We provide English translations for the convenience of non-Japanese speakers. However, the Japanese shall always prevail over the English in case of any inconsistency.

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Mr. Katsunobu Kato, Minister of Health, Labour and Welfare

Request To Stop Stockpiling Avigan And Revoke Its Approval

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Purpose of the request

Concerning Avigan (generic name: favipiravir), we request the following:
1. Revoke its approval and discontinue its use and stockpiling.
2. Summarize the situation surrounding Avigan and explain it to the public.

Reasons for the request

1 INTRODUCTION

On March 11, 2022, FUJIFILM Toyama Chemical Co., Ltd. announced that at the end of March this year, it would terminate the enrollment of subjects in the ongoing domestic Phase III clinical trial of Avigan Tablets 200 mg (generic name: favipiravir, hereinafter referred to as "Avigan") in patients with COVID-19[1]. Avigan's trial will now end without showing any efficacy against COVID-19.

Avigan was submitted as a treatment for seasonal influenza. However, not only did it

fail to show non-inferiority compared to Tamiflu, but it also failed to demonstrate robust efficacy compared to a placebo[2]. Despite this, it was approved as an anti-influenza drug in March 2014 under the unusual conditions of approval that it should not be distributed but will be stockpiled in case other anti-influenza virus drugs are ineffective or insufficiently effective against new or reemerging influenza virus infections. In April 2020, at a press conference following the declaration of a state of emergency in response to the spread of COVID-19, then Prime Minister Abe stated that he intended to expand to the greatest possible extent Avigan's administration to patients wishing to take it, within the framework of "observational studies"[3]. The Ministry of Health, Labour and Welfare (hereinafter referred to as the MHLW) issued a notification that it would permit the conditional use of Avigan for the treatment of COVID-19 to those participating in an observational study by Fujita Health University. This study is called the "Study of Background Factors and Treatment Effects in COVID-19 Patients Treated with Favipiravir and Other Antiviral Drugs (Observational Study)" (hereinafter referred to as the "Fujita study")[4]. Since then, the drug has been used in approximately 15,000 patients for the treatment of COVID-19.

We issued our opinion three times[5,6,7], calling for the immediate suspension of Avigan's use, etc. However, in light of the recent completion of the clinical trial, we request that the MHLW revoke Avigan's approval, stop its use and stockpiling, summarize the situation surrounding the drug, and explain it to the public. The details of our request are as follows.

2 SERIOUS RISKS

2.1 Risks indicated during the approval review

2.1.1 Strong teratogenicity

Avigan's teratogenicity had already been identified through the review at the time of approval, etc.[8,9,10,11].

First, in animal studies, early embryonic lethality (rats) and teratogenicity (monkeys, mice, rats, and rabbits) were observed even at doses similar to or lower than clinical exposure.

In addition, it has been confirmed that the drug is transferred into semen and metabolites of the drug are transferred into breast milk. Therefore, in its warning section, the package insert states that a pregnancy test is mandatory, that

contraception is also required for male patients during the administration period and for seven days after the end of administration, and that administration based on written consent is requested for both male and female patients[12].

2.1.2 Other serious side effects observed in animal experiments[13]

In a one-month oral dose study in juvenile dogs, the following was observed: death during treatment, lung changes, atrophy or regression of lymphoid tissue, hemorrhagic necrosis of hepatocytes, systemic oedema or vascular dilation, degeneration/necrosis or mineralization of papillary muscle in the heart, and the degeneration of skeletal muscle fiber.

In a one-month oral dose study in juvenile rats, the following was observed: abnormal gait, increased CK, histopathological changes in the testis, degeneration and coagulation necrosis of hepatocytes, and atrophy and vacuolization of the skeletal muscle fiber.

In a study of cynomolgus monkeys infected with highly pathogenic avian influenza, in both the favipiravir high-dose group and the low-dose group, one of three animals respectively, a total of two, died. No deaths occurred in the control group.

2.1.3 Significant potential risks described in the risk management plan

The risk management plan for Avigan lists the following: gout attacks due to increased blood uric acid, shock, anaphylaxis, pneumonia, fulminant hepatitis, hepatic dysfunction, jaundice, toxic epidermal necrolysis, cutaneous mucosal eye syndrome, acute kidney injury, leukopenia, neutropenia, thrombocytopenia, neuropsychiatric symptoms (disturbance of consciousness, abnormal behavior, delirium, hallucination, delusion, convulsion, etc.), and hemorrhagic colitis[14].

2.2 Risks indicated by use against COVID-19

2.2.1 High mortality rate in patients with mild illnesses and patients under 60 years old

In April 2021, the third interim report of the Fujita study[15] (hereinafter referred to as "Fujita Report 3") was published by the Favipiravir Observational Study Group of Fujita Health University. It shows that the mortality rate for mildly ill patients with known outcomes within a month of hospitalization was extremely high among Avigan users compared to data from registry studies not restricted to Avigan users. It also shows that the mortality rate of patients under 60 years old in the Fujita study was more than three times higher and nearly double for all ages.

Table 1 Comparison of Patient Mortality Rates (%) by Symptom Category*

	Mild	Moderate	Severe	Overall
Fujita Report 3	3.6%	13.2%	27.6%	8.0%
Registry study paper	0.4%	14.6%	33.5%	7.5%

* To compare mortality rates, we used the "percentage of patients with a known outcome at approximately one month after hospitalization who were discharged dead" from the Fujita study and the "percentage of patients who were discharged dead during hospitalization" from the paper based on data from the registry study.

Table 2 Mortality Rate by Age Group

	Under 60	Over 60	Overall
Fujita Report 3	1.1%	12.7%	8.0%
COVID-19 Registry Japan's data	0.3%	10.7%	4.2%

2.2.2 Issues surrounding the management system

Issues surrounding the management system were also presented.

2.2.2.1 Avigan taken by a pregnant woman

In June 2021, FUJIFILM Toyama Chemical Co., Ltd. distributed a notice to relevant institutions that a case was reported in which a patient with a confirmed negative pregnancy test prior to Avigan administration was found, after administration, to have been possibly pregnant at the time of taking Avigan.

The difficulty of pregnancy control has already been shown by the fact that even during clinical studies of the drug, which were supposed to have been strictly controlled, seven pregnancies were observed within 90 days after the end of the study treatment. The review report also points out the difficulty of carrying out a pregnancy test before Avigan is prescribed and the fact that influenza patients would be so exhausted that they may not be able to accurately understand the content of the informed consent form. It states that "it would be difficult to take these measures in routine clinical practice … 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.[16]"

2.2.2.2 Avigan's administration to non-hospitalized patients

In addition, the Isumi Medical Center, a public hospital in Isumi City, Chiba Prefecture, was found to have used the drug on 98 non-hospitalized patients. These patients were not eligible for the administration requirements from the perspective of teratogenic risk management[17].

In response to this, Fujita Medical University said that it would conduct a questionnaire survey. This indicates that the university does not have a grasp of the actual conditions of Avigan's use, which demonstrates the problematic nature of the "observational study" that is supposed to verify the drug's efficacy.

3 FAILURE TO DEMONSTRATE EFFICACY

3.1 Failure to prove efficacy against seasonal influenza

As mentioned above, Avigan was submitted as a treatment for seasonal influenza. However, not only did it fail to show non-inferiority compared to Tamiflu, but it also failed to demonstrate robust efficacy compared to a placebo[18]. During deliberations by a health ministry advisory panel, the Pharmaceuticals and Medical Devