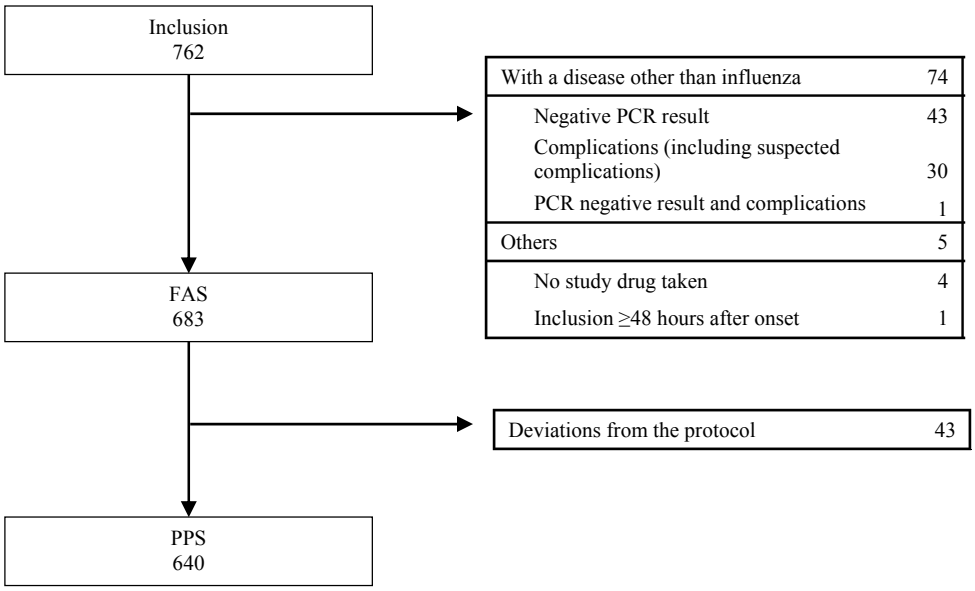
Definition of the analysis sets (final version of the analysis protocol/study protocol)

5.1 Analysis set
The analysis set is defined below. GCP non-compliant patients will be excluded from all the analyses.

5.1.1 Efficacy analysis set

(1) Full analysis set for the efficacy evaluation (FAS)
The FAS consists of the patients who have been enrolled in the study and have not met the following.
1) Patients who do not meet the key inclusion criteria (definitive diagnosis of influenza is difficult, complications of other viral or bacterial respiratory infections are suspected, etc.)
2) Patients who have not taken the study drug at all
3) Patients in whom no data on the influenza symptoms after enrollment in the study are available.

(2) Per-protocol set (PPS)
The PPS consists of the patients who have been included in the FAS as defined in (1) and have not had any of the following factors that would affect the drug effect evaluation and serves as the primary analysis set in this study.
1) Patients who have violated the inclusion and exclusion criteria other than those defined for the FAS
2) Patients who have used prohibited concomitant drugs (except for those in whom the primary endpoint can be evaluated)
3) Patients who have not discontinued the study treatment regardless of meeting the discontinuation criteria
4) Patients who have violated the setting of the dosage and administration, and treatment duration
5) Patients in whom evaluation of the primary endpoint is difficult



FAS and PPS proposed by the applicant

Of the conducted clinical studies involving the approved influenza antiviral drugs, comparative studies verifying non-inferiority to the control drug (oseltamivir phosphate) was to use the FAS for the primary analysis in accordance with the ITT principle. In Study 312 of favipiravir, however, of 762 patients enrolled in the study, 122 patients were excluded from the PPS that was used for the primary analysis. The PPS was a subset of the FAS, and of the enrolled patients, 74 patients (approximately 10% of the patients enrolled in the study) were excluded from the FAS because these patients were assessed to have a disease other than influenza by a case review committee held separately.[187]

PMDA considers as follows:
It is more appropriate to use the FAS for the primary analysis in Study 312 in accordance with the ITT principle. Irrespective of whether the FAS or PPS was used for the primary analysis, the exclusion of patients with a disease other than influenza from the analysis set in accordance with the decision at the case review committee may lead to an imbalance between the randomized groups, though balanced randomization should be ensured for the drug effect evaluation in a comparative study. Handling of patients with a disease other than influenza at the case review committee will therefore be further investigated in accordance with the statistical principle for clinical studies instructed in the "Statistical Principles for Clinical Trials" (PMSB/ELD Notification No. 1047 dated November 30, 1998, ICH E9 guideline). Hereinafter, unless otherwise specified, the FAS and PPS serve the primary analysis set and secondary analysis set, respectively.

PMDA asked the applicant to explain on what basis the case review committee decided to exclude patients with a disease other than influenza from the efficacy analysis set.

The applicant responded as follows:
Patients negative for influenza virus by the reverse transcription-polymerase chain reaction (RT-PCR) assay were excluded as those with a disease other than influenza for the following reason:

[187] The case review committee was held before unblinding.

According to HSB/TIDCD Notification No. 0513001 by the Director of Tuberculosis and Infectious Diseases Control Division, Health Service Bureau, MHLW, dated May 13, 2009, "Re-revision of definitions of patients with pandemic influenza and notification format,"[188] issued before the start of this study, patients with the positive rapid influenza diagnostic test (RIDT) result are classified as those with pseudo-symptoms; in this study in which many patients with 2009 pandemic influenza A (H1N1) virus infection were expected to be enrolled, subjects with the kit positive result only were also classified as patients with pseudo symptoms in accordance with the above notification; these patients with pseudo symptoms were subjected to RT-PCR test considered to be the most sensitive to sub-type isolates, and those with the influenza virus-specific sequence detected (positive RT-PCR result) were classified as the patients with definitive influenza virus infection; and the remaining subjects with RT-PCR negative result were classified as those with a disease other than influenza.

As a general rule, of the patients with a disease other than influenza, those with complications (including suspected complications) self-rated the inflammatory reactions induced by influenza virus as the influenza symptoms. It was therefore considered important to compare the symptoms in the homogeneous population with minimal variations in patient characteristics. The influenza virus infection, however, would spread to a wide variety of people, and in some individuals, inflammatory reactions persist due to patient predispositions other than influenza virus. Such inflammatory reactions due to the characteristics of patients do not respond to any influenza antiviral drug, potentially causing large variations in data on the efficacy endpoint especially in this study comparing multiple influenza antiviral drugs with different mechanisms of actions. Before the case review, therefore, the applicant agreed with the medical experts and coordinating investigator to evaluate the efficacy in patients with uncomplicated influenza virus infection by including "subjects who have influenza virus infection but otherwise are healthy without any other diseases" in the study population. In a clinical study targeting acute infection, subjects are often enrolled as those with possible infection leaving the concurrent pathological conditions unidentified because the treatment should be provided immediately. Then, many subjects are found to have symptoms or findings that would violate the eligibility criteria after the study enrollment. Unlike clinical studies targeting chronic diseases, it is difficult to assess the eligibility during the screening period and randomize only subjects eligible for the drug effect evaluation. The case review committee procedure, therefore, was employed to identify the subjects with possible uncomplicated influenza individually under a blind condition and included them in Study 312, and the remaining subjects were excluded from this study as the unintended population. This procedure has been often applied to development of antibacterial drugs for assessment and evaluation of the patients based on a medical decision. Multiple medical experts familiar with infectious diseases especially influenza virus infection were delegated to handle the patients in this study (including those with a disease other than influenza) at the case review committee. The basic process for case review in this study until the database lock point was described below. In this study, the [redacted] case review committee (reviewed [redacted] subjects on [redacted], [redacted], [redacted] subjects on [redacted], [redacted], and [redacted] subjects on [redacted], [redacted]) was held. At the [redacted] case review committee, all of the 762 subjects enrolled were reviewed by the medical experts again to ensure consistent assessment, and the coordinating investigator confirmed the results.

- The medical experts ascertained whether or not each subject met the inclusion criteria and violated the exclusion criteria. The medical experts also investigated the patients in whom a medical decision was necessary according to the judgment of the medical expert as well as those whose examination findings including the patient characteristics, clinical course, and chest X-ray images suggested that his or her medical history, complications, and clinical course may affect the evaluation of influenza. In addition, patients who needed to be further reviewed (for instance, justification of enrollment of patients with psychiatric disorders) were

[188] http://www.mhlw.go.jp/kinkyu/kenkou/influenza/090514-03.html

identified. Based on these investigations, the medical expert prepared the standard procedure for handling the subjects (draft).

- At the case review committee, the medical experts and the above coordinating investigator discussed and finalized the standard procedure for handling the subjects. It was confirmed that the subject with the positive RT-PCR result would be handled as one with definitive influenza virus infection. The medical experts and coordinating investigator reviewed all of the subjects again and had a discussion on the patients identified previously by the medical expert for further review. It was decided that the subjects enrolled thereafter would be reviewed by the medical experts in accordance with the standard procedure for handling the subjects while consultating with the coordinating investigator. Details of only those who needed to be further reviewed would be examined by a coordinating physician assigned in rotation. It was specified that any case suspected by any coordinating physician should be reviewed by the medical experts again.

As described above, this study was designed to ensure further objective and scientific evaluation based on the development experience of other influenza antiviral drugs already commercially available.

PMDA considers as follows:
It is understandable for the applicant to select the definition of the study population as "subjects who have influenza virus infection but otherwise are healthy without any other diseases" because factors other than influenza virus infection would cause large variations in data for the drug effect evaluation. The applicant planned to identify the subjects affected by factors other than influenza virus infection based on the clinical symptoms and findings after randomization and then exclude them from the analysis set to reduce the variations in the evaluation data. This study plan, which is intended to make the target study population more eligible for the drug effect evaluation after randomization, however, is inappropriate for the reasons described in a) to c) below:

a) Based on the ITT principle and focusing on practical approaches, it is desirable that the study population in a confirmatory comparative study of an influenza antiviral drug consists of as many types of patients with the diagnosis of influenza virus infection as possible in routine clinical settings.

b) Changing the study population to "subjects who have influenza virus infection but otherwise are healthy without any other diseases" corresponds to a change of the primary study objectives or design. Changing the study population after the start of the study (enrollment of subjects) to reduce variations in data is not generally accepted as an appropriate study procedure.

c) In the drug effect evaluation of a confirmatory comparative study, priority should be given to prevention of bias rather than reduction of variations.

Even if subjects who have symptoms or findings violating the eligibility criteria of the study are identified after the study enrollment, there are limited situations where the randomized subjects can be excluded from the population used for the primary analysis without introducing potential bias in the efficacy evaluation data, as described in the ICH E9 guideline below. The exclusion of subjects with a disease other than influenza will be carefully discussed later. Of 74 patients with a disease other than influenza (including 1 subject who was assessed as having a disease other than influenza because of the negative RT-PCR result and complications), those with the RT-PCR negative result and others are to be separately discussed in details.

[5.2.1 Full Analysis Set, ICH E9 guideline (excerpt)]
There are a limited number of circumstances that might lead to excluding randomised subjects

from the full analysis set including the failure to satisfy major entry criteria (eligibility violations), the failure to take at least one dose of trial medication and the lack of any data post randomisation. Such exclusions should always be justified. Subjects who fail to satisfy an entry criterion may be excluded from the analysis without the possibility of introducing bias only under the following circumstances:

- The entry criterion was measured prior to randomisation;
- The detection of the relevant eligibility violations can be made completely objectively;
- All subjects receive equal scrutiny for eligibility violations; (This may be difficult to ensure in an open-label study, or even in a double-blind study if the data are unblinded prior to this scrutiny, emphasising the importance of the blind review.)
- All detected violations of the particular entry criterion are excluded.

i) Disease other than influenza determined by the negative RT-PCR result

In Study 312, all of the randomized subjects tested positive for influenza by a rapid influenza diagnostic test (RIDT), but those with the negative RT-PCR result were excluded from the efficacy evaluation after randomization. The applicant explained the reason for the exclusion as follows: Based on the assumption that many patients with pandemic influenza A (H1N1) 2009 virus infection would be enrolled in this study and in accordance with the notification, patients with the positive RIDT result were classified as those with a pseudo-positive result and then subjected to the RT-PCR test considered to be the most sensitive to sub-type isolates. As a result, those with the positive RT-PCR result were classified as patients with a definitive influenza virus infection, and those with the negative RT-PCR result were classified as patients with a disease other than influenza and was excluded.

PMDA confirmed with the minutes of the case review committee that the decision to exclude patients with the negative RT-PCR result was made after randomization. It was also confirmed that 44 patients were were assessed to have a disease other than influenza based on the negative RT-PCR result, and of these, 4 patients were excluded from the analysis because their negative RT-PCR results led to a failure to identify the virus type, despite the fact that a viral culture test performed in parallel with this study showed the isolation of virus from the specimens collected at the enrollment.

As described above, the case review committee decided that the patients with the negative RT-PCR result at would be excluded from the study population as those with a disease other than influenza. Based on the following points on the descriptions in the protocol,[189] PMDA considers that such decision is not consistent with the concept of the study population specified in the protocol.

- The "1.4 Reason for justifying this study" section states that, "To distinguish seasonal influenza (type A) virus infection from pandemic influenza virus infection exactly, a definitive diagnosis should be made based on RT-PCR testing, etc. Such a practice, however, takes so much time that it is not practical for the influenza treatment. In this study, therefore, all of the patients tested positive by influenza rapid diagnostic test will be included."
- The "(1) Full analysis set for the efficacy evaluation (FAS), 5.1.1 Efficacy analysis set" section states to the effect that patients who do not meet the key inclusion criteria (definitive diagnosis of influenza is difficult, complications of other viral or bacterial respiratory infection is suspected, etc.) should be excluded, but the key inclusion criteria did not specify the use of an RT-PCR test. It is therefore interpreted that the protocol did not clearly specify the exclusion of the patients with the negative RT-PCR result from the FAS.

[189] Study protocol [redacted] (final version, prepared on [redacted]) P. 29

PMDA considers as follows:
As described in the protocol, a definitive diagnosis based on RT-PCR testing, etc. should be made to distinguish seasonal influenza (type A) virus infection from pandemic influenza virus infection and sub-type influenza virus infection exactly. In clinical practice, however, individuals showing clinical symptoms during the influenza season are treated as patients with influenza virus infection, which is an acute infection, based on the rapid diagnostic test performed before diagnosis is correctly made based on the time-consuming RT-PCR test. Such patients were also included in the efficacy analysis set in a confirmatory comparative study of an influenza antiviral drug of the same class. Therefore, it is desirable that the study population in a confirmatory comparative study of an influenza antiviral drug consists of as many types of the subjects with the diagnosis of influenza virus infection as possible in routine clinical settings to focus on practical comparative approaches in accordance with the ITT principle.

According to the applicant's explaination, the patients with influenza virus detected by RT-PCR were deemded as those with definitive diagnosis in accordance with HSB/TIDCD Notification No. 0513001 dated May 13, 2009 ("Re-revision of definitions of patients with pandemic influenza and notification format"), in which the patients with the positive RIDT result are classified as those with pseudo symptoms. This classification, however, was only intended to present the guideline for the notification of pandemic influenza A (H1N1) 2009 virus, and its viewpoint is different from that of the diagnosis of influenza virus infections including seasonal influenza infection. It is therefore inappropriate to use this guideline as the rationale for selecting the study population.

From a statistical viewpoint, PMDA considers as follows:
The problem characteristic to the RIDT kit for detecting pandemic influenza in clinical diagnosis practices is its low sensitivity (high pseudo-negative rate), while the specificity is known to be generally high (low pseudo positive rate).[190] Given the characteristics of the RIDT kit, as far as patients with pyrexia and influenza symptoms who tested positive for influenza were assessed as meeting the inclusion criteria (not meeting the exclusion criteria) by the investigator or sub-investigator and included in the study, it is considerably possible that the positive predictive value of the positive RIDT result in these subjects (posterior probability that the positive RIDT result is turned to be true positive) was not low enough to interpret the study data; and the sensitivity of the RT-PCR test is not assured to be always 100%. Therefore, the applicant's explanation cannot justify that the patients with a negative RT-PCR result were categorized as those with a disease other than influenza and were excluded from the study after randomization.

Based on the above, PMDA has concluded that 44 patients with the negative RT-PCR results should not have been excluded from the study population and primary analysis set as those with a disease other than influenza, and thus the re-analysis should be performed after including these patients, because they at least provided the positive RIDT result in the same way as in the daily clinical practices and then were randomized. Of these 44 patients, 40 produced the negative RT-PCR results and no virus was isolated from their specimens collected at the enrollment. In consideration of this, it has been concluded that they may be excluded from the PPS, which can be used for the secondary analysis.

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

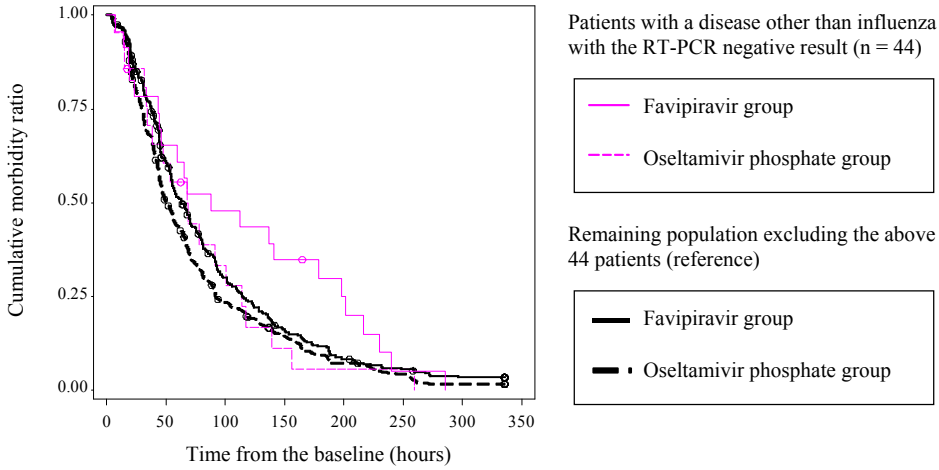
PMDA also asked the applicant to submit the following figures and tables to compare distributions of the time to alleviation of major influenza symptoms between the groups for 44

[190] Centers for Disease Control and Prevention (CDC). Performance of rapid influenza diagnostic tests during two school outbreaks of 2009 pandemic influenza A (H1N1) virus infection - Connecticut, 2009. *MMWR Morb Mortal Wkly Rep.* 2009;58(37):1029-1032.

patients who were classified as those with a disease other than influenza because of the negative RT-PCR result.

PMDA reviewed the time to alleviation of major influenza symptoms in the 44 excluded patients and found a difference of approximately 20 hours in median time to alleviation and a trend toward a larger difference in the Kaplan-Meier curves. In light of data properties in the excluded population, PMDA considers that it is important to review the re-analysis result and discuss the robustness of the results. The results of the re-analysis will be discussed in "4.(iii).B.(1).2) Efficacy in the global phase III study."

Distribution of the time to alleviation of major influenza symptoms in patients with a disease other than influenza with the negative RT-PCR result



	Population excluding the above 44 patients (reference)		Patients with a disease other than influenza with the negative RT-PCR result (n = 44)	
	Favipiravir group	Oseltamivir phosphate group	Favipiravir group	Oseltamivir phosphate group
Number of patients	354	359	23	21
Median	62.7	50.4	87.8	67.5
[95% CI]	[55.4, 70.0]	[44.8, 57.2]	[45.8, 178.5]	[38.2, 100.3]
Log-rank test	*P* = 0.016		*P* = 0.174	
Hazard ratio	0.830		0.644	
[95% CI]	[0.712, 0.966]		[0.339, 1.221]	

ii) Patients with a disease other than influenza showing no negative RT-PCR result

At the case review committee, the patients in question were reviewed based on the list of such patients prepared by the applicant in advance. The "patients in question" were largely divided into the following 2 types:

- Patients who possibly violated the GCP or deviated from the protocol
- Patients in whom clinical symptoms and findings after the study enrollment require medical review in terms of whether or not exclusion should be decided in accordance with the protocol although there are apparently no deviations

These patients include those identified the criteria set in advance based on the opinion of the medical experts or coordinating investigators, those individually identified by the medical experts, and those identified in accordance with the protocol by the applicant.

Of the patients with a disease other than influenza who had been identified from the list of the patients in question and reviewed at the case review committee, 31 patients were found to have a disease other than influenza due to other reasons than the negative PCR result.

The applicant explained these 31 patients as follows:
The number of the patients assessed to have a disease other than influenza at the case review committee and the reasons are shown in the table below. All of the patients who had or were assessed to have the following complications at the study enrollment were classified as those with a disease other than influenza: the complications specified in the exclusion criteria in the protocol included "d) Patients who are suspected to have viral or bacterial respiratory infection concurrently (pneumonia, bronchitis, otitis media, sinusitis, etc.) other than influenza virus infection (sputum purulent or sputum viscous purulent, lung infiltration in chest X-ray image)," "e) Patients with chronic respiratory disease (bronchitis chronic, diffuse panbronchiolitis, bronchiectasis, emphysema, pulmonary fibrosis, asthma bronchial, old pulmonary tuberculosis, or chronic obstructive pulmonary disease)," and "i) Patients who are suspected to be concurrently immunocompromised such as HIV positive patients." On the other hand, whether or not patients with complications classified as "those ineligible for drug effect evaluation" was included was individually determined based on the medical decision of the medical experts or coordinating investigators in terms of the effects of such complications on the drug effect evaluation.

Number of patients assessed to have a disease other than influenza due to complications (including suspected complications) and the major reason for assessment

Reason for identifying the patient as one with a disease other than influenza	Number of patients
Violation of exclusion criterion d)	18
Violation of exclusion criterion e)	2
Violation of exclusion criterion i)	1
Patient ineligible for drug effect evaluation	9
Total	30*

* One patient with the negative RT-PCR result is not included.

PMDA considers as follows:
A total of 21 patients were assessed by the applicant to have violated the exclusion criteria d), e), and i). There are only 3 patients who were excluded due to the complications at the enrollment that was related to the exclusion criteria (bronchitis bacterial, tuberculosis, HIV [1 patient each]), that is, those who were assessed to have complications with the term of the condition entered in the electronic data capture (EDC) by the investigator or sub-investigator. Of the remaining 18 patients, on the other hand, 16 patients were excluded due to the complications not identified at the enrollment such as infections possibly affecting the efficacy evaluation or due to violation of the exclusion criteria only with sputum at the enrollment, which was considered to suggest concurrent bacterial infection.

The applicant excluded these patients due to the complications. These patients for whom the reason for exclusion, presented by the applicant, was complications of "other respiratory infections," were assessed to violate the exclusion criterion d) at the enrollment only based on the clinical symptoms and findings after randomization even though the specific complications were not identified. Whether or not the exclusion criterion was actually violated is unclear.

List of reasons for excluding the patients assessed to have a disease other than influenza at the case review committee

Reason for exclusion	Complications	Favipiravir group	Oseltamivir phosphate group	Classification of patients*
		Number of patients	Number of patients	
Violation of exclusion criterion d) n = 18	Bronchitis bacterial	1	0	(b)
	Tuberculosis	0	1	(b)
	Mycoplasma infection	1	0	(d)
	Other respiratory infection	5	3	(a)
		2	0	(c)*
		5	0	(d)
Violation of exclusion criterion e) n = 2	Old pulmonary tuberculosis	1	0	(d)
	Chronic obstructive pulmonary disease	1	0	(d)
Violation of exclusion criterion i) 1 patient	HIV	1	0	(b)
Patient difficult for drug effect evaluation n = 9	Reflux oesophagitis	1	1	(c)
	Depression	1	0	(c)
	Migraine	1	0	(c)
	Anxiety disorder	1	0	(c)
	Hyperthyroidism	1	0	(c)
	Depression, generalised anxiety disorder	1	0	(c)
	Mastectomy	1	0	(d)
	Others	0	1	(e)
		24	6	

(a) Patient excluded due to violation against the exclusion criteria only with sputum at the entry, which was considered to suggest concurrent bacterial infection.
(b) Patient excluded due to the complications at the entry related to the exclusion criteria
(c) Patient excluded due to the complications at the entry possibly affecting the efficacy evaluation
(d) Patient excluded due to the complications not identified at the entry such as infections possibly affecting the efficacy evaluation
(e) Patient excluded for other reasons (discontinued due to the patient's personal reasons before relief of the symptoms was assessed)

* The complications other than respiratory infections were also described as reasons for the exclusion. PMDA classified them as the complications at the enrollment unrelated to the exclusion criteria and included in (c). The other respiratory infections were not identified at the enrollment.

Furthermore, irrespective of whether or not the violation of the exclusion criteria was clear, PMDA's view on the exclusion of the patients after randomization is as follows:
The applicant claimed that most of the reasons for the exclusion were violation of the eligibility criteria. Whether or not the exclusion of subjects from the analysis set due to violation of the eligibility criteria would cause bias depends on whether or not it can be ensure that the individual decisions on the exclusion are statistically independent of the efficacy outcome and the assigned groups, or whether or not the exclusion was objectively decided due to the violation of the eligibility criteria assessed before randomization. To review them more specifically, the viewpoints described in the ICH E9 guideline [see "4.(iii).B.(1).1).(c) Efficacy analysis set"] should be taken into account.

PMDA carried out a detailed investigation and review on whether or not the exclusion of 31 patients with a disease other than influenza showing no negative RT-PCR result from the analysis set after randomization did not cause bias, from the following viewpoints:

- Whether or not the presence of complications or suspected complications, explained as the rationale for the exclusion of the patients from the analysis set, was assessed before randomization of the patients who apparently did not deviate from the protocol (violation of

the eligibility criteria), but were eventually assessed as ineligible by the applicant.
- Whether or not the exclusion of the patients from the analysis set was decided after randomization of the patients who were assessed to have complications before randomization.
- Whether or not the patient screening and the exclusion (detection of violations) were objectively made for all of the 31 patients with a disease other than influenza.

As a result, it was confirmed that the following decision on the exclusion were made.

- Some of the complications leading to the decision on exclusion were not identified at the entry of patients in the study by the investigator or sub-investigator. Due to persistent symptoms or inconsistent clinical course, the patients were considered to have possibly had any complication at the study entry that was related to the exclusion criteria. Therefore, the assessment of the complications was not made before randomization.
- Some of the complications identified at the study entry had not been expected to affect assessment of the influenza symptoms at the time of planning of the study, but served as the rationale for the exclusion of these patients after randomization because such complications may possibly have affected the assessment consequently due to persistent symptoms if it they had been identified at the study entry.
- Screening of the patients to be excluded and the decision of their exclusion highly depended on subjective assessments such as visual observation of the symptoms over time. Some of the patients who had identical complications at the entry were not excluded. The exclusion was thus implemented based on the subjective assessment.

PMDA concluded as follows:
The above review indicated that the exclusion was decided based on subjective assessment after randomization, seemingly depending on the treatment result. Considering that such exclusion potentially introduced bias in the efficacy evaluation, the 31 patients with a disease other than influenza showing no negative RT-PCR result should not have been excluded from the primary analysis set in accordance with the ITT principle, and the re-analysis should be performed including these patients. The same can be said for the secondary analysis set, and the bias potential due to the exclusion should be eliminated wherever possible. The PPS should additionally include 27 patients left after excluding 4 patients with the complications related to the exclusion criteria identified at the study entry by the investigator or sub-investigator (2 patients with bronchitis bacterial, 1 with HIV infection, 1 with tuberculosis) from the above 31 patients.

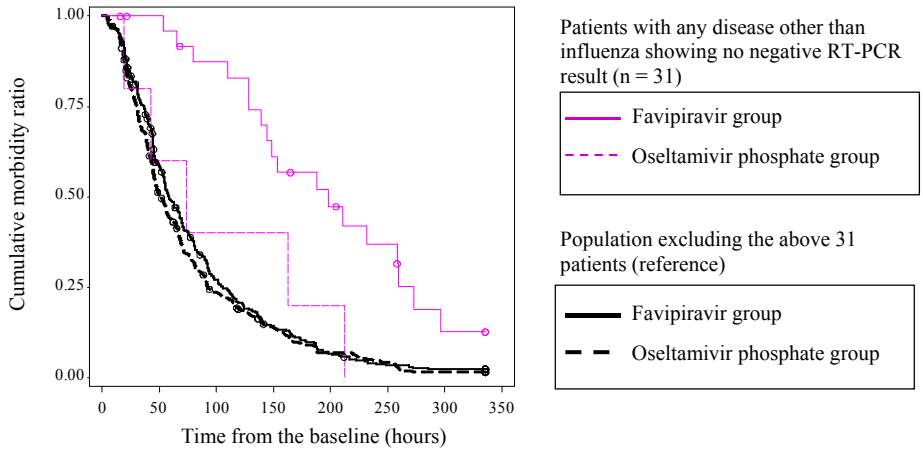
The above conclusion of PMDA will be discussed at the Expert Discussion.

In addition, PMDA asked the applicant to submit the following figures and tables to compare distributions of the time to alleviation of major influenza symptoms between the groups for 31 patients with a disease other than influenza showing no negative RT-PCR result and to compare distribution of the time to alleviation of major influenza symptoms in these 31 patients with that of the time to alleviation of major influenza symptoms in the overall population.

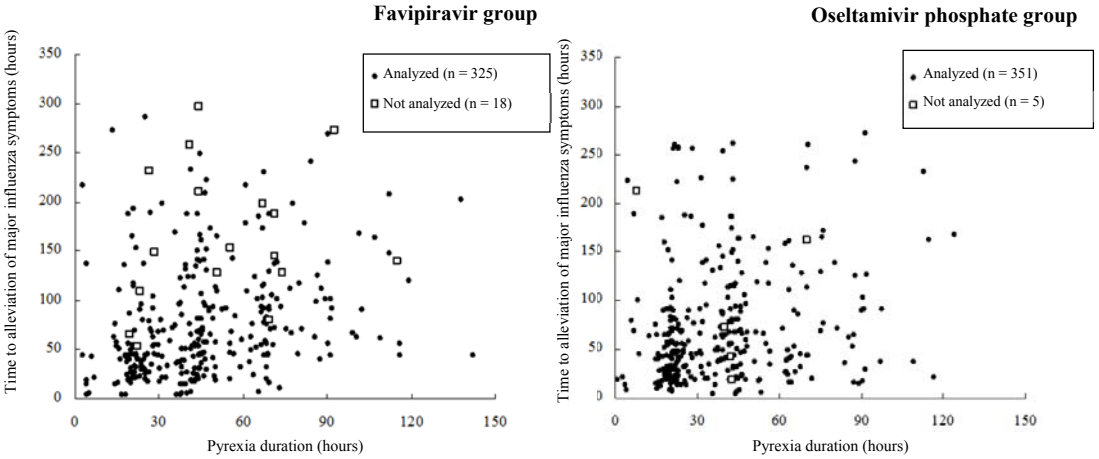
PMDA investigated the time to alleviation of major influenza symptoms, the primary endpoint, in 31 patients who were excluded because they were assessed to have a disease other than influenza showing no negative RT-PCR result, and found that there was considerable imbalance in the number of patients excluded between the dose groups; the time to alleviation of major influenza symptoms in the patients excluded from the favipiravir group was statistically significantly longer than that in the patients excluded from the control group, and the median time to alleviation of major influenza symptoms in the patients excluded differed between the groups by approximately 125 hours; and furthermore the Kaplan-Meier curve also differed largely from those of other groups. It was confirmed that this exclusion of the 31 patients had a risk of a significant impact on the efficacy evaluation of favipiravir. Especially, the distribution of the time

to alleviation of major influenza symptoms in the patients with a disease other than influenza excluded from the favipiravir group disproportionally shifted toward a longer period compared with that in the overall favipiravir group. On the other hand, there were no remarkable trends in effects that lead to an assumption that causes other than influenza virus infection would make the efficacy evaluation difficult, such as a trend of the distribution clearly diverged from that of the time to alleviation of major influenza symptoms in the overall favipiravir group. In light of data properties in the excluded population, PMDA considers it important to review the re-analysis result and discuss the robustness of the results. The results of the re-analysis will be discussed in "4.(iii).B.(1).2) Efficacy in the global phase III study."

Distribution of the time to alleviation of major influenza symptoms in patients with a disease other than influenza showing no negative RT-PCR result



	Population excluding the above 31 patients (reference)		Patients with a disease other than influenza showing no negative RT-PCR result (n = 31)	
	Favipiravir group	Oseltamivir phosphate group	Favipiravir group	Oseltamivir phosphate group
Number of patients	352	374	25	6
Median	58.2	51.0	198.0	73.3
[95% CI]	[54.0, 67.5]	[45.6, 57.6]	[144.7, 259.5]	[18.7, 212.6]
Log-rank test	*P* = 0.168		*P* = 0.023	
Hazard ratio	0.899		0.322	
[95% CI]	[0.774, 1.046]		[0.114, 0.907]	



Patient numbers outside the scatter plot (pyrexia duration, time to alleviation of major influenza symptoms)
Favipiravir group; analyzed, 312111803 (236.1, 44.4); not analyzed, 312405402 (228.0, 259.5)
Oseltamivir phosphate group; analyzed, 312142002 (185.7, 219.2), 312405504 (318.5, 188.0)

Comparison of distributions between 31 patients excluded (not analyzed) and the remaining patients (analyzed)
(scatter plots of the time to alleviation of major influenza symptoms and pyrexia duration)

(d) Patients removed from the efficacy evaluation on the day of adverse event onset

According to the minutes of the third case review committee, it was decided that "the following patients who have experienced an adverse event before recovering from the influzenza symptoms should be removed from the efficacy evaluation on the day of adverse event onset."

PMDA asked the applicant to explain the reason for such removal from the efficacy evaluation, the screening method of the patients to be reviewed, and the inclusion criteria.

The applicant explained as follows:
The removal of the patients from the efficacy evaluation was decided because the 10 influenza symptoms (cough, pharyngolaryngeal pain, headache, nasal congestion, feeling hot, myalgia, general malaise, neck pain, nocturnal awakening, and anorexia) were to be rated, but they were not specific to influenza virus infection. Similar symptoms can occur due to other diseases. If patients with persistent concurrent symptoms are included in the evaluation, the drug effect could be excessively underestimated compared with the original effect.[191] For appropriate evaluation of the drug effect, the case review committee decided that the patient with an adverse event considered to affect the endpoint of the influenza symptoms should be removed from the evaluation at the onset of the adverse event; only the data to the onset should be evaluated.

Of the adverse events reviewed, headache, low back pain, pain muscle, and insomnia (1 patient each) and otitis externa (2 patients) were considered to have no impact on the influenza symptoms evaluation, and the patients with the above adverse events were not removed. Of 22 patients removed, 19 patients were included in the analysis as censored (drop-out) ones. The remaining 3

[191] The applicant listed the following cases. Acute sinusitis frequently develops as an event secondary to viral upper respiratory inflammation and its common symptoms include nasal discharge, nasal congestion, facial pain or pressure sensation, headache, cough, sneezing, and pyrexia (Harrison's Principles of Internal Medicine). In patients in whom acute sinusitis has developed before influenza symptoms alleviate, it is highly difficult to distinguish the symptom associated with the original influenza virus infection from that associated with the secondary sinusitis. There were concerns about the following matter: in the effect evaluation of influenza antiviral drugs, which do not have any therapeutic effect on sinusitis, the drug effect would be excessively underestimated compared with the original effect if the patient has persistent nasal congestion symptoms due to complication of sinusitis.

patients already had complications before their enrollment in the study, leading to the decision at the case review committee that the appropriate evaluation of influenza symptoms was impossible, and thus these patients were removed from the analysis (FAS and PPS proposed at the submission) as those with a disease other than influenza.

PMDA considers as follows:
In general, it is difficult to clearly distinguish the influenza symptoms from those attributable to the other causes. The removal of the patients from the efficacy evaluation was decided on the day of onset of a particular adverse event according to subjective assessment based on the patient outcome data at the case review committee after randomization, and the measured time to alleviation of major influenza symptoms in the relevant patient was not included in the analysis. As discussed in "4.(iii).B.(1).1).(b) Primary endpoint" and "4.(iii).B.(1).1).(c) Efficacy analysis set," such removal thus have a risk of introducing a bias in the efficacy evaluation of favipiravir. The data from the patients removed from the efficacy evaluation on the day of onset of adverse event should be re-analyzed as the time to alleviation of major influenza symptoms (with event) measured after the day of onset of adverse event, and not analyzed as censored (drop-out) data.

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

4.(iii).B.(1).2) Efficacy in the global phase III study
As discussed in "4.(iii).B.(1).1) Efficacy evaluation method," PMDA has concluded that the FAS should be used for the primary efficacy analysis in the global phase III study (Study 312), and all of the 74 patients with a disease other than influenza excluded from the proposed FAS should be included in the FAS. In addition, it is acceptable that the PPS, the population for the secondary analysis, does not include 4 patients who violated the exclusion criteria due to HIV, bronchitis bacterial, or tuberculosis present at the time of inclusion in the study or 40 patients with the negative RT-PCR result and no virus isolated, but other patients with a disease other than influenza should not have been excluded from the PPS as with the FAS. PMDA has concluded that the time to alleviation of major influenza symptoms, the primary efficacy endpoint, should be evaluated using the patient-rated Flu-iiQ scores. The time to alleviation of influenza symptoms in the patients removed from the analysis on the day of adverse event onset due to the complications should be analyzed as the time to alleviation of major influenza symptoms (with event) measured after the day of onset of adverse events and not analyzed as censored (drop-out) data.

PMDA communicated these issues to the applicant and requested to perform re-analysis based on the above FAS (PMDA FAS) and PPS (PMDA PPS) in addition to the proposed PPS. The efficacy results from Study 312 were reviewed as shown in (a) to (e) below. As a result, it has been concluded that in the proposed PPS, non-inferiority of the favipiravir group to the oseltamivir phosphate group was demonstrated, but the efficacy of favipiravir in patients with seasonal influenza virus infection has not been demonstrated by the robust results due to the following points.

- The analysis using the PMDA FAS (proposed PPS + patients with a disease other than influenza) on the primary endpoint has not demonstrated non-inferiority of the favipiravir group to the oseltamivir phosphate group, and the time to alleviation of major influenza symptoms in the favipiravir group was statistically significantly longer than that in the oseltamivir phosphate group (hazard ratio, 0.818; 95% CI, 0.707-0.948; median time to alleviation of major influenza symptoms, 11.9 hours). Similar results were obtained by the analysis using the PMDA PPS as well.

In addition, the following results are considered not to support the efficacy of favipiravir with robustness.

- In terms of the pyrexia duration, which is an objective measure and the secondary endpoint, the favipiravir group was statistically significantly inferior to the oseltamivir phosphate group in both proposed FAS and PPS.
- No placebo-controlled comparative study has been conducted for favipiravir, and clear evidence demonstrating the clinical effect of favipiravir has not been obtained so far.

(a) Use of the global phase III study (foreign data)

PMDA asked the applicant to discuss whether or not the efficacy results from Study 312 indicate any difference between ethnic groups.

The applicant responded as follows:

Analysis results on the time to alleviation of major symptoms in Study 312 by country (PPS) are shown in the table below. The analysis on the time to alleviation of major influenza symptoms by country did not show any considerable difference in the hazard ratio between oseltamivir phosphate and favipiravir in any of Japan, Korea, and Taiwan. The time to alleviation of major influenza symptoms differed among these countries; the time to alleviation in the favipiravir group was 50.8 hours in Japan, 128.3 hours in Korea, and 82.7 hours in Taiwan, while that in the oseltamivir phosphate group was 44.5 hours, 107.3 hours, and 67.1 hours, respectively. These differences were considered to be caused by the difference in the number of the patients included the study among these countries; in Japan, 233 patients were included in the favipiravir group and 249 patients in the oseltamivir phosphate group (≥200 patients in each group), while in Korea, 33 patients in the favipiravir group and 30 patients in the oseltamivir phosphate group, showing the smaller number of patients included in Korea than in Japan. The percentage of each influenza virus type or sub-type by country is shown in the table below. Distribution of the influenza virus types and subtypes largely differed among these countries; the 2009 pandemic influenza A (H1N1) virus accounted for 96.5% (465 of 488 patients) in Japan, influenza A (H3N2) virus accounted for 85.5% (106 of 116 patients) in Taiwan, and influenza Type B virus accounted for 74.6% (47 of 61 patients) in Korea.

As described above, it could not be ruled out that the differences in the number of patients included and in the distribution of the influenza virus types and subtypes among these countries led to the difference in the time to alleviation of major influenza symptoms among them.

To investigate the effect of the difference in the time to alleviation of major influenza symptoms among these countries, the interaction was investigated by the Cox proportional hazard model additionally including the interaction between the country and drug effect. The *P*-values of the interaction between the country and drug effect were 0.701 (Korea) and 0.937 (Taiwan), thus the interaction was not significant. Furthermore, the hazard ratio (95% CI) of favipiravir to oseltamivir phosphate obtained by the Cox proportional hazard model using the country as a covariate, was 0.848 (0.726, 0.990), which was similar to the hazard ratio of 0.839 obtained by the Cox proportional hazard model including only the effect in each dose group. The effect of the country on the comparison result (hazard ratio of the drug effect) of the time to alleviation of major symptoms between the groups was considered to be not large (the table below).

Time to alleviation of major influenza symptoms by country (PPS)

	Japan		Korea		Taiwan	
	Favipiravir (n = 233)	Oseltamivir phosphate (n = 249)	Favipiravir (n = 33)	Oseltamivir phosphate (n = 30)	Favipiravir (n = 63)	Oseltamivir phosphate (n = 61)
Time to alleviation of major influenza symptoms						
Median (hours) 95% CI	50.8 45.3, 55.5	44.5 39.6, 47.3	128.3 80.0, 137.2	107.3 73.3, 149.5	82.7 67.8, 101.2	67.1 48.8, 90.5
Difference in median	6.3		21.0		15.6	
Hazard ratio (95% CI)	0.845 (0.705, 1.013)		0.897 (0.540, 1.492)		0.820 (0.565, 1.192)	
P-value[a)]	0.069		0.676		0.298	

	Non-Japan		Overall	
	Favipiravir (n = 96)	Oseltamivir phosphate (n = 91)	Favipiravir (n = 329)	Oseltamivir phosphate (n = 340)
Time to alleviation of major influenza symptoms				
Median (hours) 95% CI	89.5 77.7, 111.5	79.8 64.5, 105.1	58.2 54.0, 69.3	48.4 44.6, 56.3
Difference in median	9.7		9.8	
Hazard ratio (95% CI)	0.847 (0.627, 1.144)		0.839 (0.718, 0.980)	
P-value[a)]	0.278		0.027	

a) Log-rank test

Percentage of influenza virus type or sub-type by country

	A (H1N1) 2009	A (H3N2)	B	Unknown
Total	488 (72.9%)	116 (17.3%)	61 (9.1%)	4 (0.6%)
Japan	465 (96.5%)	10 (2.1%)	6 (1.2%)	1 (0.2%)
Korea	13 (20.6%)	0 (0%)	47 (74.6%)	3 (4.8%)
Taiwan	10 (8.1%)	106 (85.5%)	8 (6.5%)	0 (0%)

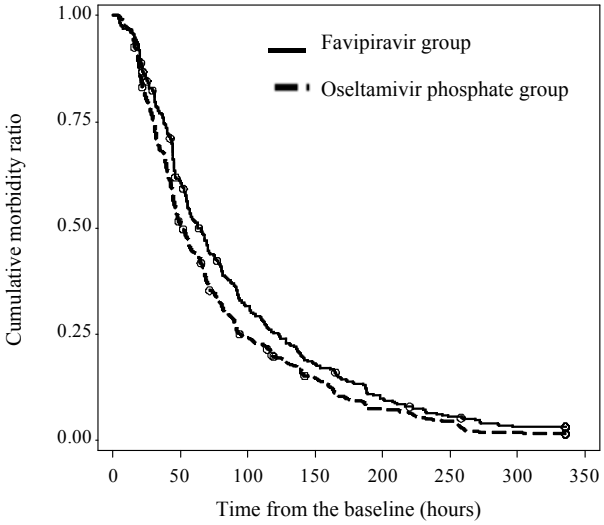
Number of patients (%)

PMDA considers as follows:
Concerning the differences in efficacy results among the countries, it cannot be ruled out that the differences in the number of patients included and in the distribution of the influenza virus types and subtypes among these countries led to the difference in the time to alleviation of major symptoms among them, as explained by the applicant. Also, the analysis result by the Cox proportional hazard model did not indicate statistically significant interaction between the country and the dose group, and thus it was considered that the difference in efficacy between oseltamivir phosphate and favipiravir isnot considerably different among the countries.

In consideration of the above, PMDA accepted the applicant's explanation and has concluded that there is no particular problem with evaluating the efficacy of favipiravir based on the data from Study 312 containing foreign data.

(b) Primary efficacy results
PMDA reviewed the results from re-analysis using the PMDA FAS, considered appropriate for the primary efficacy analysis, as described below. Although 762 patients were randomized, the actual ITT population consists of 757 randomized patients after excluding 5 patients from the proposed FAS due to reasons besides having a disease other than influenza.

Results from re-analysis in the PMDA FAS (actual ITT population)



	Favipiravir group	Oseltamivir phosphate group
Number of patients	377	380
Median	63.1	51.2
[95% CI]	[55.5, 70.4]	[45.9, 57.6]
Log-rank test	*P* = 0.007	
Hazard ratio	0.818	
[95% CI]	[0.707, 0.948]	
Adjusted hazard ratio[a)]	0.818	
[95% CI]	0.706, 0.948	

a) Covariate; body temperature at the baseline, time from onset to treatment, country, virus titer at the time of inclusion, use of antipyretic analgesics just before the start of the study treatment

PMDA reviewed the results of the following analyses: the analysis using the proposed PPS, which was used for the primary efficacy analysis at the time of submission; the re-analysis using the PMDA FAS, which is considered by PMDA to be appropriate as the population used for the primary efficacy analysis by; the re-analysis using the population excluding some of the patients with a disease other than influenza who were excluded by the applicant to investigate the sensitivity; analyses on the data before and after physician's review of the time to alleviation of major influenza symptoms which is the primary endpoint; and analyses on the data before and after removal of the patients due to onset of a particular adverse event. The results are as shown in the table below.

Analysis results at the time of submission, PMDA's re-analysis results and sensitivity analysis results (major results at the time of submission or re-analysis indicated in bold)

mITT or ITT population[b)]	Analysis population	Dose group	Number of patients	Number of the patients excluded from the analysis (disease duration)	Difference in median time to alleviation of major influenza symptoms Hazard ratio (95% CI)		
					Flu-iiQ score reviewed by physician	Flu-iiQ score rated by patient	Flu-iiQ score rated by patient + no-removal from study group[a)]
Proposed by applicant Actual ITT- (patients with the negative PCR result + those with complications) Excluding all of the 74 patients with a disease other than influenza	Proposed FAS	Favipiravir group	330	47 (144.7)	7.1 hours 0.938 (0.803, 1.096)	8.0 hours 0.918 (0.785, 1.072)	6.9 hours 0.910 (0.780, 1.062)
		Control group	353	27 (68.3)			
	Proposed PPS	Favipiravir group	306	71 (139.4)	**7.7 hours 0.955 (0.815, 1.118)**	7.2 hours 0.935 (0.797, 1.095)	7.1 hours 0.938 (0.800, 1.098)
		Control group	334	46 (68.3)			
Actual ITT- (patients with the negative PCR result) Excluding only the 44 patients with a disease other than influenza withthe negative RT-PCR result	FAS[c)]	Favipiravir group	354	23 (87.8)	11.4 hours 0.843* (0.724, 0.982)	12.3 hours 0.830* (0.712, 0.966)	12.8 hours 0.824* (0.709, 0.959)
		Control group	359	21 (67.5)			
	PPS[c)]	Favipiravir group	326	51 (123.8)	9.0 hours 0.855* (0.732, 0.999)	9.3 hours 0.842* (0.720, 0.984)	9.2 hours 0.845* (0.723, 0.988)
		Control group	339	41 (68.3)			
Actual ITT- (patients with negative virus result) Excluding only the 40 patients with the negative RT-PCR and no virus isolated	FAS[c)]	Favipiravir group	357	20 (66.3)	13.1 hours 0.839* (0.720, 0.976)	12.7 hours 0.824* (0.708, 0.960)	12.3 hours 0.819* (0.705, 0.952)
		Control group	360	20 (67.5)			
	PPS[c)]	Favipiravir group	329	48 (112.3)	9.2 hours 0.850* (0.728, 0.992)	11.7 hours 0.835* (0.715, 0.976)	9.8 hours 0.839* (0.718, 0.980)
		Control group	340	40 (68.3)			
Actual ITT- (patients with complications) Excluding only the 31 patients with a disease other than influenza showing no negative RT-PCR result	FAS[c)]	Favipiravir group	352	25 (198.0)	6.4 hours 0.918 (0.790, 1.067)	7.2 hours 0.899 (0.774, 1.046)	6.6 hours 0.901 (0.776, 1.046)
		Control group	374	6 (73.3)			
	PPS[c)]	Favipiravir group	309	68 (139.4)	7.1 hours 0.947 (0.809, 1.109)	7.2 hours 0.926 (0.790, 1.084)	7.2 hours 0.929 (0.793, 1.088)
		Control group	335	45 (68.3)			
Re-analysis recommended by PMDA Actual ITT population No patients excluded	PMDA FAS	Favipiravir group	377	0	11.7 hours 0.828* (0.714, 0.960)	13.9 hours 0.816* (0.704, 0.947)	11.9 hours 0.818* (0.707, 0.948)
		Control group	380	0			
	PMDA PPS	Favipiravir group	329	48 (112.3)	9.2 hours 0.850* (0.728, 0.992)	11.7 hours 0.835* (0.715, 0.976)	9.8 hours 0.839* (0.718, 0.980)
		Control group	340	40 (68.3)			

Control group: Oseltamivir phosphate group

*No non-inferiority to the oseltamivir phosphate group demonstrated, and statistically significantly inferior to the control group (within the thick frame)

a) Results from the analysis based on the Flu-iiQ score rated by the patients without removing patients due to onset of adverse events from the efficacy evaluation

b) The mITT (modified ITT) population is defined as the population with some of the patients excluded and deemed as the actual ITT population to investigate the sensitivity

c) The FAS and PPS for sensitivity analysis. Analysis set obtained by applying the inclusion criteria for PMDA FAS and PPS to the mITT population

PMDA considers as follows:

According to the results of the analysis using the proposed PPS, which was used for the primary efficacy analysis at the time of submission, the lower limit of the 95% CI of the hazard ratio for the difference in the time to alleviation of major influenza symptoms between the groups was 0.815, which was not below the non-inferiority margin of 0.784. However, the efficacy of

favipiravir is not demonstrated for the following reasons: the re-analysis using the PMDA FAS, which is considered by PMDA to be appropriate as the population used for the primary efficacy analysis, did not show non-inferiority; the time to alleviation of major influenza symptoms in the favipiravir group was statistically significantly longer than that in the oseltamivir phosphate group; the difference of the efficacy from the oseltamivir phosphate is not clinically acceptable in terms of the points described below; and all of the analyses using the PMDA PPS and the populations for sensitivity analysis consistently showed that the favipiravir group not only failed to demonstrate non-inferiority to the oseltamivir phosphate group, but also showed that it is statistically significantly inferior to the control group, as observed in the PMDA's major re-analysis, except for the analysis using the population established by excluding the patients with a disease other than influenza and showing no negative RT-PCR result from the actual ITT population.

- The difference in the median time to alleviation of major influenza symptoms between the favipiravir group and oseltamivir phosphate group was as large as 11.9 hours, which was almost equivalent to half a day.
- In a placebo-controlled study of oseltamivir phosphate previously conducted in Japan as the pivotal study for the approval, the difference in the median time to alleviation of major influenza symptoms from the placebo group was 23.3 hours. In light of this result, it is difficult not only to ensure the superiority to the hypothetical placebo but also to expect the minimum efficacy.
- The point estimate of the hazard ratio between the favipiravir group and the oseltamivir phosphate group was 0.818 (close to the non-inferiority margin of 0.784). This was not close to 1.0, the value indicating that the effect would be equivalent to that of oseltamivir phosphate.
- The lower limit of 95% CI was 0.707, which was far below the non-inferiority margin, indicating that the efficacy of favipiravir would be inferior to oseltamivir phosphate in a clinically unacceptable manner.

(c) Secondary endpoint (pyrexia duration)

PMDA confirmed that the pyrexia duration of the favipiravir group in Study 312 was statistically significantly inferior to the oseltamivir phosphate group in any of the analyses using the proposed PPS, PMDA FAS, and PMDA PPS.

Pyrexia duration (patient evaluation)

Analysis set	Dose group	Number of patients	Median pyrexia duration (95% CI)	Difference in median pyrexia duration Hazard ratio (95% CI)
Proposed PPS	Favipiravir group	304	43.0 (40.2, 44.8)	5.5 hours 0.802 (0.685,0.939)
	Oseltamivir phosphate group	333	37.5 (29.7, 39.6)	
PMDA FAS	Favipiravir group	375	44.3 (42.6, 45.6)	6.2 hours 0.767 (0.664, 0.887)
	Oseltamivir phosphate group	379	38.1 (31.9, 39.7)	
PMDA PPS	Favipiravir group	327	43.9 (41.5, 45.0)	6.3 hours 0.774 (0.664, 0.903)
	Oseltamivir phosphate group	339	37.6 (31.1, 39.6)	

(d) Efficacy by time from symptom onset to treatment

The applicant explained the time to alleviation of major influenza symptoms by time from symptom onset to treatment as follows:

In the oseltamivir phosphate group, the median time to alleviation in patients treated at <12 hours after symptom onset was the shortest (<45 hours) among those treated at different timings. For this reason, the hazard ratio was considerably decreased in patients treated at <12 hours after symptom onset. This result suggested that oseltamivir phosphate was expected to show a significant improvement in the time to alleviation if used at <12 hours after symptom onset, but not that favipiravir was inferior to oseltamivir phosphate in improving the time to alleviation in patients treated within 12 hours after symptom onset. In other words, in the sub-group treated <12

hours after onset, the improvement rate in the favipiravir group appeared to be relatively inferior to that in the oseltamivir phosphate group, reflecting that the effect of oseltamivir phosphate tends to be greater as the treatment is started earlier.

Time to alleviation of major influenza symptoms by time from onset to treatment (patient rating, PPS)

Time from onset to treatment	Dose group	Number of subjects	Median	Hazard ratio[a)] (95% CI)
<12 hours	Favipiravir group Oseltamivir phosphate group	32 45	60.8 44.6	0.667 (0.411, 1.083)
≥12 hours and <24 hours	Favipiravir group Oseltamivir phosphate group	117 110	52.3 51.0	0.900 (0.689, 1.174)
≥24 hours and <36 hours	Favipiravir group Oseltamivir phosphate group	109 113	67.5 57.6	0.877 (0.670, 1.149)
≥36 hours and <48 hours	Favipiravir group Oseltamivir phosphate group	71 72	57.5 48.9	0.830 (0.593, 1.162)

a) Obtained by the Cox regression equation without covariate

PMDA considers as follows:
In the sub-group of patients treated at <12 hours after onset, the time to alleviation of major influenza symptoms in the favipiravir group was inferior to that in the oseltamivir phosphate group. In the other subgroups treated at different timings, the time to alleviation of major influenza symptoms in the favipiravir group consistently tended to be inferior to that in the oseltamivir group as well. Therefore, the data by time from onset to treatment have not suggested the efficacy of favipiravir compared with oseltamivir phosphate.

(e) Efficacy by virus type or sub-type

The applicant explained the efficacy by virus type or sub-type as shown in the table below.

Time to alleviation of major influenza symptoms based on the patient rating

Level	Statistics	Proposed PPS		PMDA FAS		PMDA PPS	
		Favipiravir group	Oseltamivir phosphate group	Favipiravir group	Oseltamivir phosphate group	Favipiravir group	Oseltamivir phosphate group
2009 pandemic influenza A (H1N1) virus	n[a)]	228	246	264	263	241	247
	Median	50.2	44.8	54.5	45.9	52.6	44.8
	95% CI	44.7, 55.4	40.7, 49.4	46.6, 62.4	42.5, 51.2	45.5, 56.7	40.6, 49.4
	Difference in median[b)]	5.4		8.6		7.8	
	Hazard ratio[c)]	0.916		0.793		0.827	
	95% CI	0.763, 1.100		0.666, 0.945		0.691, 0.991	
	Adjusted hazard ratio[d)]	0.930		0.797		0.839	
	95% CI	0.773, 1.118		0.668, 0.951		0.700, 1.007	
Infulenza A (H3N2) virus	n[a)]	51	60	57	63	54	62
	Median	70.0	64.4	81.3	64.5	81.0	64.3
	95% CI	54.9, 89.5	43.0, 86.4	62.7, 97.8	43.0, 86.4	62.7, 91.5	43.0, 81.1
	Difference in median[b)]	5.6		16.8		16.8	
	Hazard ratio[c)]	0.868		0.776		0.771	
	95% CI	0.587, 1.285		0.532, 1.133		0.524, 1.134	
	Adjusted hazard ratio[d)]	0.955		0.874		0.845	
	95% CI	0.634, 1.437		0.588, 1.298		0.565, 1.262	

Level	Statistics	Proposed PPS		PMDA FAS		PMDA PPS	
		Favipiravir group	Oseltamivir phosphate group	Favipiravir group	Oseltamivir phosphate group	Favipiravir group	Oseltamivir phosphate group
Influenza B virus	n[a)]	27	28	33	33	31	30
	Median	80.7	114.8	104.3	118.5	90.8	114.8
	95% CI	71.5, 135.9	77.9, 158.5	75.4, 135.9	77.9, 158.5	75.4, 135.9	73.3, 158.5
	Difference in median[b)]	-34.1		-14.2		-23.9	
	Hazard ratio[c)]	1.366		1.170		1.162	
	95% CI	0.779, 2.394		0.703, 1.948		0.688, 1.960	
	Adjusted hazard ratio[d)]	1.278		1.182		1.218	
	95% CI	0.699, 2.338		0.660, 2.117		0.675, 2.198	
Unknown viruses	n[a)]	0	0	23	21	3	1
	Median	-	-	87.8	68.3	137.2	77.7
	95% CI	-	-	45.8, 178.5	38.2, 114.4	-	-
	Difference in median[b)]	-		19.4		-	
	Hazard ratio[c)]	-		0.716		-	
	95% CI	-		0.383, 1.338		-	
	Adjusted hazard ratio[d)]	-		0.812		-	
	95% CI	-		0.393, 1.680		-	

a) Number of subjects with pyrexia at the baseline
b) Favipiravir group - oseltamivir phosphate group
c) No covariate
d) Covariate; body temperature at the baseline, time from onset to treatment, country, virus titer at the time of inclusion, use of antipyretic analgesics just before the start of the study treatment

PMDA's view on the efficacy of favipiravir by virus type or sub-type based on the results from analyses using the proposed PPS, PMDA FAS, and PPS is as follows:
In patients with influenza type A (H1N1) and A (H3N2) virus infection, the time to alleviation of major influenza symptoms in the favipiravir group consistently tended to be longer than that in the control group, while in patients with influenza type B virus infection, the time to alleviation of major influenza symptoms in the favipiravir group tended to be shorter than that in the control group. Yet, the number of the patients with influenza type B virus infection in this study was only limited to around 30 in each group, which is not enough to ensure the evaluation of difference between the groups with sufficient precision. Therefore, the efficacy of favipiravir against influenza type B virus infection is unclear at present. The efficacy of favipiravir against any virus type or sub-type has not been demonstrated.

4.(iii).B.(1).3) Others

(a) Highly pathogenic avian influenza virus infection

PMDA asked the applicant to explain the clinical efficacy of favipiravir in patients with highly pathogenic avian influenza A virus sub-type H5N1 infection.

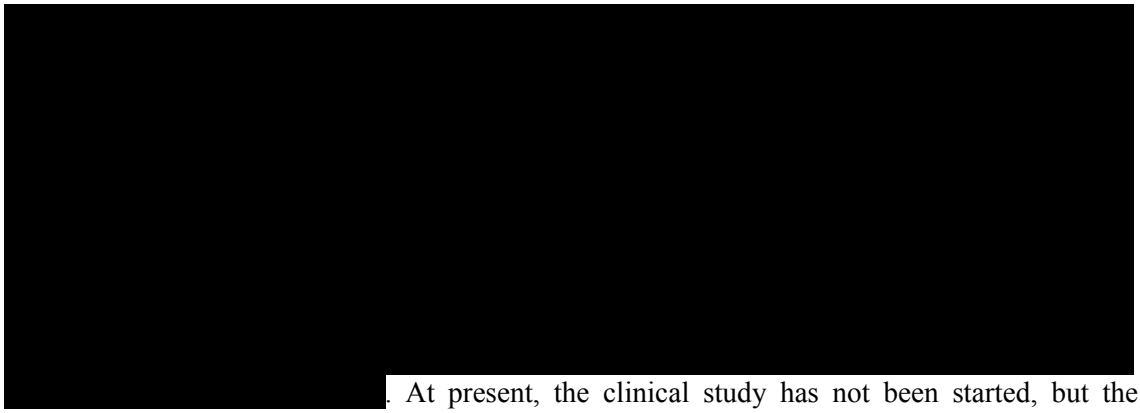
The applicant responded as follows:
According to the WHO report, definitive diagnosis of highly pathogenic avian influenza A (H5N1) virus infection has been given to 555 patients since 2003, and of these, 324 patients died (as of June 3, 2011). In 2011 alone, of 39 patients with a definitive diagnosis, 18 patients died, indicating that the mortality remains high. To treat the avian flu infection, oseltamivir phosphate and other neuraminidase inhibitors are mainly used. Some patients received a regimen of oseltamivir phosphate 150 mg BID for 10 days, in which both clinical dose and treatment duration were greater than those in the usual regimen.[192]

[192] Committee of the second world health organization consultation on clinical aspects of human infection with avian influenza A (H5N1) virus

de Jong, et al. reported therapeutic effects of neuraminidase inhibitors in 8 patients with highly pathogenic avian influenza A (H5N1) virus infection. According to the report, of 8 patients, 4 patients survived responding to the inhibitor, but the remaining 4 patients died.[193] de Jong et al. described that of 4 patients who died, 3 patients were confirmed to have the residual virus, and of the 3 patients with the residual virus, 2 patients were found to have the virus resistant to oseltamivir.

As described above, some of the patients with highly pathogenic avian influenza A (H5N1) virus infection responded to the neuraminidase inhibitors, but the effects of the influenza antiviral drugs have not been established.

Both favipiravir alone and favipiravir in combination with oseltamivir phosphate have been demonstrated to have the effects against oseltamivir-resistant highly pathogenic avian influenza A (H5N1) virus, although the relevant data are from non-clinical studies [see "3.(i).A.(1).3).(b) Effect of concomitant use in the mouse infection model"]. With respect to the clinical data, the clinical study for interaction with oseltamivir phosphate was conducted on the assumption of the concomitant use of favipiravir with neuraminidase inhibitors, and the tolerability was confirmed [see "4.(ii).A.(5).2) Study of favipiravir in combination with oseltamivir in healthy adult Japanese subjects"]. As described above, to treat patients with highly pathogenic avian influenza A (H5N1) virus infection who are unlikely to respond sufficiently to the currently available therapies, the use of favipiravir alone or in combination with neuraminidase inhibitors is expected to be beneficial.



. At present, the clinical study has not been started, but the preparation will be implemented.

Although the applicant's claim on the non-clinical data is not denied, PMDA has concluded that the clinical positioning of favipiravir and its efficacy in the treatment of patients with influenza A (H5N1) virus infection are unclear for the following reasons: (i) the non-clinical data cannot be directly applied to humans; (ii) in a non-clinical study of favipiravir in monkeys, deaths occurred only in the favipiravir group, and thus the re-study is currently ongoing [see "3.(iii).B.(5) Deaths in the pharmacology study in monkeys infected with influenza virus"]; (iii) the currently available data do not robustly support the efficacy of favipiravir in the treatment of patients with seasonal influenza virus infection [see "4.(iii).B.(1).2) Efficacy in the global phase III study"]; and (iv) favipiravir has not yet been administered to patients with highly pathogenic avian influenza A (H5N1) virus at all.

[193] de Jong MD, Tran TT, Truong HK, Vo MH, Smith GJ, Nguyen VC., et al. Oseltamivir resistance during treatment of influenza A (H5N1) infection. *N Engl J MED.* 2005;353:2667-2672.

4.(iii).B.(2). Safety

PMDA evaluated the safety of favipiravir mainly based on the data from Study 312 in terms of the teratogenicity risk noted in the non-clinical studies.

PMDA considers as follows:

Favipiravir has raised considerable concern about the teratogenicity risk in humans, and thus it is important to take strict measures for ensuring the proper use of favipiravir for the treatment of influenza virus infection, which is a common disease. Even if measures for the proper use are taken to avoid the teratogenicity risk, it will be impossible to completely prevent pregnant women from receiving favipiravir or women from becoming pregnant after receiving favipiravir during the influenza season. There may be cases where women would become aware of pregnancy or become pregnant after receiving favipiravir. Such risks can be a highly significant safety concern posed by favipiravir.

In addition, based on the data from Study 312, PMDA has concluded that greater attention needs to be paid to increased blood uric acid levels in patients treated with favipiravir than in those treated with oseltamivir phosphate. Drugs that interact with favipiravir used concomitantly have not been investigated thoroughly, and the safety of such concomitant use is unknown. Furthermore, there is only limited experience with the use of favipiravir in the elderly, patients with underlying medical conditions (chronic metabolic diseases including diabetes mellitus, chronic renal impairment, chronic respiratory disorders, and chronic cardiac diseases), and immunocompromised patients. The applicant should caution that these issues have yet to be investigated, and should thus conduct additional investigation immediately, thereby confirming a certain level of safety to ensure the proper use.

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

4.(iii).B.(2).1) Teratogenicity risk

Favipiravir has raised considerable concern about the teratogenicity risk in humans because it is suggested that favipiravir may cause delayed development or death of embryos during the early stage of pregnancy, in which a pregnancy test may give a negative result. The teratogenicity of favipiravir was observed in all the animal species (4 species) assessed in embryo-fetal developmental studies; and the exposure causing teratogenicity in animals is comparable to that in humans receiving favipiravir in accordance with the proposed dosage and administration [see "3.(iii).B.(1) Effects on embryo-fetal development].

PMDA asked the applicant to explain the provisions included in the protocol about the use in women during pregnancy and lactation and use in men whose partner is pregnant or may possibly be pregnant (e.g., obtaining informed consent, carrying out pregnancy test, and advising caution to physicians and patients) as well as experience with the use in women during pregnancy, parturiency or lactation in Japanese clinical studies.

The applicant responded as follows:

In the Japanese clinical studies in which women of childbearing potential were allowed to be enrolled, the exclusion criteria as specified in the protocol stated that neither pregnant nor lactating women were allowed to participate in the study. In Study JP205, Study 312, patient pharmacokinetics study (Study JP313) and the QT evaluation study (Study JP115) conducted in parallel with Study 312, pregnancy was ruled out by a pregnancy test at the clinical trial site before the study treatment and at the end of the study. Whether the female subject was breast-feeding or not was also confirmed by the investigator etc. at the clinical trial site during history taking before the informed consent was obtained.

In the Japanese clinical studies, all male subjects were informed of the contraception requirements and its period prescribed in the protocol and then provided the informed consent before the study participation. In studies after the phase III clinical studies (Study 312, Study JP313, food effect study [Study JP114], Study JP115), the exclusion criteria specified in the informed consent form included a clear statement "men who may not be able to use condoms during the period of 90 days after the end of the study treatment."

In the Japanese clinical studies, all female subjects tested negative for pregnancy before study participation and after the end of the study. There were no cases where the study drug was given to women during pregnancy or lactation.

The contraception period of 90 days after the end of the study treatment was specified in the protocol, and whether or not the female subjects or male subjects' partners were pregnant during this period was surveyed. Within 90 days after the end of the study treatment, 6 of 762 subjects in Study 312 and 1 of 68 subjects in Study JP115 became pregnant or made their partner pregnant. Of these, 3 subjects (2 males and 1 female) took favipiravir, and 4 (1 male and 3 females) took oseltamivir phosphate. All of the subjects were confirmed to be appropriately informed of the contraception requirements and reproduction toxicity at the medical institution before providing the informed consent. The conception was considered to have occurred 10 days after the end of the treatment or later in all of the relevant subjects, based on the fact that the female subjects were confirmed to have tested negative for pregnancy before the study treatment and based on the date of pregnancy diagnosis or the first date of the last menstrual cycle. Of the 3 subjects receiving favipiravir, 2 had normal neonates (1 had not given birth).

In Study 312, it was found that 1 lactating woman received the study drug. In response to the inquiry from the woman, she was instructed to cease lactation. The case was urgently reported to the sponsor, and then discontinuation of the study was decided.

Based on the measures for safety management in the above Japanese clinical studies and actual treatment status, PMDA asked the applicant to explain the specific future measures for the proper use of favipiravir in women who are pregnant or may possibly be pregnant (premenopausal females [or females of childbearing potential]) and lactating women as well as men whose partner is pregnant or may possibly be pregnant, and then how they would seek cooperation from the medical practice.

The applicant explained as follows:
In the Japanese clinical studies, 7 subjects were pregnant or made their partner pregnant within 90 days after the end of the study treatment, although the subjects were considered to have been aware of the contraception requirements thoroughly because they were informed of the contraception period and reproduction toxicity before their enrollment. It was suggested that the awareness of contraception was lowered as days passed from the end of the treatment. Based on this fact, the applicant considers it important to provide information to physicians and pharmacists appropriately and to implement concise and appropriate risk communication with the patients after marketing. Taking it into account that favipiravir may be indicated for acute diseases; that any physician or pharmacist may use favipiravir; and that special medical situations in the season or pandemic may be involved, the applicant plans to take precaution measures as shown in (a) to (d) below.

(a) Precautionary statements provided in the package insert
Precautionary statements for the teratogenicity risk, necessity of the informed consent, and contraception period will be provided in the "WARNINGS," "CONTRAINDICATIONS," and "PRECAUTIONS" sections in the package insert.

(b) Actions toward physicians and pharmacists

The following measures are plannned. Influenza antiviral drugs may be used by any physician or pharmacist. To ensure that relevant information is communicated to physicians and pharmacists without the involvement of medical representatives, the applicant plans to:

- Send notices on the precautions for use of favipiravir to the medical and pharmacist associations and request them to use the check sheet for confirmation of non-pregnancy and ask these associations to post the notices on their websites in order to ensure that all physicians and dispensing pharmacists are informed of the precautions.
- Send notices similar to the above to members of the Japanese Association for Infectious Diseases, the Japanese Society of Chemotherapy, and the Japan Physicians Association, and request these associations to post the notices on their websites.
- Request the Japan Society of Obstetrics & Gynecology to include information on the precautions for use of favipiravir in the following notices posted on its website, "Q&A about actions for pandemic influenza (H1N1) infection in pregnant or puerperal women (for medical professionals)" and "Q&A about actions for pandemic influenza (H1N1) infection in women during pregnancy or lactation (for general public)." In the event favipiravir was used in a pregnant woman or if a consultation on such use is requested, the applicant plans to request the relevant medical professional to take appropriate actions in accordance with the above.
- Request the Japanese Association for Infectious Diseases and Japan Physicians Association to include the precautions for use of favipiravir (contraindications in pregnant women, requirement of the confirmation of non-pregnancy in women of childbearing potential before use, thorough contraception measures from the start of the treatment to 7 days after the end of the treatment) in the "Clinical applications of influenza antiviral drugs, recommended by the Japanese Association for Infectious Diseases (revised version)" and "Influenza Manual," respectively.
- Post the above information and all the related materials on its website that has links to the websites of the above academic associations, thereby providing precautions on its own website in a similar manner.

(c) Information materials

In addition to the conventional information materials, the applicant plans to prepare the "patient medication guide," "written information for physicians and pharmacists," and "written explanation on the teratogenicity potential." As an additional information material, the applicant intends to prepare a "check sheet" that will be used by physicians and pharmacists before prescription of favipiravir to ensure that women of childbearing potential have been informed of the necessary information and that the women are not pregnant.

The check sheet will be inserted in the package of the product so that it can be delivered with every package of favipiravir.

(d) Others

As described above, to prevent the use of favipiravir in pregnant women who are not aware of their own pregnancy, the applicant plans to establish a system consisting of multiple sessions of explanation and confirmation given by physicians and pharmacists. Based on comments from the medical experts who are specialized in the use of drug products during pregnancy, the applicant plans to:

- [redacted]

- Actively collect information about cases in which the patient has become aware of her pregnancy or his partner's pregnancy or has become pregnant after the use of favipiravir and follow such cases until the delivery (the method currently under consideration).
- [redacted]

PMDA considers as follows:
The applicant is required to establish ever stricter measures for the proper use of favipiravir and therefore should develop the relevant plan and verify its feasibility carefully because the conventional precautions for drugs potentially having a teratogenicity risk and measures for their proper use are not sufficient, as favipiravir may be readily used due to the following background: even in the clinical studies where women of childbearing potential were informed of the teratogenicity risk before providing consent, some women became pregnant, albeit after the end of the study treatment; and influenza virus infection is an acute disease affecting a large number of people during the influenza season.

Given the risk of teratogenicity, the measures for the proper use of favipiravir should include the following two requirements: i) whether or not favipiravir is used should be carefully judged in consideration of the use of other approved influenza antiviral drugs; and ii) the provision of adequate precautions and information about the teratogenicity risk to healthcare professionals in clinical practice is important and essential.

Although the applicant proposed additional precautionary measures, such as distribution of the check sheet and announcement of the precautions and information on websites, those measures are only complementary from the following viewpoints.

- Whether or not the check sheet for confirmation of non-pregnancy is used may depend on the physician or pharmacist.
- The announcement of the precautions on websites of the relevant academic associations and companies cannot ensure full awareness among physicians and patients because not all of them visit these sites.

To avoid the use of favipiravir in pregnant or possibly pregnant women for whom favipiravir is contraindicated, the pregnancy test is accordingly more reliable than these measures. Thus, female patients of childbearing potential should undergo a pregnancy test before favipiravir is prescribed. Furthermore, male patients should be also thoroughly informed of a 7-day contraception period [see "3.(iii).B.(1) Effects on embryo-fetal development]. After that, both male and female patients should be requested to provide his or her consent in writing.

Even if the above strict measures for the proper use in terms of contraception are implemented, it would be difficult to take these measures in routine clinical practice for the following grounds related to clinical characteristics of influenza virus infection: (1) during the influenza season, the process in which a positive result of RIDT is followed by a pregnancy test would be technically complicated and take extra time, and thus it is not practical; (2) at an outpatient clinic during nights and on weekends, such an appropriate confirmation would be more difficult; and (3) patients with influenza virus infection would be so exhausted that they may not be able to understand the content of the informed consent form accurately. Especially, given the fact that pregnancy occurred even in clinical studies, it is impossible to completely prevent cases in which pregnancy is recognized or occurs after use of favipiravir. Therefore, PMDA has concluded that the teratogenicity risk is a highly significant safety concern of favipiravir at present.

The above conclusion of PMDA and measures for proper use of favipiravir will be discussed at the Expert Discussion.

4.(iii).B.(2).2) Overall safety of favipiravir

The applicant explained the safety of favipiravir as follows:

The adverse events and adverse drug reactions in 3 clinical studies (Study JP205, Study 312 and Study JP313) in adult patients with influenza virus infection are as shown in the table below.

Adverse events and adverse drug reactions reported in ≥2% of patients with influenza virus infection (pooled analysis of the phase II/III studies [Studies JP205, 312, and JP313] in adult patients with influenza virus infection)

		Adverse events				Adverse drug reactions			
Total dose (mg)		Favipiravir			Oseltamivir phosphate	Favipiravir			Oseltamivir phosphate
		Low dose	High dose	Proposed dose		Low dose	High dose	Proposed dose	
		2800	3600	4800		2800	3600	4800	
Number of subjects (n)		52	55	394	433	52	55	394	433
Adverse events		20 (38.5%)	22 (40.0)	124 (31.5)	119 (27.5)	20 (38.5)	22 (40.0)	124 (31.5)	119 (27.5)
Adverse events of which a causal relationship cannot be ruled out		8 (15.4%)	14 (25.5)	78 (19.8)	70 (16.2)	8 (15.4)	14 (25.5)	78 (19.8)	70 (16.2)
SOC, HLGT/PT									
Gastrointestinal disorders									
	Diarrhea	4 (7.7)	8 (14.5)	25 (6.3)	29 (6.7)	3 (5.8)	5 (9.1)	16 (4.1)	24 (5.5)
	Nausea		1 (1.8)	3 (0.8)	13 (3.0)			3 (0.8)	11 (2.5)
	Vomiting	2 (3.8)	1 (1.8)	2 (0.5)	10 (2.3)	1 (1.9)	1 (1.8)	1 (0.3)	7 (1.6)
Investigations									
Metabolic, nutritional and blood gas investigations									
	Blood uric acid increased		1 (1.8)	22 (5.6)	1 (0.2)		1 (1.8)	22 (5.6)	1 (0.2)

Number of subjects with AE and/or ADR (%)
Oseltamivir phosphate: 75 mg/day, BID for 5 days
Blank column means absence of the onset of the adverse event.

The relatively common adverse events in the proposed favipiravir dose group included diarrhea (6.3%, 25 of 394 subjects) and blood uric acid increased (5.6%, 22 of 394 subjects). Of the adverse events of which a causal relationship with the study drug cannot be ruled out, relatively common ones in the proposed dose group included blood uric acid increased (5.6%, 22 of 394 subjects) and diarrhea (4.1%, 16 of 394 subjects).

The incidence of blood uric acid increased in the proposed favipiravir dose group was higher than those in the low-dose and high-dose favipiravir groups (Study JP205), and it increased with increasing doses of favipiravir. The incidence of diarrhea was comparable to that in the oseltamivir phosphate group (6.7%, 29 of 433 subjects).

The incidences of nausea and vomiting, the relatively common adverse events in the oseltamivir phosphate group, were 3.0% (13 of 433 subjects) and 2.3% (10 of 433 subjects), respectively, while those in the proposed favipiravir dose group were 0.8% (3 of 394 subjects) and 0.5% (2 of 394 subjects), respectively, which were lower than those in the oseltamivir phosphate group.

No deaths occurred. The serious adverse events included pneumonia in 1 subject in the low-dose favipiravir group, haematochezia in 1 subject in the high-dose favipiravir group, and cellulitis in 1 subject in the proposed favipiravir dose group, and abortion spontaneous in 1 subject in the control group. Except for haematochezia, the causal relationships of these events with the study drug were ruled out, and the outcome of all the events was reported as resolved. The adverse events leading to treatment discontinuation included vertigo in 1 subject in the high-dose favipiravir group, and enteritis infectious and eczema in 1 subject each in the proposed favipiravir dose group as well as gastroenteritis in 2 subjects, and herpes simplex, vomiting, urticaria, eczema, pruritis, and rash in 1 subject each (some events occurred in the same subject) in the control group. The causal relationship of all the events, except for enteritis infectious in the proposed favipiravir dose group and herpes simplex in the control group, with the study drug could not be ruled out, but all of the events resolved.

Regarding the safety of favipiravir, PMDA considers as follows:
In the favipiravir groups, no serious adverse events occurred. The most common adverse event was blood uric acid increased, which occurred more frequently than in the control group. The incidence of this event tended to increase with the dose and the details are to be discussed in the "4.(iii).B.(2).3) Blood uric acid increased" section. Although diarrhea frequently occurred in the favipiravir group, its incidence was comparable to that in the oseltamivir phosphate group (active control group). Thus, it is not particularly problematic at present.

4.(iii).B.(2).3) Blood uric acid increased

The applicant explained the blood uric acid increased associated with favipiravir and related events, as follows:
Adverse events related to the blood and urine uric acid levels following administration of favipiravir are listed in the table below.

The incidence of blood uric acid increased (including hyperuricaemia) was 9.9% in Japanese healthy adults (24 of 242 subjects, 26 events) and 4.8% in patients with influenza virus infection (24 of 501 subjects, 24 events), while it occurred in 5.8% (23 of 394 subjects, 23 events) of the subjects treated with the proposed favipiravir dose. No adverse events of blood uric acid increased occurred in healthy adults in the US. The adverse event of urine uric acid decreased occurred in 1.7% of the healthy adult Japanese subjects (4 of 242 subjects, 4 events), and blood uric acid increased also occurred in all of the 4 subjects. Neither subjective symptoms associated with changes in blood uric acid levels nor gout attack were reported in all subjects including those with these adverse events.

Adverse events related to blood and urine uric acid levels by severity and by causal relationship

Japanese healthy adults[a)]

Adverse events	Number of subjects	Severity					
		Mild		Moderate		Severe	
SOC, HLGT			Causal relationship[c)]	Causal relationship[c)]		Causal relationship[c)]	
PT		1-4	1-5	1-4	1-5	1-4	1-5
Investigations							
Metabolic, nutritional and blood gas investigations							
Blood uric acid increased	242	24 (9.9%)	24 (9.9%)				
Renal urinary system tests and urinalysis							
Urine uric acid decreased	242	4 (1.7%)	4 (1.7%)				

Influenza virus infection patients[b)]

Adverse events	Number of subjects	Severity					
		Mild		Moderate		Severe	
SOC, HLGT			Causal relationship[c)]	Causal relationship[c)]		Causal relationship[c)]	
PT		1-4	1-5	1-4	1-5	1-4	1-5
Metabolism and nutrition disorders							
Hyperuricaemia	501	1 (0.2%)	1 (0.2%)				
Investigations							
Metabolic, nutritional and blood gas investigations							
Blood uric acid increased	501	23 (4.6%)	23 (4.6%)				

Number of subjects with AE or/and ADR (%)

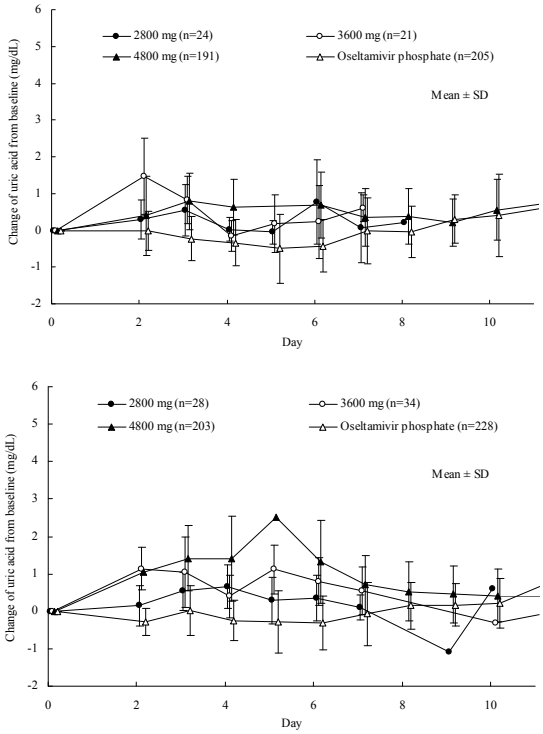
a) Single-dose study, preliminary food effect study, repeated-dose study, single-dose study in elderly, additional repeated-dose study, repeated-dose study in the elderly, drug-interaction study of favipiravir in combination with theophylline, drug-interaction study of favipiravir in combination with oseltamivir, bioequivalence study, high-dose repeated-dose study, food effect study, QT evaluation study

b) Dose-response study, comparative study, pharmacokinetics study in patients

c) 1, Definitely related; 2, Probably related; 3, Possibly related; 4, Possibly unrelated; 5, Unrelated

Changes in blood uric acid levels from the baseline in patients with influenza virus infection over time in a study in such patients are shown in the table below.

The change in blood uric acid levels in the subjects receiving favipiravir tended to increase slightly on Day 3 in both male and female subjects treated with any dosage regimen, and the change trended to resolve 1 day after the end of the treatment. Female subjects experienced large changes in blood uric acid levels more frequently than did male subjects. The numbers of both male and female subjects with large changes in blood uric acid levels increased with the increasing total dose. In the subjects receiving oseltamivir phosphate, the blood uric acid levels remained almost unchanged in both male and female subjects.



2800 mg: Dose-response study (low dose)
3600 mg: Dose-response study (high dose)
4800 mg: Comparative study and pharmacokinetics study in patients

Changes in blood uric acid levelsin patients with influenza virus infection over time (top: male, bottom: female)

PMDA asked the applicant to explain the effects of the interaction between favipiravir and a concomitant drug causing hyperuricaemia on the blood uric acid level and their views on whether or not caution should be advised.

The applicant explained as follows:
The increase in blood uric acid levels associated with favipiravir is considered to be a consequence of the following mechanism: favipiravir and its metabolite, M1, inhibit OAT1 and OAT3, leading to decreased tubular secretion of uric acid, and M1 also enhances URAT1-madiated reabsorption of uric acid, collectively resulting in decreased excretion of uric acid [see "4.(ii).A.(1).5].(a) Human transports"]. Drugs leading to increases in blood uric acid levels are largely classified into 2 types according to the mechanism of action: drugs leading to "excessive uric acid production" and ones leading to "decreased uric acid excretion." The former drugs enhance biosynthesis and degradation of purine bodies, and the latter drugs decrease the glomerular filtration rate and affect the uric acid transport in the renal tubules.

(a) Drugs leading to excessive uric acid production
Theophylline is one of the drugs leading to excessive uric acid production, and its concomitant use with favipiravir has been investigated in the drug-interaction study of favipiravir in combination with theophylline (Study JP108). The maximum increases in blood uric acid levels from the baseline were 17% in the subjects receiving theophylline alone and 28% in those receiving both drugs. The blood uric acid level was increased by theophylline, and further increased by theophylline concomitantly used with favipiravir, but the additional increase was about 10%. The value was below 16%, which was the mean increase with favipiravir alone. The applicant considered that the may be increased due to concomitant use

of a uric acid production inhibitor with favipiravir, but a synergistic increase is unlikely.

(b) Drugs leading to decreased uric acid excretion
Of the subjects who received favipiravir, 3 subjects in Study JP313 and Study 312 concomitantly received uricosuric agents. The maximum increases in blood uric acid levels from the baseline in these patients were 2% to 35%, which were not largely different from the increase of 13% to 36% in the patients who received favipiravir in Study JP313 and Study 312. The applicant considered it unlikely that the blood uric acid level increases synergistically due to concomitant use of favipiravir with drugs leading to decreased uric acid excretion.

As described in the above (a) and (b), concomitant use of favipiravir with uric acid production inhibitors or uricosuric agents is unlikely to increase the blood uric acid level synergistically. The transient increase in blood uric acid levels due to concomitant use of those drugs is unlikely to result in subjective symptoms such as a gout attack in consideration that favipiravir may not be used for long periods of time for the proposed indication, and the blood uric acid level was restored after the end of administration of favipiravir. It has been, however, known that pyrazinamide, an antituberculous drug, increases the blood uric acid level through URAT1, the same urate transporter as that affected by favipiravir.[194] The adverse reactions to pyrazinamide include gout,[195] though its frequency is unknown. Although pyrazinamide has not been concomitantly used with favipiravir, it cannot be ruled out that the concomitant use increases the blood uric acid level synergistically through the same URAT1, and thus pyrazinamide is to be listed in the "Precautions for concomitant use" section.

PMDA considers as follows:
The currently available information confirmed that the increase in blood uric acid levels after administration of favipiravir did not cause particular clinical issues. However, the applicant should provide the information about the dose-dependent increasing trend of the blood uric acid level after administration of favipiravir and collect information about the relevant adverse events. In addition, the clinical studies included the limited number of subjects with high uric acid levels at the baseline and those with renal impairment. For this reason, it cannot be ruled out that patients with such conditions may experience clinical symptoms due to the increase in blood uric acid levels after administration of favipiravir. Therefore, it is necessary to advise the above matter. Furthermore, caution should be exercised on patients who have already been receiving a drug product known to increase the blood uric acid level, and information about the increase in blood uric acid levels after administration of favipiravir should be collected continuously.

4.(iii).B.(2).4) Safety in patients with underlying medical conditions and immunocompromised patients

The applicant explained the safety of favipiravir in the elderly, patients with underlying medical conditions (chronic metabolic diseases including diabetes mellitus, chronic renal impairment, chronic respiratory disorders, and chronic cardiac diseases) or immunocompromised patients in the high-risk patient population with patient background factors that may affect the severity of the influenza virus infection and recovery.

(a) Safety in the elderly
Of 394 patients who received favipiravir in Study 312 and Study JP313, five were elderly. Of the 5 elderly patients, 2 experienced adverse events (2 of 5 subjects), while the incidences in young patients and in non-elderly ones were 29.6% (84 of 284 subjects) and 36.2% (38 of 105 subjects), respectively. Adverse events in the elderly include bronchitis and blood uric acid increased (1

[194] Makoto Hosoyamada. Molecular mechanism of the uric acid transporters. *Japanese Society of Gout and Nucleic Acid Metabolism*. 2004;28:1-5.
[195] Daiichi Sankyo Company, Limited. Package insert of Pyramide Powder (pyrazinamide). Revised in June 2009 (version 8).

each), but both events were also reported in the young and non-elderly patients, and they were mild in severity. Bronchitis was a secondary infection attributable to influenza virus infection, and a causal relationship was ruled out. Following administration of Cravit (levofloxacin), the event resolved. The blood uric acid level was 6.5 mg/dL on Day 1 and it increased to 8.8 mg/dL on both Days 4 and 6, and the change was thus considered as an adverse event. In the patient who experienced the concerned event, the blood uric acid level was returned to 6.8 mg/dL on Day 15, and the change was comparable to those in young and non-elderly patients who experienced the event.

Although a simple comparison is not possible due to the limited number of elderly patients, the incidence of adverse events did not increase with the increasing age in the patients receiving favipiravir. The blood uric acid increased, an adverse event specific to favipiravir, is a consequence of the following mechanism: favipiravir and M1 inhibit OAT1 and OAT3, leading to decreased tubular secretion of uric acid, and M1 enhances URAT1-mediated reabsorption of uric acid, collectively resulting in decreased excretion of uric acid. The applicant considered that the risk of the blood uric acid increased would not be intensified by the age or pathological conditions of the underlying disease.

The body weight, however, may be lower in the elderly than in the non-elderly. In consideration that the body weight was a variable factor in the pharmacokinetics, the package insert includes precautions stating that "blood favipiravir concentrations may be increased in the elderly compared with the non-elderly, and attention should be paid to the general condition of the patient during the treatment."

(b) Safety in patients with chronic renal impairment

Using the CL_{cr} level in the patient as an indicator of chronic renal impairment, the patients were divided into subgroups as follows: $CL_{cr} \geq 80$ mL/min (normal renal function), $CL_{cr} \geq 50$ mL/min and <80 mL/min (mild renal impairment), $CL_{cr} \geq 30$ mL/min and <50 mL/min (moderate renal impairment), and $CL_{cr} < 30$ mL/min (severe renal impairment). Comparisons were then made among these subgroups.

None of the patients had severe renal impairment, and 1 patient was classified into the moderate renal impairment subgroup and 30 patients into the mild renal impairment subgroup. The patient with moderate renal impairment was elderly (CL_{cr} 42.4 mL/min).

The incidence of adverse events was 100% (1 of 1 subject) in the moderate renal impairment subgroup and 43.3% (13 of 30 subjects) in the mild renal impairment subgroup. The adverse event in the patient with moderate renal impairment was 1 mild event of blood uric acid increased, which was also reported in the patients with normal renal function. The incidence of the adverse events in the patients with mild renal impairment was slightly higher than that in the patients with normal renal function (30.3%, 110 of 363 subjects). In the oseltamivir phosphate group, the incidence of adverse events in the patients with mild renal impairment (52.4%, 22 of 42 subjects) was also higher than that in the patients with normal renal function (24.8%, 97 of 391 subjects). The increase in the favipiravir group was smaller than that in the oseltamivir phosphate group, and the incidence in the patients with mild renal impairment was lower in favipiravir group than in the oseltamivir phosphate group.

Favipiravir is metabolized to M1, which is then excreted in the urine. The elimination of favipiravir largely depends on the metabolic clearance of M1 and is additionally attributed to renal excretion of M1. In patients with renal impairment, the plasma concentration of M1 may be affected. The above 1 patient with moderate renal impairment was enrolled in Study JP313, and the trough plasma concentration of M1 in this patient was 2.23 μg/mL, while the mean trough in other patients in that study was 0.88 μg/mL. Based on this fact, the plasma M1 concentration

would be increased approximately 2.5 times even in patients with moderate renal impairment. When favipiravir was administered at NOAEL in the 2-week repeated oral dose toxicity studies in monkeys and rabbits, the AUCs of M1 were 2 to 4 times greater than that in humans at the proposed dose. The adverse events attributable to M1 were, therefore, unlikely to occur even in patients with renal impairment.

(c) Safety in patients with chronic metabolic diseases including diabetes mellitus, chronic respiratory diseases, and chronic cardiac diseases as well as immunocompromised patients

In clinical studies of favipiravir, neither patients with chronic respiratory diseases nor immunocompromised patients were included. In Study 312, one patient with diabetes mellitus and 1 with glucose tolerance impaired fell under the category of patients with chronic metabolic diseases including diabetes mellitus, and 1 patients with tricuspid valve stenosis was a patient with chronic cardiac diseases, but none of these subjects experienced adverse events.

In consideration of the above (a) to (c), the applicant explained as follows:
Although the applicant could not make a claim clearly due to the limited numbers of the elderly, patients with underlying medical conditions (chronic metabolic diseases including diabetes mellitus, chronic renal impairment, chronic respiratory diseases, and chronic cardiac diseases) and immunocompromised patients, the risk of adverse events (frequency and severity) did not tend to increase in the above patients. Blood uric acid increased, an adverse event specific to favipiravir, is known to occur in a manner dependent on the exposure of favipiravir. Since the pharmacokinetics of favipiravir is largely affected by aldehyde oxidase (AO), the plasma favipiravir concentration is not influenced by underlying medical conditions or weakened immune system. The applicant, therefore, considered that these pathological conditions do not cause blood uric acid increased. None of the adverse events except for blood uric acid increased were dependent on the favipiravir exposure.

Based on the above, precautions for use of favipiravir in the elderly should be included in the package insert, because the exposure (pharmacokinetics) may be increased depending on the body weight, which is relatively low in the elderly. Although neither underlying medical conditions nor weakened immune system would change the exposure of favipiravir, the experience with use of favipiravir in the patients with underlying medical conditions and immunocompromised patients is limited. The applicant, therefore, considered that the package insert needs to state to the effect that the information on the use of favipiravir in the patient populations is not sufficient.

The applicant is planning to conduct a clinical study to evaluate the efficacy of favipiravir in patients with high risk factors and collect the safety information from those patients.

PMDA considers as follows:
The experience with use of favipiravir in the elderly, patients with underlying medical conditions (chronic metabolic diseases including diabetes mellitus, chronic renal impairment, chronic respiratory disease, and chronic cardiac disease) and immunocompromised patients, who are all classified as high-risk patients, is extremely limited or absent, and thus the safety of favipiravir in these patients remains unknown. Therefore, it is desirable to conduct clinical studies in high-risk patients for safety evaluation, and it is necessary to advise caution about the above matters until a certain amount of safety information becomes available.

4.(iii).B.(2).5) Pediatric and adolescent patients

In the toxicity studies of favipiravir in juvenile animals, toxicological findings such as histopathological change in the testis, atrophy of the skeletal muscle fibers and gait abnormal were observed [see “3.(iii).A.(6).6) Juvenile animal toxicity studies”].

The applicant explained the development plan and use of favipiravir in pediatric patients as follows:
In the 1-month repeated oral dose toxicity study in juvenile rats, histopathological change in the testis, atrophy of the skeletal muscle fibers, and gait abnormal were observed, but these toxicological findings is difficult to detect in humans. On the other hand, in consideration that favipiravir is an influenza antiviral drug with a new mechanism of action, the applicant considered it necessary to evaluate the risk in pediatric patients appropriately before starting the development of favipiravir for pediatric use in the future. To develop favipiravir for pediatric use, additional toxicity studies are required. Before the studies, the study plan will be designed to evaluate the risk in pediatric patients appropriately by setting the treatment duration corresponding to the duration of clinical use of favipiravir and by selecting animals to reflect the age of the intended pediatric patients, and with such a study plan, the applicant expects to identify the NOAEL and investigate the relationship between the exposure and toxicity development such as toxicity in the testis.

In consideration of the above, the package insert will include a precautionary statement that "pediatric use is not desirable." In addition, it will be advised in the package insert that no clinical studies in pediatric patients have been conducted with the toxicity data in juvenile animals included.

Following administration of approved influenza antiviral drugs, development of neuropsychiatric symptoms such as abnormal behavior was reported. The applicant explained the neuropsychiatric symptoms after administration of favipiravir as follows:
The clinical studies of favipiravir in patients with influenza virus infection did not include subjects aged <20 years.

In patients who received favipiravir according to the proposed dosage regimen, no neuropsychiatric symptoms (consciousness disturbed, abnormal behaviour, delirium, delusion, convulsion) occurred. Adverse events of mental disorders in the clinical studies included anxiety and insomnia (1 subject each) in the proposed dose group (394 subjects in total) and nightmare (1 subject) in the control group (433 subjects). Those of nervous system disorders included headache, headache tension, and cervicobrachial syndrome (1 subject each) in the low dose group (52 subjects in total), headache, dysgeusia, and intercostal neuralgia (1 subject each) in the proposed dose group, and headache and dizziness (3 subjects each) and head discomfort and cervicobrachial syndrome (1 subject each) in the control group. Of these, the events for which a causal relationship with the study drug could not be ruled out were dysgeusia in the proposed dose group and headache and dizziness (2 subjects each) and nightmare (1 subject) in the control group.

PMDA considers as follows:
Based on the currently available information, pediatric use of favipiravir is not recommended, because the safety of favipiravir in pediatric patients is considered to be unknown for the following reasons: (1) toxicological findings were noted in the toxicity studies in juvenile animals; (2) at present, the effects of favipiravir on development of the testis and on growth of the skeletal muscles have not yet been thoroughly investigated, though such information is necessary especially from the viewpoint of long-term prognoses; (3) there is no experience with the use of favipiravir in pediatric patients. Although no neuropsychiatric symptoms occurred after administration of favipiravir, influenza-related abnormal behaviors in pediatric patients have not been investigated. Therefore, it is necessary to advise caution against development of neuropsychiatric symptoms such as abnormal behaviors in pediatric patients receiving favipiravir as with other drugs of the same class and to continue collecting the safety information in the future.

4.(iii).B.(2).6) Drug interactions

PMDA asked the applicant to explain the risk of concomitant use of favipiravir with aldehyde oxidaze (AO) inhibitors, acetaminophen, oral contraceptives, CYP2C8 substrate drugs, and AO substrate drugs, which may interact with favipiravir used concomitantly, as well as specific measures to provide precautions in the package insert.

The applicant responded as follows:

(a) AO inhibitors

Judging from the currently available pharmacokinetic data [see "3.(ii).A.(3) Metabolism and (5) Pharmacokinetic drug interactions," and "4.(ii).A.(1) Study using human biomaterials and (2) Investigation in healthy adults subjects"], the risk of concomitant use of favipiravir with AO inhibitors may not be high. Currently, a drug interaction study of favipiravir with raloxifene hydrochloride, an AO inhibitor, is under preparation, and if the risk of concomitant use is suggested by this study, precautions will be provided in the package insert.

(b) AO substrate drugs

Based on the currently available pharmacokinetic data, drugs that act as AO substrates and would require special attention are hydralazine hydrochloride, which shows a high relative contribution of AO, and famciclovir and sulindac, whose effect may be decreased by concomitant favipiravir. A drug interaction study with hydralazine hydrochloride is under preparation, and if the risk of concomitant use is suggested by this study, precautions will be provided in the package insert. Whether or not a drug interaction study with famciclovir or sulindac is conducted will be decided after data on the drug interaction with hydralazine hydrochloride are confirmed.

(c) Acetaminophen

A study assessing drug-drug interaction between favipiravir and acetaminophen was conducted in healthy adult male and female subjects aged 19 to 50 years in the US [see "4.(ii).B.(4).3) Other drug interactions"]. Adverse events in this study included dry skin on the face, headache, upper respiratory tract infection, and left antecubital pain (1 subject each), and a causal relationship was ruled out for all the event, except for headache in 1 subject. All of them resolved. The applicant considered that the increased plasma acetaminophen concentration due to concomitantly used favipiravir does not induce acetaminophen poisoning symptoms. In Study JP313 and Study 312, the incidence of adverse events in patients with influenza virus infection who received favipiravir in accordance with the proposed dosage regimen and who used acetaminophen concomitantly was 34.0% (83 of 244 subjects). The risk ratio (95% confidence interval) of the incidence of adverse events in patients who received favipiravir in combination with acetaminophen to that in the patients who received favipiravir alone (27.3%, 41 of 150 subjects) was 1.245 (0.909, 1.704), indicating that the incidence was not increased due to concomitantly used acetaminophen. Of the adverse events that occurred during the concomitant use of the two drugs, diarrhea occurred the most frequently (7.4%, 18 of 244 subjects).

Based on the above results, the applicant considered it unnecessary to restrict concomitant use of favipiravir and acetaminophen or to include such use in the "Precautions" section in the package insert.

(d) Oral contraceptives

Favipiravir was found to have reproductive toxicity in experimental animals. For this reason, favipiravir is contraindicated for women who are pregnant or may possibly be pregnant, but can be administered to other women (female adults). FDA recommended that the applicant conduct a study to confirm that concomitant use of favipiravir with oral contraceptives would not lead to decreased plasma concentrations of the oral contraceptives that result in decreased effectiveness.

Recently, low-dose oral contraceptives have been mainly used for contraception. Although ethinyl estradiol, an active ingredient of such contraceptives, has an AO inhibitory effect, the applicant considered that it is unlikely to affect the pharmacokinetics of favipiravir, because the total dose of ethinyl estradiol for 28 weeks is as low as 0.68 mg and thus its effect is negligible as long as it is used at a regular dose. Ethinyl estradiol is metabolized mainly by CYP2C9 and CYP3A4,[196] while favipiravir has weak inhibitory effects against CYP2C9 and CYP3A4 and does not induce any CYP enzymes. The applicant, therefore, considered that concomitant use of favipiravir and ethinyl estradiol does not affect the plasma ethinyl estradiol concentration.

In Study JP313 and Study 312 conducted according to the proposed dosage regimen, only 1 subject concomitantly used favipiravir and oral contraceptives and reported rhinitis and dysgeusia as adverse events, which were not considered specific to favipiravir or ethinyl estradiol.

As described above, the applicant considered it unnecessary to place particular restrictions on concomitant use of favipiravir and oral contraceptives in the package insert. If the study data in the US indicate that such a concomitant use should be restricted, the applicant will consider the inclusion of restrictions on the concomitant use in the package insert.

(e) CYP2C8 substrate drugs

In the FDA guidance for drug interactions (draft),[197] rosiglitazone and repaglinide, antidiabetic drugs, as well as paclitaxel, an antineoplastic drug, are listed as drugs with a high relative contribution of CYP2C8. Of these, repaglinide and paclitaxel are used in Japan. In Study JP313 and Study 312, none of the subjects received favipiravir with repaglinide or paclitaxel concomitantly, and the safety of concomitant use of favipiravir with repaglinide or paclitaxel could not be evaluated.

Favipiravir may decrease the metabolic clearance of repaglinide or paclitaxel by approximately 50% and thereby increase the plasma concentration of repaglinide or paclitaxel at the concentration around C_{max} (78.9 μg/mL) estimated based on the data from the subjects showing little AO activity following administration of favipiravir at the proposed dose in the high-dose repeated dose study (Study JP111). In the case of concomitant use of favipiravir with repaglinide, it cannot be ruled out that the risk of hypoglycemia,[198] a serious adverse drug reaction, is increased. In the case of concomitant use of favipiravir with paclitaxel, it cannot be ruled out that the risk of white blood cell decreased and peripheral neuropathy,[199] serious adverse drug reactions, is increased. A drug interaction study with favipiravir and repaglinide is under preparation, and if the risk of such concomitant use is suggested by this study, precautions will be provided in the package insert.

PMDA considers as follows:

The drug interaction studies conducted in the process for development of favipiravir until submission of the regulatory application only covered combinations of favipiravir with theophylline (Study JP108) and with oseltamivir (Study JP109) [see "4.(ii).A.(5) Drug-drug interactions]. Most of the drugs which may interact with favipiravir have not been clinically investigated, and experience with use of such drugs is limited in the clinical studies. The safety, therefore, remains unknown. For the use of favipiravir, caution should be advised on the

[196] Aska Pharmaceutical. Co., Ltd. Package insert of Ange 21 Tablets, Ange 28 Tablets (levonorgestrel/ethinyl estradiol tablets), revised in July 2010 (version 10)

[197] Guidance for Industry. Drug Interaction Studies —Study Design, Data Analysis, and Implications for Dosing and Labeling (DRAFT GUIDANCE). U.S. Department of Health and Human Services Food and Drug Administration (FDA). September 2006.

[198] Sumitomo Dainippon Pharma Co., Ltd. Package insert of Surepost Tablets 0.25 mg, Surepost Tablets 0.5 mg (repaglinide tablets), January 2011 (version 1)

[199] Bristol-Myers Squibb K.K. Package insert of Taxol for injection 30 mg, Taxol for injection 100 mg (paclitaxel for injection) revised in January 2010 (version 18)

concomitant drugs. The applicant should promptly conduct the drug interaction studies currently under preparation, and then, based on their results, re-consider whether or not precautions should be provided.

4.(iii).B.(2).7) QT/QTc interval prolongation

The applicant explained whether or not favipiravir may prolong the QT/QTc interval, as follows: Changes in QTcF and ΔQTcF from the baseline up to 4 hours after administration of the study drug including t_{max} were investigated by dose level of the first dose (≤200, 400, 600, 800, 1200, 1600, 2000 and 2400 mg) in Japanese healthy adults. As performed above, changes in QTcF and ΔQTcF were investigated by dose level (≤200, 400, 600, 800 and 1200 mg) in US healthy adults.

As a result, neither QTcF nor ΔQTcF was found to be dose-dependent in Japanese or US healthy adults. The relative contribution of ΔQTcF with respect to the plasma favipiravir concentration was 0.0032 in Japanese healthy adults and 0.0095 in the US healthy adults; no correlation was found for both populations, and ΔQTc did not increase in a favipiravir concentration-dependent manner. The relative contribution of maximum ΔQTcF to the cumulative AUC of favipiravir was 0.0123 in Japanese healthy adults and 0.0338 in the US healthy adults; no correlation was found for both populations, and ΔQTc did not increase with the increasing AUC of favipiravir.

Even in patients with influenza virus infection, no trend toward QT/QTc interval prolongation was observed, and ΔQTc >60 msec was observed in 5 patients with influenza virus infection, but the QTc value was small; the finding was thus of no clinical concern. Adverse events related to heart diseases occurred in 6 subjects (palpitation [3 subjects]; blood pressure increased, blood pressure decreased, and supraventricular extrasystoles [1 subject each]), but all of these events were mild in severity and the outcomes of the events were reported as resolved, not affecting QT/QTc interval prolongation.

The above data demonstrated that favipiravir does not prolong the QT/QTc interval.

PMDA accepted the applicant's explanation.

4.(iii).B.(2).8) Safety in patients with hepatic impairment

As discussed in "4.(ii).B.(2) Effects of hepatic impairment on pharmacokinetics of favipiravir and M1," PMDA considers as follows:

It should be advised in the package insert that plasma favipiravir concentrations may increase in patients with hepatic impairment patients, and the relationship between the severity of hepatic impairment and the plasma favipiravir concentrations has not been investigated, for the following reasons: (1) at present, no pharmacokinetics studies in patients with hepatic impairment have been conducted and thus there is no information about the relationship between the severity of hepatic impairment and plasma favipiravir concentrations; and (2) based on the pharmacokinetic profile of favipiravir, it cannot be ruled out that plasma favipiravir concentrations may increase due to hepatic impairment. In addition, it is important to collect information about the pharmacokinetics and safety of favipiravir in patients with hepatic impairment. Therefore, the applicant should conduct a pharmacokinetic study in the concerned patients promptly, and then should review the use of favipiravir in those patients including necessity of the dose adjustment when new findings become available. The obtained information should be appropriately provided to healthcare professionals in clinical practice.

III. Results of Compliance Assessment Concerning the Data Submitted in the New Drug Application and Conclusion by PMDA

1. PMDA's conclusion on the results of document-based GLP/GCP inspections and data integrity assessment

A document-based inspection and data integrity assessment were conducted in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application. As a result, PMDA concluded that there should be no problem with conducting a regulatory review based on the submitted product application documents.

2. PMDA's conclusion on the results of GCP on-site inspection

GCP on-site inspection took place in accordance with the provisions of the Pharmaceutical Affairs Act for the data submitted in the new drug application (5.3.3.1.1, 5.3.4.2.1, 5.3.5.1.1, 5.3.5.1.2). As a result, protocol deviations (documents on the safety during the study were not prepared and such documents were not provided to the subjects) were found at some clinical trial sites. In addition, even though the above protocol deviations had been detected by the monitors, some of the cases with deviations were accepted by the sponsor. Although the above issues to be improved were found, PMDA concluded that the clinical studies as a whole had been conducted in compliance with GCP and thus there should be no problem with conducting a regulatory review based on the submitted application documents.

IV. Overall Evaluation

Based on the submitted data on favipiravir, PMDA has concluded that the benefits outweighing the risk are not clear at present for the following reasons: the concern about the teratogenicity risk in humans raised by the non-clinical data is considerable; the efficacy has not been demonstrated with robustness; and for treatment of seasonal influenza virus infection, which is the proposed indication, other therapeutic drugs are already available. With the application data package submitted in this application, it is therefore difficult to approve favipiravir for the proposed indication.

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

Review Report (2)

December 12, 2013

I. Product Submitted for Registration

[Brand name]	Avigan Tablet 200 mg
[Non-proprietary name]	Favipiravir
[Applicant]	Toyama Chemical Co., Ltd.
[Date of application]	March 30, 2011

II. Content of the Review

The outline of the comments on the Review Report (1) from the Expert Discussion (Expert Discussion [first round]) and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections. The expert advisors selected for the Expert Discussion (first round) were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by the Pharmaceuticals and Medical Devices Agency" (PMDA Administrative Rule No. 8/2008 dated December 25, 2008).

(1) Efficacy evaluation method

1) Non-inferiority margin

To investigate the size of the non-inferiority margin in the global phase III study (Study 312) from a clinical viewpoint, PMDA obtained the difference in the median time to alleviation of major influenza symptoms from the non-inferiority margin expressed as the hazard ratio. The difference was 13.2 hours, which was considered to be not an unacceptably large non-inferiority margin from the clinical viewpoint. PMDA has therefore concluded that the efficacy evaluation based on the predetermined non-inferiority margin does not cause particular issues.

The above conclusion of PMDA was supported by the expert advisors.

2) Primary endpoint

PMDA considers it inappropriate that the investigator or sub-investigator reviewed the patient-rated Flu-iiQ score, because the Flu-iiQ, an assessment measure of influenza symptoms, is a PRO designed to assess patient conditions obtained directly from patients. Thus, the time to alleviation of major influenza symptoms, the primary endpoint in the global phase III study (Study 312), should be re-analyzed based on the patient-rated Flu-iiQ score.

The above conclusion of PMDA was supported by the expert advisors.

3) Efficacy analysis set

Although the efficacy analysis set in the global phase III study (Study 312) was initially defined as the PPS, PMDA has concluded that the FAS should be used in accordance with the ITT principle. At the case review committee, the patients who were found to have a disease other than influenza and then excluded from the analysis set accounted for 9.7% of the included subjects (74 of 762 subjects), consisting of 43 patients with the negative RT-PCR result, 30 patients with complications (including suspected complications), and 1 patient with the negative RT-PCR result and also with complications. In this study, the patients with the negative RT-PCR result (44 patients) actually presented the positive RIDT result, as done in routine clinical practice, and then were randomized. It has been therefore concluded that the patients with the negative RT-PCR result should not be excluded from the efficacy analysis and the efficacy of favipiravir should be evaluated based on the results of the analysis using the population that includes these patients.

Although it is inappropriate to exclude the patients with complications (including suspected complications) based on the individual assessment, exclusion of 31 patients with a disease other than influenza showing no negative RT-PCR result was decided based on subjective judgment after randomization, which seemed to be dependent on the treatment result. In accordance with the ITT principle, they should not have been excluded from the efficacy analysis. PMDA has thus concluded that the efficacy of favipiravir should be evaluated based on the results from the analysis using the population that includes these patients.

The following comments on the above conclusion of PMDA were raised from the expert advisors.

It is difficult to prevent intentional or non-intentional bias from being introduced into the PPS. Decision of exclusion even before unblinding can cause bias. In the global phase III study (Study 312), the PPS was defined as the efficacy analysis set. The exclusion or inclusion of the patients was decided according to the discussion at the case review committee, and this definition would cause bias. The decision of the exclusion or inclusion of the patients based on the information obtained after randomization and after the start of the study treatment would considerably compromise the appropriateness of the analysis of the study data and therefore require caution and discretion.

In the evaluation of influenza antiviral drugs, the difference between the placebo and test drug is small. The bias introduced into the results of the analysis in the PPS which excluded specific patients according to the decision of the case review committee, was judged to have a remarkable impact on the evaluation of this study. In addition, although the global phase III study (Study 312) was conducted as a non-inferiority trial, the patients who did not sufficiently responded to the test drug were selectively excluded base on the decision made at the case review committee, and the bias introduced by such an exclusion tended to shift the conclusion toward non-inferiority. Furthermore, the decision was made based on the data on influenza symptoms that comprised the primary endpoint, and thus the resultant bias was direct. Many patients with the long time to alleviation of major influenza symptoms were excluded from the favipiravir group. The efficacy of favipiravir should not have been evaluated based on the results of the analysis in the PPS claimed by the applicant, but should have been evaluated based on the analysis results in the FAS in accordance with the ITT principle.

Taking account of the above comments from the expert advisors, PMDA has concluded that 74 patients who were assessed to have a disease other than influenza at the case review committee should have been included in the efficacy analysis in accordance with the ITT principle. The PMDA's conclusion is considered to be supported by the expert advisors.

(2) Efficacy

Taking the investigation in the above "(1) Efficacy evaluation method" section into account, PMDA evaluated the efficacy of favipiravir using the FAS (PMDA FAS) for the primary efficacy analysis in the global phase III study (Study 312). As a result, the analysis of the primary endpoint in the PMDA FAS did not demonstrate non-inferiority of the favipiravir group to the oseltamivir phosphate group; the time to alleviation of influenza symptoms in the favipiravir group was statistically significantly longer than that in the oseltamivir phosphate group (hazard ratio [95% CI] 0.818 [0.707-0.948]). PMDA has concluded that the efficacy of favipiravir for the treatment of influenza virus infection was not demonstrated with robustness. The pyrexia duration (the secondary endpoint) in the favipiravir group was statistically significantly inferior to that in the oseltamivir phosphate group in both proposed FAS and PPS. The submitted data do not provide clear evidence demonstrating the clinical effect of favipiravir. Based on the study data available as of the date of the Expert Discussion, it has been therefore concluded that the efficacy of favipiravir for "treatment of influenza A or B virus infection," the proposed indication of favipiravir, has not been demonstrated.

The above conclusion of PMDA was supported by the expert advisors.

(3) Safety

1) Teratogenicity risk

PMDA considers as follows:

It is necessary to take ever stricter measures for the proper use of favipiravir because conventional precautions and measures for proper use of drugs with a teratogenicity risk are not sufficient for favipiravir. This is because "influenza A or B virus infection" (the proposed indication) is an acute disease affecting a fairly large number of people during the influenza season and because favipiravir would cause much concern about the teratogenicity risk in humans regarding the points below.

- Reproductive and developmental toxicity data suggest that favipiravir may cause delayed development of a human embryo or its death if it is administered to a woman at an early stage of pregnancy who may have a negative pregnancy test result.
- Favipiravir was found to have teratogenicity in all the animal species (4 species) evaluated in embryo-fetal studies.
- The favipiravir exposure at which the teratogenicity was observed in animals is comparable to that in humans at the proposed dose.

Accordingly, favipiravir must be contraindicated for use in pregnant women or women who may possibly be pregnant. Women of childbearing potential should undergo a pregnancy test before use of favipiravir and should be informed of the contraception period after the treatment when favipiravir is prescribed eventually. Furthermore, men should also use contraception for 7 days. The patients should be thoroughly informed of the above matters and consent should be obtained from them in writing.

Even if, however, such measures for the proper use of favipiravir are taken to avoid the teratogenicity risk, it would be impossible to prevent the use of favipiravir in pregnant women and the occurrence of pregnancy after use of favipiravir during the season of influenza. Actually, pregnancy occurred in the clinical studies. In consideration of the above, cases in which pregnancy is recognized or occurs after use of favipiravir are highly likely, and PMDA therefore has concluded that the teratogenicity risk is a highly significant safety concern of favipiravir.

The above conclusion of PMDA was supported by the expert advisors, and additional comments were presented as follows:

- The high risk of teratogenicity is unacceptable because therapeutic drugs against currently prevalent influenza viruses are available.
- It is considerably difficult to thoroughly advise caution in clinical settings. In addition, the patient may possibly give a part of the prescribed drug to his/her family members or acquaintances, and therefore it is extremely difficult to avoid the teratogenicity risk of favipiravir.
- Even if precautions are provided in the package insert, it is practically difficult to clearly identify women of childbearing potential or men of high fertility potential in routine clinical practice.

The following comments on patients for which favipiravir is indicated in consideration of the teratogenicity risk were raised from the expert advisors at the Expert Discussion:

- From the viewpoint of avoidance of the teratogenicity risk, it may be necessary to take the following measures: (a) allowing the use of favipiravir only in postmenopausal women (or age should be indicated specifically, for instance, aged ≥50 years) and/or (b) imposing

restrictions on the use of favipiravir in men of high fertility potential (for instance, aged 15 to 65 years). Even if, however, such restriction measures were in place, the patient may possibly give a part of the prescribed drug to his/her family members or acquaintances, and therefore it is difficult to avoid the teratogenicity risk of favipiravir; countermeasures are necessary.

- Although favipiravir is contraindicated for pregnant women and women who may possibly be pregnant, it is difficult to apply the contraindication practically, because (a) it would be difficult to explain the precautions about the teratogenicity risk in clinical settings; (b) it is difficult to perform a pregnancy test in clinical settings; (c) the pregnancy test is not covered by health insurance, leading to mixed billing; and (d) some women may try to "deny the pregnancy" even if they are pregnant.
- Development of favipiravir itself may be acceptable, but women should not use favipiravir in clinical settings because of its teratogenicity risk.
- It may be possible that the use of favipiravir is limited to patients hospitalized with severe influenza infection because the use can be sufficiently controlled in the hospital or the limitation can be applied to the use in high-risk or elderly patients. At present, no safety data in such patient populations are available, and thus the investigation is required.
- A thorough management system such as the Thalidomide Education and Risk Management System (TERMS) for thalidomide may be necessary, but it is not practical because it should be noted that the burden on the hospital operating the system is considerably large.

PMDA considers as follows:
The patients for which favipiravir is indicated should be clearly restricted, because pregnancy occurred in the phase III global study of favipiravir in patients with seasonal influenza virus infection (Study 312) though the contraception requirements were in place; and it is practically difficult to take measures thoroughly for avoidance of the teratogenicity risk in routine clinical practice. In addition, even if the intended patients are restricted, the patients may give the unused drugs to other persons. To ensure that the patients can recognize the risk of favipiravir sufficiently and use it properly, a reliable management system should be further considered.

2) Safety issues other than the teratogenicity risk
Concerning the following points, PMDA has concluded that the investigations should be implemented immediately, and caution should be thoroughly advised until a certain amount of safety information is collected.

- In the phase III global study (Study 312), the incidence of blood uric acid increased in the favipiravir group was higher than that in the oseltamivir phosphate group. Caution, therefore, should be advised.
- No sufficient investigation has been made on many drugs with which favipiravir may interact when used concomitantly (AO inhibitors, AO substrate drugs, CYP2C8 substrate drugs), and thus the safety of the concomitant use remains unknown.
- Although it cannot be ruled out that hepatic impairment may increase plasma favipiravir concentrations, no pharmacokinetics studies in patients with hepatic impairment have been conducted at present, and thus it is unknown to what extent hepatic impairment in each severity would change plasma favipiravir concentrations.
- In light of data from juvenile animal toxicity studies, favipiravir should not be recommended for pediatric use at present.
- Experience with use of favipiravir in high-risk patients is extremely limited.

The above conclusion of PMDA was supported by the expert advisors.

(4) Risk and benefit of favipiravir in patients with seasonal influenza virus infection
PMDA considers as follows:

Presently, the benefit of favipiravir in patients with seasonal influenza virus infection has not been demonstrated, while the teratogenicity risk of favipiravir has raised considerable concern about its use, and it is difficult to avoid the risk in daily clinical practices for influenza virus infection.

PMDA has therefore concluded that favipiravir cannot be approved presently as a therapeutic drug indicated for the treatment of "influenza A or B virus infection," as proposed.

The above conclusion of PMDA was supported by the expert advisors.

III. PMDA's evaluation in view of the comments raised in the Expert Discussion (first round)

The data submitted before the Expert Discussion (first round) did not demonstrate the efficacy of favipiravir for the treatment of seasonal influenza virus infection, and thus PMDA has concluded that favipiravir cannot be approved with the proposed indication of "treatment of influenza A or B virus infection."

Favipiravir is, however, designated for priority review, because there is significance in making this drug available in clinical practice as early as possible from the viewpoint of crisis management due to its new mechanism of action. PMDA asked the applicant to investigate the following points immediately and to take relevant actions.

- To continue developing favipiravir as a drug potentially indicated for seasonal influenza virus infection, the efficacy and safety of favipiravir should be confirmed by conducting a supplemental clinical study. Based on the data from the placebo controlled phase II study (Study US204) currently ongoing in the US, the dosage regimen of favipiravir should be re-investigated, and then the design and treatment population of the supplemental clinical study should be thoroughly examined to conduct the study.

IV. Corrections in the Review Report (1)

The applicant informed PMDA that the data included in the Review Report (1) needed to be corrected since the responses to the inquiries from PMDA were found to have many errors and matters that need supplemental information, although the interpretation of the results would not be affected by these corrections. The applicant's responses had been submitted after the end of the Expert Discussion.

PMDA ascertained whether the corrections presented by the applicant would affect the previous review. As a result, the presented corrections were confirmed to be related to matters that need supplemental information and to errors due to mistakes in preparation of the data set for analysis, not affecting the previous evaluation of favipiravir. The above corrections are accepted, and the Review Report (1) will be corrected (due to a wide variety of corrections, the Review Report (1) has been revised already).

PMDA also instructed the applicant to submit the data for product application and the supplemental data after thoroughly inspecting the data, and the applicant accepted it.

V. Outline of Submissions after the Expert Discussion (first round) and the Subsequent Review

After the Expert Discussion (first round), additional data became available from the US placebo-controlled phase II study in patients with seasonal influenza virus infection (Study US204). In this study, the pairwise comparison of the time to alleviation of major influenza symptoms, which

was the primary efficacy endpoint, between the favipiravir group and placebo group did not show a statistically significant difference. However, the additional analysis in Study US204 suggested the efficacy in the patients who received favipiravir at a high-dose and in whom C_{min} on Day 2 was ≥20 μg/mL. MediVector Inc. in the US conducted the supplemental phase I/II study (Study US213) to investigate the dosage regiment of favipiravir. It was informed that the data from Study US213 suggested the efficacy of favipiravir in comparison with the placebo. In a recent update on pandemic influenza, the first human case of infection with avian influenza A (H7N9) virus was reported in March 2013, and this virus strain was reported to be less sensitive to the existing neuraminidase inhibitors. Under such circumstances, pandemic influenza crisis management requires urgent actions. Following its consultation with the MHLW, PMDA sent the applicant inquiries about the potential of favipiravir used for the crisis management and its efficacy, and implemented the additional review.

The applicant additionally submitted the report on the current status of development of favipiravir in the US as well as data from 3 studies in Japan and foreign countries including the phase I study (Study JP118), which was additionally conducted in Japan to develop favipiravir at the high-dose. A summary of the submitted data is as shown below.

Summary of the additionally submitted data

(1) US phase II study (Study US204) (studied period, [redacted] to [redacted])

A placebo controlled, randomized, double-blind parallel-group comparative study was conducted in the US to investigate the efficacy and safety of favipiravir in patients with influenza virus infection (number of patients enrolled; 134 subjects in the favipiravir low-dose group, 195 subjects in the favipiravir high-dose group, 201 subjects in the placebo group).

Favipiravir was orally administered for 5 days in accordance with the following dosage regimen: in the favipiravir low-dose group, 1000 mg BID on Day 1 and then 400 mg BID from Day 2 to Day 5; in the favipiravir high-dose group,[200] 1200 mg BID on Day 1 and then 800 mg BID from Day 2 to Day 5.In the placebo group, placebo was administered BID from Day 1 to Day 5.

Of 530 randomized subjects, 518 subjects who received the study drug were included in the safety analysis, and 333 subjects excluding those who tested negative for influenza A or B virus by PCR or viral culture testing on Day 1 (88 subjects in the favipiravir low-dose group, 121 subjects in the favipiravir high-dose group, 124 subjects in the placebo group) were included in the ITTI, which was use for the efficacy analysis.

The median values (95% CIs) of the time to alleviation of major influenza symptoms,[201] the primary efficacy endpoint, were 100.4 (82.4, 119.8) hours in the favipiravir low-dose group, 86.5 (79.2, 102.1) hours in the favipiravir high-dose group, and 91.9 (70.3, 105.4) hours in the placebo group. The pairwise comparisons of the favipiravir low-dose group and favipiravir high-dose group with the placebo group did not show a statistically significant difference ($P > 0.05$, Gehan-Wilcoxon test, test multiplicity adjusted by step-down procedure).

Adverse events occurred in 47 of 132 subjects (35.6%) in the favipiravir low-dose group, in 65 of 189 subjects (34.4%) in the favipiravir high-dose group, and in 79 of 197 subjects (40.1%) in the placebo group. The adverse drug reactions occurred in 25 of 132 subjects (18.9%) in the favipiravir low-dose group, in 37 of 189 subjects (19.6%) in the favipiravir high-dose group, and

[200] The dosage regimen for the US subjects leading to the plasma concentration profile comparable to that after treatment with favipiravir according to the proposed dosage regimen in Japan

[201] Time to "alleviate" all of the 6 major influenza symptoms (cough, pharyngeal pain, headache, nasal congestion, myalgia, and general malaise) (when all scores decrease to ≤ "1") and to reach the condition in which the body temperature has been maintained at ≤38°C in patients aged ≥20 years to <65 years or at ≤37.8°C in patients aged ≥65 years for ≥21.5 hours, from the start of the study treatment

in 41 of 197 subjects (20.8%) in the placebo group.

Adverse events reported by ≥5% of subjects in at least one of the groups included diarrhoea (2.3% [3 of 132 subjects] in the favipiravir low-dose group, 4.8% [9 of 189 subjects] in the favipiravir high-dose group, 5.1% [10 of 197 subjects] in the placebo group). No deaths occurred. Serious adverse events occurred in 3 subjects (2 subjects in the favipiravir low-dose group [vulval abscess, hepatic encephalopathy] and 1 subject in the placebo group [bronchial obstruction]), but all of their causal relationships with the study drug were ruled out. Eighteen adverse events leading to treatment discontinuation occurred in 8 subjects (4 events in 3 subjects in the favipiravir low-dose group [cough, urticaria, pruritus, rash], 9 events in 3 subjects in the favipiravir high-dose group [sinusitis, decreased appetite, headache, bronchial hyperreactivity, cough, diarrhoea, nausea, vomiting, and proteinuria], and 5 events in 2 subjects in the placebo group [influenza, headache, vertigo, palpitations, blood uric acid increased]). Except for 7 events in 6 subjects (4 events in 3 subjects in the favipiravir low-dose group [cough, urticaria, pruritus, rash], 1 event in 1 subject in the favipiravir high-dose group [proteinuria], 2 events in 2 subjects in the placebo group [influenza, blood uric acid increased]), all of their causal relationships with the study drug were ruled out.

(2) US phase I/II study (Study US213)[202,203]

A placebo controlled, randomized, double-blind parallel-group comparative study was conducted in the US to investigate the safety and pharmacokinetics of favipiravir in healthy adult subjects and patients with influenza virus infection. This clinical study consisted of 2 parts: Part A[204] was intended to investigate the safety and pharmacokinetics of favipiravir administered to healthy adult subjects in accordance with the new dosage regimens;[205] and Part B was intended to investigate the safety and pharmacokinetics of favipiravir administered to patients with influenza virus infection in accordance with the new dosage regimens based on the results from Part A[206] (184 subjects in the favipiravir BID group, 182 subjects in the favipiravir TID group, 184 subjects in the placebo group [92 subjects each in the placebo BID group, in the placebo TID group]).

The dosage regimen for Part B was as follows:

BID group:	Favipiravir or placebo was orally administered at 1800 mg twice daily on Day 1, followed by 800 mg orally administered twice daily from Day 2 to Day 5 (1800 mg/800 mg BID)
TID group:	Favipiravir or placebo was orally administered at 2400 mg for the first dose on Day 1, and at 600 mg for the second and third doses on Day 1, followed by 600 mg orally administered 3 times daily from Day 2 to Day 5 (2400 mg/600 mg TID)

Of the subjects included in Part B, 271 subjects (101 in the favipiravir BID group, 82 in the favipiravir TID group, 88 in the placebo group) were included in the ITTI, which served as the efficacy analysis set.

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[202] From the abstract and slides for presentation at the influenza international conference (ISIRV Options for the Control of Influenza VIII, September 5-10, 2013, Cape Town, Republic of South Africa) held by the International Society for Influenza and Other Respiratory Virus Diseases (ISIRV)

[203] From the abstract and slides for presentation at the 53rd Interscience Conference on Antimicrobial Agents and Chemotherapy (ICAAC; September 10-13, 2013, Denver, US)

[204] Dosage regimen: [Regimen 1] Favipiravir or placebo was orally administered at 1200 mg 3 times daily on Day 1, followed by 600 mg orally administered 3 times daily from Day 2 to Day 5; [Regimen 2] Favipiravir or placebo was orally administered at 2400 mg for the first dose on Day 1, and at 600 mg for the second and third doses on Day 1, followed by 600 mg orally administered 3 times daily from Day 2 to Day 5

[205] It was originally planned to investigate what dosage regimen would lead to C_{min} >20 μg/mL on Day 2.

[206] The TID dosage regimen expected to lead to C_{min} >20 μg/mL on Day 2 was set based on the results from Part A, and the BID dosage regimen expected to lead to C_{min} >20 μg/mL on Day 2 was set based on simulation results using the data from the US high-dose phase I study (Study US103c).

The time to alleviation of major influenza symptoms[207] (median), the primary efficacy endpoint, was 82.3 hours in the favipiravir BID group and 97.3 hours in the placebo group. Their pairwise comparison showed a statistically significant difference (P = 0.010, Gehan-Wilcoxon test). On the other hand, the pairwise comparison between the favipiravir TID group and placebo group did not show a significant difference (P = 0.414, Gehan-Wilcoxon test). The Kaplan-Meier curve of the time to alleviation of major influenza symptoms for each group is shown in the figure below.

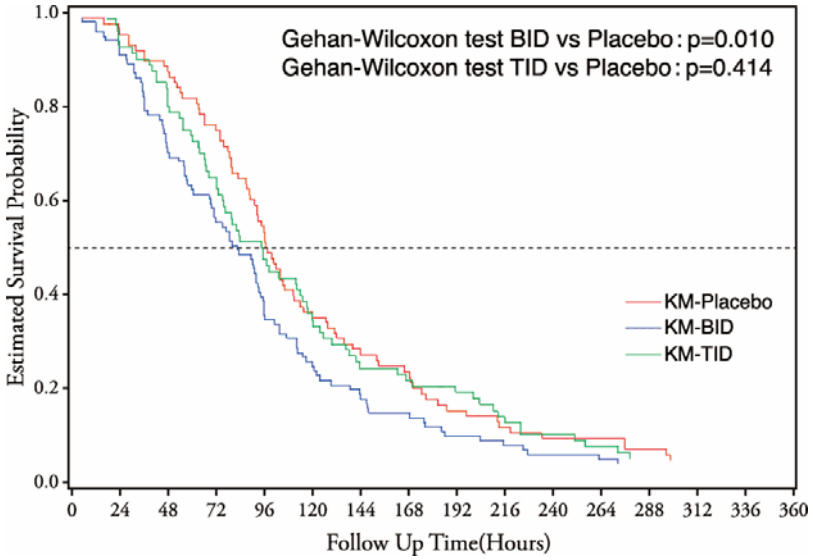

Figure. Time to alleviation of major 6 influenza symptoms and pyrexia (hours)

The median C_{min} on Day 2 exceeded 20 μg/mL in the favipiravir BID group but did not exceed 20 μg/mL in the favipiravir TID group.

Adverse events occurred in 67 of 550 subjects treated in Part B. All of the adverse events were mild to moderate, and their causal relationships with the study drug were ruled out. No serious adverse events occurred. Adverse events reported by ≥5 subjects included diarrhoea (10 subjects), headache (7 subjects), sinusitis (6 subjects), and epistaxis (5 subjects). The blood uric acid level increased, but returned to the baseline value immediately after the end of the treatment without any gout symptoms.

(3) Japanese phase I study (Study JP118) ([redacted] to [redacted])

A Japanese phase I study was conducted to investigate the pharmacokinetics, safety, and tolerability of favipiravir in healthy adult male subjects treated with the high-dose of favipiravir.

[207] Although the definition has not been clearly described, 6 major influenza symptoms (cough, pharyngeal pain, headache, nasal congestion, myalgia, general malaise) and duration of pyrexia were used.

The dosage regimen was as follows:

(a) Group 1: BID group*
Cohort 1
Favipiravir was orally administered at 1600 mg twice daily on Day 1, followed by 400 mg orally administered twice daily from Day 2 to Day 6 (1600/400 mg BID)
Cohort 2
Favipiravir was orally administered at 1200 mg twice daily on Day 1, followed by 600 mg orally administered twice daily from Day 2 to Day 6 (1200/600 mg BID)

(b) Group 2: TID group*
Cohort 3
Favipiravir was orally administered at 1600 mg for the first dose on Day 1, and at 400 mg for the second and third doses on Day 1, followed by 400 mg 3 times daily from Day 2 to Day 6 (1600/400 mg TID)
Cohort 4
Favipiravir was orally administered at 2000 mg for the first dose on Day 1, and at 400 mg for the second and third doses on Day 1, followed by 400 mg 3 times daily from Day 2 to Day 6 (2000/400 mg TID)

*Only 1 dose on Day 6 in all dose groups

Pharmacokinetic parameters in the BID groups (1600/400 mg BID group, 1200/600 mg BID group) and TID groups (1600/400 mg TID group, 2000/400 mg TID group) are as shown in the table below. The C_{max} and AUC values of favipiravir in the 1600/400 mg BID group, 1600/400 mg TID group, and 2000/400 mg TID group decreased after the multiple doses compared with those on Day 1 (after the first dose), but those in the 1200/600 mg BID group increased after the multiple doses. In any dose group, CL/F decreased after the multiple doses.

Table. Pharmacokinetic parameters in the subjects receiving favipiravir BID

	1600/400 mg BID				1200/600 mg BID			
	Favipiravir		M1		Favipiravir		M1	
	Day 1 (1600 mg)	Day 6 (400 mg)	Day 1 (1600 mg)	Day 6 (400 mg)	Day 1 (1200 mg)	Day 6 (600 mg)	Day 1 (1200 mg)	Day 6 (600 mg)
Number of subjects evaluated	6	6	6	6	6	6	6	6
C_{max}[a)] (μg/mL)	59.43 (15.1)	30.56 (13.4)	15.34 (28.4)	2.37 (22.3)	47.86 (28.9)	61.50 (41.4)	14.40 (16.4)	2.73 (20.3)
t_{max}[b)] (hr)	1.0 (0.5, 1.5)	1.0 (0.5, 2)	1.3 (0.75, 1.5)	1.3 (0.75, 4)	0.9 (0.5, 1.5)	0.8 (0.5, 1.5)	1.0 (0.75, 1.5)	1.0 (1, 1.5)
AUC[a),d)] (μg·hr/mL)	397.79 (30.3)	193.69 (27.1)	86.08 (11.1)	19.24 (14.6)	229.65 (50.1)	470.53 (54.8)	71.64 (10.3)	26.39 (9.9)
$t_{1/2}$[c)] (hr)	4.6 (1.2)	4.5 (0.2)	4.1 (0.8)	6.1 (0.5)	3.4 (1.5)	5.8 (2.0)	3.0 (0.6)	11.3 (6.9)
CL/F[c)] (L/hr)	4.16 (1.12)	1.69 (0.53)	-	-	5.88 (3.03)	1.04 (0.80)	-	-
Vd/F[c)] (L)	25.91 (2.69)	10.98 (3.34)	-	-	23.18 (2.27)	7.33 (4.38)	-	-

τ = 12 hours
a) Geometric mean (CV%), b) Median (minimum, maximum), c) Mean (SD), d) $AUC_{0-\infty}$ for Day 1 and AUC_{τ} for Day 6

Table. Pharmacokinetic parameters in the subjects receiving favipiravir TID

	1600/400 mg TID				2000/400 mg TID			
	Favipiravir		M1		Favipiravir		M1	
	Day 1 (1600 mg)	Day 6 (400 mg)	Day 1 (1600 mg)	Day 6 (400 mg)	Day 1 (2000 mg)	Day 6 (400 mg)	Day 1 (2000 mg)	Day 6 (400 mg)
Number of subjects evaluated	6	6	6	6	6	6	6	6
C_{max}[a)] (μg/mL)	63.00 (16.4)	52.89 (34.3)	16.92 (15.5)	2.44 (17.2)	84.80 (21.0)	52.13 (39.5)	18.20 (16.7)	2.53 (14.9)
t_{max}[b)] (hr)	0.8 (0.5, 1.5)	0.9 (0.5, 1)	1.0 (0.75, 2)	0.9 (0.5, 1)	1.0 (0.75, 2)	0.9 (0.5, 1.5)	1.3 (1, 1.5)	0.9 (0.75, 2)
AUC[a),d)] (μg·hr/mL)	344.85 (42.5)	238.27 (41.5)	80.05 (15.9)	12.70 (16.4)	628.05 (20.5)	248.27 (45.5)	81.29 (9.9)	13.55 (15.7)
$t_{1/2}$[c)] (hr)	3.9 (1.4)	5.4 (1.7)	2.8 (0.3)	9.4 (4.8)	5.4 (1.1)	5.7 (3.4)	2.7 (0.4)	12.5 (14.4)
CL/F[c)] (L/hr)	4.89 (1.55)	0.79 (0.44)	-	-	3.25 (0.74)	0.80 (0.52)	-	-
Vd/F[c)] (L)	25.02 (1.83)	5.27 (1.72)	-	-	24.36 (1.63)	5.15 (2.36)	-	-

τ = 6 hours

a) Geometric mean (CV%), b) Median (minimum, maximum), c) Mean (SD), d) $AUC_{0-\infty}$ for Day 1 and AUC_{τ} for Day 6

Adverse events occurred in 4 of 6 subjects (5 events, 66.7%) in the 1600/400 mg BID group, in 6 of 6 subjects (9 events, 100%) in the 1200/600 mg BID group, in 6 of 6 subjects (8 events, 100%) in the 1600/400 mg TID group, in 4 of 6 subjects (5 events, 66.7%) in the 2000/400 mg TID group, and in 1 of 8 subjects (1 event, 12.5%) in the placebo group. Adverse drug reactions occurred in 4 of 6 subjects (5 events, 66.7%) in the 1600/400 mg BID group, in 6 of 6 subjects (9 events, 100%) in the 1200/600 mg BID group, in 6 of 6 subjects (7 events, 100%) in the 1600/400 mg TID group, in 4 of 6 subjects (4 events, 66.7%) in the 2000/400 mg TID group, and in 1 of 8 subjects (1 event, 12.5%) in the placebo group. Neither deaths nor serious adverse events occurred.

Outline of the additional review by PMDA

PMDA asked the applicant to explain the development strategy of favipiravir, taking account of the additionally submitted clinical data as well as development status of favipiravir and circumstances related to the influenza infection after the Expert Discussion (first round).

The applicant explained as follows:

- In Study US204, pairwise comparison of the favipiravir group (low-dose group, high-dose group) with the placebo group did not show a statistically significant difference.
- [redacted].
- Since the first human case of infection with avian influenza A (H7N9) virus was reported in March 2013 by the WHO,[208] the infection cases have been sporadically reported.[209] It is said that even patients who survived avian influenza A (H7N9) virus infection had severe influenza symptoms, frequently requiring management in the intensive care unit or being complicated by acute respiratory distress syndrome.[210] Furthermore, the basic research report has indicated that humans do not have immunity against avian influenza type A (H7N9) virus, and the strain of avian influenza A (H7N9) virus is less sensitive to the existing neuraminidase inhibitors in animal experiments.[211] In addition, the mortality in human cases of avian influenza A (H7N9) virus infection tends to be higher than that of seasonal influenza virus infection, and infection cases potentially caused by direct transmission from humans to humans have been also

[208] WHO Global Alert and Response (GAR). H7N9 avian influenza human infections in China (April 1, 2013) (http://www.who.int/csr/don/2013_04_01/en/index.html)

[209] WHO Global Alert and Response (GAR). Human infection with avian influenza A(H7N9) virus – update (November 6, 2013) (http://www.who.int/csr/don/2013_11_06/en/)

[210] Issued by the Influenza Committee, the Japanese Association for Infectious Diseases. The recommendations from the Japanese Association for Infectious Diseases, "Actions against avian influenza A (H7N9), tentative version" dated May 17, 2013

[211] Watanabe T et al., *Nature*. 2013;501:551-555.

reported.[212]

- Favipiravir has a mechanism of action different from those of the existing influenza antiviral drugs. Literatures of non-clinical studies reported that a statistically significant difference was found in survival on Day 21 in mice infected with human-derived oseltamivir-resistant influenza A (H5N1) virus between favipiravir and the control drug;[213] and the lung virus load in animals infected with avian influenza A (H7N9) virus was significantly lower in the favipiravir group than in the control drug group.[211]

Based on the above, favipiravir is expected to be effective for the treatment of infection with influenza virus strains which are resistant to the existing influenza antiviral drugs such as oseltamivir phosphate and zanamivir hydrate through a new mechanism of action. From a viewpoint of crisis management, favipiravir can be positioned as "a drug prepared for spreading of infection with highly pathogenic influenza virus strains which are resistant to the existing influenza antiviral drugs such as oseltamivir phosphate and zanamivir hydrate." In light of the adverse reactions to favipiravir such as teratogenicity, the applicant understand the necessity of strict distribution management and thorough safety measures in order to prevent favipiravir from being used for treatment of seasonal influenza virus infection.

PMDA asked the applicant to discuss the case where Japanese subjects receive favipiravir in accordance with the dosage regimen equivalent to those in the US phase I/II study (Study US213) which presented efficacy.

The applicant responded as follows:
In Part B in Study US213, the dosage regimen of 1800 mg/800 mg BID presented efficacy. The plasma concentration profiles with 2 sets of the dosage regimen in the BID groups in Study JP118 (1600 mg/400 mg BID and 1200 mg/600 mg BID) are as shown in the figures below. In the 1600 mg/400 mg BID group, C_{min} decreased on Day 2. The data from the 1200 mg/600 mg BID group, however, suggested that this regimen was expected to maintain the plasma concentration without decreasing C_{min}. The estimated plasma concentration profile in the US subjects treated with favipiravir 1800 mg/800 mg[214] BID was compared with the estimated ones with 2 sets of the dosage regimen in the BID groups in Study JP118. As a result, in Japanese subjects treated with favipiravir 1600 mg BID on Day 1, the plasma concentration profile would be comparable to that in the US subjects on Day 1 (1800 mg BID).

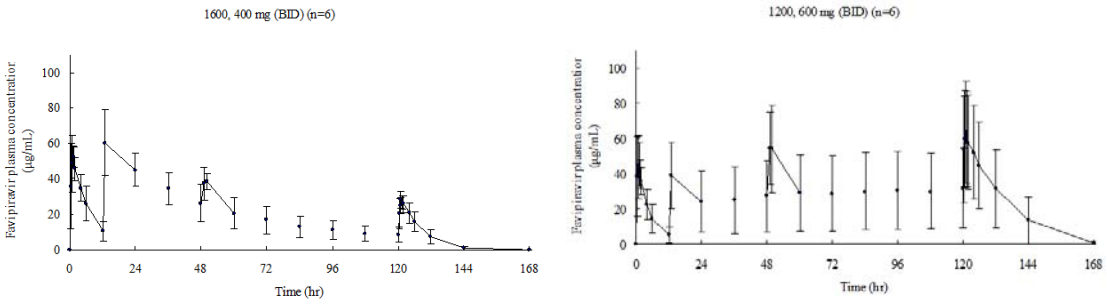

Figure. Plasma concentration profile of favipiravir (mean ± SD)

Based on the above investigation, although a clinical pharmacology study with the dosage regimen of favipiravir 1600 mg/600 mg BID in Japanese subjects has not been conducted, the

[212] Shi J, Xie J et al., Virus Infection in Shanghai. *PLos One.* 2013;8:e77651.
[213] Kiso M et al., *Proc Natl Acad Sci USA.* 2010;107(2):882-887.
[214] As the pharmacokinetic data of favipiravir 1800 mg/800 mg BID to the US subjects were not available, the plasma concentration profile was estimated based on the data of favipiravir 1600 mg/800 mg BID and 1800 mg/600 mg BID of 12 US subjects in the US high -dose phase I study (Study US103c).

plasma concentration profile in Japanese subjects with the above dosage regimen was estimated from the data in the BID groups in Study JP118[215] and compared with that in the US subjects treated with favipiravir 1800 mg/800 mg BID,[214] which presented the clinical efficacy in Study US213. As a result, the plasma concentration profile in Japanese subjects treated with favipiravir 1600 mg/600 mg BID was thought to be comparable to that in the US subjects treated with favipiravir 1800 mg/800 mg BID throughout the treatment period.

Based on the above, the applicant considersthat it should be it is justifiable to select the following dosage regimen: favipiravir should be orally administered at 1600 mg twice daily on Day 1, and at 600 mg twice daily from Day 2 to Day 5.

PMDA considers as follows:
Although no pharmacokinetic data from patients treated with the dosage regimen of favipiravir 1800 mg/800 mg BID, which demonstrated the efficacy in the US phase I/II study (Study US213), are available, the plasma favipiravir concentrations in the US subjects estimated from the plasma drug concentrations in the healthy adult US subjects were compared with the data from the Japanese phase I study in healthy adult Japanese subjects (Study JP118). Based on the comparison, the plasma concentrations in Japanese subjects treated with favipiravir 1600 mg/600 mg BID can be expected to be comparable to those in the US subjects. Since there were no particular safety issues in the US subjects, it is acceptable to select the dosage regimen of favipiravir 1600 mg/600 mg BID in Japanese subjects.

Also, favipiravir is expected to be effective in treating infection with influenza virus strains which are resistant to the existing influenza antiviral drugs such as oseltamivir phosphate and zanamivir hydrate, because it has a mechanism of action different from those of the existing drugs. PMDA has therefore concluded that favipiravir is positioned as “a drug as part of the preparedness for the spread of infection with a highly pathogenic influenza virus strain which is resistant to the existing influenza antiviral drugs such as oseltamivir phosphate and zanamivir hydrate,” the indication of favipiravir should be “treatement of highly pathogenic influenza virus infection (limited to the cases where the existing influenza antiviral drugs are ineffective or insufficiently effective).” Also, the conditions can be imposed that strict distribution management and thorough safety measures should be in place to prevent favipiravir from being used for seasonal influenza virus infection. Accordingly, favipiravir may be approved on the premise of development of crisis management plans against highly pathogenic influenza virus.

Furthermore, the dosage regimen in Japanese subjects discussed here (favipiravir 1600 mg/600 mg BID) lead to the favipiravir exposure higher than that after the treatment with the proposed dosage regimen, and thus the ratio of the resultant clinical exposure to the non-clinical exposure was reduced compared with that after the treatment with the proposed dosage regimen, as described in the “3.(i).B.(4) Safety pharmacology,” “3.(iii).A. Summary of the Submitted Data,” and “3.(iii).B. Outline of the review by PMDA” sections of the Review Report (1). It should be noted that the dosage regimen in question may increase the risks of teratogenicity suggested in the non-clinical studies and other safety issues.

In addition, no data have been obtained from the clinical study conducted to verify the efficacy of favipiravir administered to Japanese patients with influenza virus infection in accordance with the new dosage regimen. In consideration of this, the currently ongoing development targeting seasonal influenza infection should be continued to verify the efficacy and safety of favipiravir administered to Japanese patients with influenza virus infection in accordance with the new

[215] To incorporate the theory of the irreversible enzymatic inhibition into the 1-compartment model with the primary absorption process using data on the plasma concentration (17 subjects) obtained from Study JP103 and Study JP106, the MBI-PK Model was constructed by adding the enzymatic compartment (WinNonlin Ver.5.0.1).

dosage regimen.

Of the issues addressed in the above review, points to be particularly noted will be discussed at the Expert Discussion (second round).

Review Report (3)

January 21, 2014

I. Product Submitted for Registration

[Brand name]	Avigan Tablet 200 mg
[Non-proprietary name]	Favipiravir
[Applicant]	Toyama Chemical Co., Ltd.
[Date of application]	March 30, 2011

II. Content of the Review

The outline of the comments on the Review Report (2) from the Expert Discussion (Expert Discussion [second round]) and the subsequent review by the Pharmaceuticals and Medical Devices Agency (PMDA) is described in the following sections. The expert advisors selected for the Expert Discussion (first round) served as those for the Expert Discussion (second round). They were nominated based on their declarations etc. concerning the product submitted for registration, in accordance with the provisions of the "Rules for Convening Expert Discussions etc. by the Pharmaceuticals and Medical Devices Agency" (PMDA Administration Rule No. 20-8 dated December 25, 2008).

Regarding the "V. Outline of Submissions after the Expert Discussion (first round) and the Subsequent Review" section of the Review Report (2), the following comments were raised by the expert advisors:

(1) Indication

PMDA has concluded that it is appropriate to select "treatment of highly pathogenic influenza virus infections (limited to patients in whom other influenza antiviral drugs are ineffective or not sufficiently effective)" as the indication of favipiravir.

The following comments on the above conclusion of PMDA were raised by the expert advisors:

- In the US phase II study (Study US204), the time to alleviation of major influenza symptoms, the primary efficacy endpoint, was compared pairwise between each of the favipiravir groups (1000 mg/400 mg BID and 1200 mg/800 mg BID) and the placebo group, but no statistically significant differences were found. In the US phase I/II study (Study US213), a statistically significant difference was found in pairwise comparison of the time to alleviation of major influenza symptoms, the primary efficacy endpoint, between the 1800 mg/800 mg BID group and the placebo group, but not between the 2400 mg/600 mg TID group and the placebo group, and the cause of such a discrepancy remains unknown. In consideration of the above results, it is difficult to conclude that the efficacy of favipiravir was demonstrated in the clinical studies. The use of a drug without documented efficacy in patients is in a life-threatening situation during a pandemic, therefore, not justified.
- The "Precautions for Indications" section in the package insert should include a clear statement that the efficacy of favipiravir for the treatment of seasonal influenza A or B virus infection has not been sufficiently demonstrated. In addition, it should be clearly stated in the package insert that no statistically significant differences were found in pairwise comparison between the 2400 mg/600 mg TID group and the placebo group in the US phase I/II study (Study US213).
- The efficacy of favipiravir for the treatment of highly pathogenic influenza virus infection was only supported by the non-clinical studies using avian influenza A (H5N1) and A (H7N9) virus strains. It should be noted that the efficacy in humans has not been investigated.

- The term "highly pathogenic" is generally used for avian influenza virus, meaning that the virus strain is highly pathogenic in birds, and thus the current description may cause misunderstanding. It is necessary to explain in the "Indication" section that the indication for favipiravir is the treatment of infection with influenza that is "highly pathogenic" in humans.
- The indication recommended by PMDA may cause confusion that the drug is intended to be used only against avian influenza A (H5N1) and A (H7N9) virus infections. With the new mechanism of action, however, favipiravir is expected to be effective when used concomitantly with an approved influenza antiviral drug and to exert a potent activity to inhibit viral replication, and thus it will be used to improve the prognosis in severe cases of influenza virus infection which currently have difficulty in lifesaving. It is appropriate to select "treatment of severe influenza virus infection and influenza virus infection in high-risk patients potentially resulting in severe conditions" as the indication of favipiravir.

Taking account of the above comments from the expert advisors, PMDA considers as follows:
According to the data submitted as of now, the efficacy of favipiravir for the treatment of avian influenza A (H5N1) and A (H7N9) virus infections was only investigated in non-clinical studies, and the efficacy against seasonal influenza A or B virus infection has not been sufficiently demonstrated in the Japanese and non-Japanese clinical studies. On the other hand, it may be meaningful to make favipiravir available for cases where efficacy can be expected in light of the recent outbreaks of influenza infection, in which a highly pathogenic influenza virus infection is prevalent, and some virus strains have acquired partial- or full-resistance to approved influenza antiviral drugs.

To approve favipiravir at the current stage, the following conditions should be imposed to the approval in consideration that: (1) the efficacy of favipiravir for the treatment of seasonal influenza virus infection has not been sufficiently demonstrated; (2) favipiravir has the risk of teratogenicity, etc.; and (3) the proposed dosage and administration has been selected mainly based on the foreign clinical study data while the dosage regimen have not been studied in Japan.

- Conduct a pharmacokinetic study in accordance with the approved dosage and administration in Japan, and after its completion, and submit the study data and analysis results promptly.
- Conduct a clinical study of favipiravir in patients with seasonal influenza virus infection to verify the efficacy and confirm the safety, and after its completion, submit the study data and analysis results promptly.
- Establish a strict distribution management system and take thorough safety measures in order to ensure that favipiravir is not used in patients with seasonal influenza virus infection.
- Take strict and proper measures in order to ensure that favipiravir is not administered to patients unless each individual patient, who is judged to be eligible for its use, or his/her family member is informed of the efficacy and risk of favipiravir in writing and their written informed consent is obtained prior to the start of treatment.

Taking into account a comment that the term "highly pathogenic" in the "Indication" section is generally used for avian influenza and such use of the term may lead to a misunderstanding, it is appropriate to change the proposed indication of favipiravir to "treatment of novel or re-emerging pandemic influenza virus infection (limited to cases where other influenza antiviral drugs are ineffective or not sufficiently effective)" in accordance with the definitions[216] of "novel pandemic influenza" and "re-emerging pandemic influenza" in Article 6, Paragraph 7 of the Act

[216] Novel pandemic influenza is defined as influenza which is caused by a new virus strain that has acquired the ability to be transmitted from humans to humans and of which a rapid nation-wide spread could significantly threaten the life and health of people in Japan who have not acquired immunity against the concerned infection. Re-emerging pandemic influenza is defined as influenza which is designated by the Minister of Health, Labour and Welfare to be the one which caused a pandemic in the past and had not since been circulated among people for a long time and of which a rapid nation-wide spread could significantly threaten the life and health of people in Japan because most of the people have not acquired immunity against the concerned infection.

on Prevention of Infectious Diseases and Medical Care for Patients Suffering Infectious Diseases (Act No. 114 of 1998).

PMDA instructed the applicant to take actions on the above matters, and the applicant took appropriate actions accordingly.

(2) Others

The applicant additionally submitted the data from the long-term stability studies of the drug substance and drug product, toxicity studies (1-week and 2-week repeated oral dose toxicity studies in juvenile dogs and genotoxicity studies of the impurities in the drug substance), clinical pharmacology studies (semen-distribution study in foreign healthy male adults [Study US107], phase I multiple-dose study in foreign healthy adults [Study US103c], and drug-drug interaction studies [6 studies]). The summary of the data submitted additionally and outline of the review by PMDA are presented in the following sections.

1) Retest period of the drug substance and shelf life of the drug product

For the drug substance, the 60-month long-term study data were submitted, and based on the study data, a retest period of 5 years has been proposed. For the drug product, the 48-month long-term study data were submitted, and based on the study data and in accordance with the "Guideline on Evaluation of Stability Data" (PFSB/ELD Notification No. 0603004 dated June 3, 2003), a shelf-life of 5 years has been proposed.

PMDA confirmed the submitted study data, and accepted the above.

2) Toxicity studies

(a) Genotoxicity evaluation of impurity substance Impurity J (Reference data, CTD 4.2.3.7.6.4 to 6)

Impurity J was found in the drug substance manufactured through the proposed manufacturing process at the maximum of [redacted] ppm, and the bacterial reverse mutation assay produced a positive result. To investigate the genotoxicity risk of Impurity J in the body, accordingly, the gene mutation assay of Impurity J in Muta™ mice (the maximum dose to be evaluated, 50 mg/kg/day) and bone-marrow micronucleus test in the 2-week repeat-dose oral toxicity study of Impurity J in mice (100 mg/kg/day, the maximum dose able to be given for 2 weeks) were conducted. None of these studies suggested genotoxicity.

The applicant considers that Impurity J has a low genotoxicity risk in clinical use, because the maximum daily intake of Impurity J at the clinical dose of favipiravir is [redacted] mg/kg (Day 1, 1600 mg BID), while the genotoxicity was not observed at a dose up to 50 mg/kg/day in the gene mutation assay in Muta™ mice.

PMDA accepted the response of the applicant.

(b) One- and two-week repeated oral dose toxicity study in juvenile dogs (Reference data, CTD 4.2.3.7.7.25)

In the 1-month repeated oral dose toxicity study in juvenile dogs (4.2.3.7.7.17) of which data were submitted in the initial application, many deaths occurred at doses of 60 mg/kg/day and 100 mg/kg/day from Day 13 and thereafter, while the treatment duration of favipiravir is 5 days. Taking the facts into account, this study was conducted to evaluate the toxicity of the repeated oral doses given for a shorter period than the above 1-month study in juvenile dogs.

Favipiravir was orally administered to male juvenile beagle dogs (8 weeks of age) at doses of 0 (gelatin capsules), 60, 100, or 160 mg/kg/day BID for 1 week. In addition, favipiravir was orally administered at doses of 0 (gelatin capsules), 60, or 100 mg/kg/day BID for 2 weeks. Some of the

animals treated with favipiravir at 100 mg/kg/day for 2 weeks were checked for the reversibility of toxicological signs after the 2-week recovery period (recovery group).

No deaths occurred in this study.

Findings in the 1-week repeated dose study included increased Na and Cl in the ≥60 mg/kg/day groups, a trend toward a decrease in food consumption and increased BUN in the ≥100 mg/kg/day groups, and a trend toward a decrease in body weight gain, increased ALP, decreased total protein, and decreased bone marrow nucleated cell count in the 160 mg/kg/day group.

Findings in the 2-week repeated dose study included a trend toward a decrease in body weight gain, increased white blood cell count, neutrophil count, BUN, Na and AST as well as decreased bone marrow nucleated cell count in the ≥60 mg/kg/day groups. Findings in the 100 mg/kg/day group included yellow fur and limbs, a decreasing trend of food consumption, cough (only 1 animal), and increased ALT and Cl as well as decreased triglycerides and total cholesterol. Findings at the end of the treatment (3 animals) included localized necrosis of hepatocytes in 1 animal and dispersed red to dark red dots in the anterior and posterior lobes in both lungs associated with mild bronchopneumonia in 1 animal. In the recovery group (3 animals), in 1 animal which showed cough during the treatment period, wheezing was observed from Day 3 of the recovery period but disappeared on Day 7, and slight bronchitis was observed after the end of the recovery period. Except for decreased bone marrow nucleated cell count and bronchitis as well as yellow fur and limbs, all of the findings observed at the end of the treatment resolved, demonstrating their reversibility.

The applicant considered that bronchitis and bronchopneumonia observed in this study were not attributable to favipiravir, although none of the control groups (4 animals) in this study showed such signs, because the incidence (2 of 6 animals) and severity (slight or mild) of these findings were comparable to those of similar findings in the following studies included in the initial application: In the repeated oral dose toxicity study in juvenile dogs (4.2.3.7.7.19), 3 of 7 animals in the control group showed bronchitis, and in the 1-month repeated oral dose toxicity study in juvenile dogs (4.2.3.7.7.17), localized inflammatory cell infiltration in the lungs was observed in 4 of 6 males and 3 of 6 females in the control group.

The applicant explained the data from this study as follows:
It is unlikely that serious adverse events are caused by the favipiravir treatment in pediatric patients for 5 days at the dose level which results in the exposure equivalent to that at the recommended dose in adults, based on the following findings: (1) the data from the repeated dose toxicity studies in juvenile dogs submitted in the initial application and the data from this study both indicated that the toxicity in juvenile dogs was exacerbated with the increasing treatment period; (2) in the 1-month repeated oral dose toxicity study (4.2.3.7.7.17) whose data were submitted in the initial application, deaths occurred in the ≥60 mg/kg/day groups, while in this study, no deaths occurred in animals treated with favipiravir at doses up to 100 mg/kg/day for 2 weeks or at doses up to 160 mg/kg/day for 1 week; (3) the toxicological findings observed in animals treated for 2 weeks in this study were mostly reversible; and (4) the estimated exposure to favipiravir in juvenile dogs in the 100 mg/kg/day group in this study (estimated AUCs on the day of the last dose, 2067 to 2217 μg·hr/mL[217]) was presumed to exceed the estimated clinical exposure in adults (maximum daily AUC, 1184 μg·hr/mL[218]). Favipiravir, however, has not been used in pediatric patients, and its safety in such patients has not been established. The use of favipiravir in pediatric patients, etc., therefore, is not considered desirable.

[217] Calculated based on AUC at the dose of 60 mg/kg/day in Study SBL063-035 (4.2.3.7.7.19).
[218] Geometric mean of daily AUC on Day 2 when it is estimated to reach the maximum according to the MBI-PK model constructed based on data from Study JP118

PMDA considers as follows:
If bronchitis and bronchopneumonia observed in this study are attributable to favipiravir, this drug may exacerbate the respiratory symptoms in patients with influenza virus infection, for whom it is indicated. Therefore, it is desirable for the applicant to re-examine tissue samples isolated from the respiratory organs of the animals used in this study histopathologically and collect additional supporting data for assessment of the relationship of favipiravir with bronchitis or bronchopneumonia.

3) Clinical pharmacology studies

(a) Semen-distribution study in foreign healthy male adults (Reference CTD 5.3.4.1.3, Study US107, [redacted] to [redacted])

Favipiravir was orally administered to foreign healthy male adults (n = 20, evaluable for pharmacokinetics) at a dose of 1200 mg BID on Day 1 and at a dose of 800 mg BID from Day 2 to Day 5 to investigate the distribution of favipiravir into the semen. Favipiravir concentrations in semen and blood plasma (geometric mean) were 18.34 and 35.94 μg/mL, respectively, on Day 3, and 0.05 and 0.09 μg/mL, respectively, 2 days after the end of the treatment. The favipiravir concentrations in both the semen and blood plasma decreased to below the lower limit of quantitation (0.02 μg/mL) in all subjects 7 days after the end of the treatment.

The semen/blood plasma concentration ratios (mean) were 0.53 on Day 3 and 0.45 at 2 days after the end of the treatment. Since the ratios were almost comparable, the applicant presumed that favipiravir was eliminated from the semen in the same manner as it did from the blood plasma. Therefore, the applicant claimed that it is appropriate to specify that men taking favipiravir should use contraception up to 7 days after the end of the treatment, because the favipiravir concentrations in both the semen and blood plasma are considered to decrease to below the lower limit of quantitation by that time.

Adverse events occurred in 2 of 20 subjects (headache and constipation [1 subject each]), but both events were mild, and their causal relationships with favipiravir were ruled out.

PMDA accepted the above applicant's explanation, and has concluded that the following actions need to be taken: (1) it is advised that male patients should use contraception up to 7 days after the end of the treatment; (2) female patients of childbearing potential should receive a pregnancy test before use of favipiravir, and the treatment should not be started until they test negative for pregnancy; and patients should be sufficiently informed of the risk related to the use of favipiravir in order to ensure that they use highly effective contraception with their partner during the treatment period and for 7 days after the end of the treatment.

(b) Phase I multiple-dose study in foreign healthy adults (Reference CTD 5.3.3.1.9, Study US103c, [redacted] to [redacted])

The tolerability, safety, and pharmacokinetics of favipiravir were evaluated in 12 foreign healthy adults (Groups 1 and 2, n = 6 subjects/group).

In Group 1, favipiravir was administered at a dose of 1600 mg twice daily on Day 1, followed by a dose of 800 mg twice daily from Day 2 to Day 5 (1600/800 mg BID). In Group 2, favipiravir was administered at a dose of 1800 mg twice daily on Day 1, followed by a dose of 600 mg twice daily from Day 2 to Day 5 (1800/600 mg BID).

The pharmacokinetic parameters are as shown in the table below. The C_{max} did not decrease after multiple doses of favipiravir compared with that on Day 1 (first dose) in the 1600/800 mg BID group, but decreased after multiple doses of favipiravir in the 1800/600 mg BID group.

Table. Pharmacokinetic parameters of plasma favipiravir and M1 concentrations

	1600/800 mg BID				1800/600 mg BID			
	Favipiravir		M1		Favipiravir		M1	
	Day 1 (1600 mg)	Day 5 (800 mg)	Day 1 (1600 mg)	Day 5 (800 mg)	Day 1 (1800 mg)	Day 5 (600 mg)	Day 1 (1800 mg)	Day 5 (600 mg)
Number of subjects evaluated	n = 6	n = 6	n = 6	n = 6	n = 6	n = 6	n = 6	n = 6
C_{max} (μg/mL)	52.62±11.03	63.42±12.93	18.02±1.13	3.71±0.40	53.52±12.44	32.32±8.06	20.02±4.44	3.50±0.49
tmax[a)] (hr)	0.75 (0.5, 2.0)	1.0 (1.0, 2.0)	0.88 (0.75, 2.0)	1.50 (0.75, 2.0)	1.0 (0.75, 2.0)	1.0 (0.5, 2.0)	1.0 (0.75, 2.0)	1.0 (0.75, 2.0)
AUC[b)] (μg·hr/mL)	296.33±96.58	570.14± 119.41	100.26±11.85	37.89±4.91	309.79± 112.14	231.89±85.31	106.18±22.62	31.34±6.11
$t_{1/2}$ (hr)	3.66 ± 0.95	5.02 ± 0.81	3.73 ± 0.57	8.48 ± 2.32	3.58 ± 1.07	4.31 ± 0.74	3.76 ± 0.79	6.27 ± 0.58
CL/F (L/hr)	5.78 ± 1.45	1.46 ± 0.30	-	-	6.79 ± 3.49	3.02 ± 1.53	-	-
Vd/F (L)	28.93 ± 3.25	10.26 ± 0.84	-	-	31.15 ± 4.86	17.66 ± 5.19	-	-

Mean ± standard deviation, a) Median (minimum, maximum), b) Value for Day 1 is $AUC_{0-\infty}$, and value for Day 5 is AUC_{τ}.
τ = 12 hours

Adverse events occurred in 1 of 6 subjects in the 1600/800 mg BID group (dyspepsia in 1 subject) and in 3 of 6 subjects in the 1800/600 mg BID group (2 events of post procedural dizziness in 1 subject, and dizziness postural, peripheral coldness, pollakiuria, and vessel puncture site haematoma in 1 subject), but all were mild. In particular, causal relationships of favipiravir with dyspepsia and pollakiuria could not be ruled out.

PMDA confirmed the tolerability and safety of favipiravir administered in accordance with the regimens of 1600/800 mg BID and 1800/600 mg BID.

(c) Drug-interaction studies (Reference CTD 5.3.3.4.3, Study US106, [redacted] to [redacted]; 5.3.3.4.4, Study US108, [redacted] to [redacted]; 5.3.3.4.5, Study US110, [redacted] to [redacted]; 5.3.3.4.6, Study US111, [redacted] to [redacted]; 5.3.3.4.7, Study JP116, [redacted] to [redacted]; 5.3.3.4.8, Study JP117, [redacted] to [redacted])

To investigate the drug-drug interactions with favipiravir, 6 studies were conducted. The ratios of the pharmacokinetic parameters (geometric mean) (90% confidence interval [CI]) of favipiravir or a concomitant drug (combination therapy/monotherapy) are as shown in the table below.

Table. Effects of concomitant drugs on pharmacokinetic parameters of favipiravir

Study number	Concomitant drug	Dosage and administration		Number of subjects	Treatment timing	Ratio of pharmacokinetic parameter of favipiravir (90% CI) (combination therapy/monotherapy)	
		Concomitant drug	Favipiravir			C_{max}	AUC
US108	Raloxifene	60 mg QD from Day 1 to Day 3	1200 mg BID on Day 1, 800 mg BID on Day 2, 800 mg QD on Day 3	17	Day 1	1.00 [0.90, 1.10]	1.03 [0.95, 1.12]
					Day 3	0.90 [0.81, 0.99]	0.85 [0.79, 0.93]
JP116	Hydralazine	5 mg QD from Day 1 to Day 5	1200 mg (first dose) and 400 mg (second dose) on Day 1, 400 mg BID from Day 2 to Day 4, 400 mg QD on Day 5	14	Day 1	0.99 [0.92, 1.06]	0.99 [0.92, 1.07]
					Day 5	0.96 [0.89, 1.04]	1.04 [0.96, 1.12]

Ratio of geometric mean (90% CI); QD, once daily; BID, twice daily

Table. Effects of favipiravir on pharmacokinetic parameters of concomitant drugs

Study number	Concomitant drug	Dosage and administration		Number of subjects	Treatment timing	Ratio of pharmacokinetic parameter of concomitant drug (90% CI) (combination therapy/monotherapy)	
		Concomitant drug	Favipiravir			C_{max}	AUC
US106	Acetaminophen	650 mg QD from Day 1 to Day 5	1200 mg BID on Day 1, 800 mg BID from Day 2 to Day 4 800 mg QD on Day 5	28	Day 1[a)]	1.03 [0.93, 1.14]	1.16 [1.08, 1.25]
					Day 5[a)]	1.08 [0.96, 1.22]	1.14 [1.04, 1.26]
					Day 1[b)]	1.18 [1.12, 1.24]	1.21 [1.16, 1.27]
					Day 5[b)]	1.22 [1.13, 1.32]	1.31 [1.22, 1.41]
					Day 1[c)]	0.51 [0.48, 0.56]	0.70 [0.66, 0.75]
					Day 5[c)]	0.47 [0.42, 0.54]	0.60 [0.52, 0.68]
US110	Norethindrone/ ethinyl estradiol combination drug	1 mg/0.035 mg QD from Day 1 to Day 5	1200 mg BID on Day 1, 800 mg BID from Day 2 to Day 4 800 mg QD on Day 5	25	Day 12[d)]	1.23 [1.16, 1.30]	1.47 [1.42, 1.52]
					Day 12[e)]	1.48 [1.42, 1.54]	1.43 [1.39, 1.47]
US111	Repaglinide	0.5 mg QD on Day 13	1200 mg BID on Day 1, 800 mg BID from Day 2 to Day 4 800 mg QD on Day 5	17	Day 13	1.28 [1.16, 1.41]	1.52 [1.37, 1.68]
JP116	Hydralazine	5 mg QD from Day 1 and Day 5	1200 mg (first dose) and 400 mg (second dose) on Day 1, 400 mg BID from Day 2 to Day 4, 400 mg QD on Day 5	14	Day 1	0.73 [0.67, 0.81]	0.87 [0.78, 0.97]
					Day 5	0.79 [0.71, 0.88]	0.91 [0.82, 1.01]

Ratio of geometric mean (90% CI); QD, once daily; BID, twice daily
a) Acetaminophen, b) Acetaminophen metabolite (glucuronide conjugate), c) Acetaminophen metabolite (sulfate conjugate)
d) Norethindrone, e) Ethinyl estradiol

The drug-drug interaction between pyrazinamide and favipiravir[219] was investigated in Japanese healthy adults (n = 14, evaluable for pharmacokinetics). The pharmacokinetic parameters of pyrazinamide alone were comparable to those of pyrazinamide in combination with favipiravir. The blood uric acid levels (mean) at the baseline, Day 5 of treatment with pyrazinamide alone, Day 3 of treatment with pyrazinamide in combination with favipiravir (Day 13), and at the post-study test (from Day 22 to Day 24) were 6.2, 11.6, 13.9, and 6.1 mg/dL, respectively. The level of uric acid in the blood increased after concomitant use of pyrazinamide and favipiravir and returned to the baseline value after the end of the treatment. Adverse events occurred in all of the 14 subjects (blood uric acid increased [14 subjects]; hepatic function abnormal [9 subjects]; vomiting [2 subjects]; and decreased appetite, headache, rhinorrhoea, nausea, arthralgia, pain in extremity, residual urine, and feeling abnormal [1 subject each]). Except for headache and rhinorrhoea, their causal relationships with the study drug could not be ruled out. A serious adverse event occurred in 1 subject (hepatic function abnormal), and was reported as resolved, according to the follow-up study. No deaths occurred.

PMDA considers as follows:
Concerning provision of precautions about concomitant drugs, mechanism of drug interactions, and effects on the blood concentrations of favipiravir or concomitant drugs as well as submission of the supporting study data, the applicant took appropriate actions by conducting non-clinical and clinical studies on drug interaction. Blood uric acid levels increased in all the subjects treated with favipiravir with pyrazinamide, although the effect on the blood drug concentration was not

[219] Pyrazinamide was administered at a dose of 1.5g QD from Day 1 to Day 15, while favipiravir was administered at a dose of 1200 mg (first dose) and a dose of 400 mg (second dose) on Day 11 and then at a dose of 400 mg BID (only once on Day 15) from Day 12 to Day 15.

significant. As a serious adverse event, hepatic function abnormal was reported as well. Hence, it is necessary to collect post-marketing information about patients to whom favipiravir is administered in combination with pyrazinamide.

III. Overall Evaluation

As a result of its review and based on the limited currently available information, PMDA has concluded that the approval of favipiravir is of significance, provided that the indication and the dosage and administration are revised as shown below, with the following conditions for approval, so that favipiravir can be made available for cases where the other influenza antiviral drugs are ineffective or not sufficiently effective in treating novel or re-emerging pandemic influenza virus infections, and where the efficacy of favipiravir is expected. The re-examination period is 8 years, both the drug substance and the drug product are classified as powerful drugs, and neither of them is classified as a biological product or a specified biological product.

[Indication] Treatment of novel or re-emerging pandemic influenza virus infections (limited to cases in which other influenza antiviral drugs are ineffective or not sufficiently effective)

[Dosage and Administration] The usual adult dosage is 1600 mg of favipiravir administered orally twice daily on Day 1, followed by 600 mg orally twice daily from Day 2 to Day 5. The total treatment duration should be 5 days.

[Conditions for Approval]

1. The applicant is required to conduct a pharmacokinetic study in accordance with the approved dosage regimen in Japan, and submit the study data and analysis results immediately after the completion of the study.

2. The applicant is required to conduct a clinical study of the product in patients with seasonal influenza virus infection to verify the efficacy and confirm the safety, and to submit the study data and analysis results immediately after the completion of the study.

3. The applicant is required to establish a strict distribution management system, and take thorough safety measures to ensure that the product is not used in patients with seasonal influenza virus infection.

4. The applicant is required to take strict and proper measures to ensure that the product is not adminitered to patients unless each individual patient, who is judged to be eligible for its use, or his/her family member is informed of the efficacy and risk of the product in writing and their written informed consent is obtained prior to the start of treatment.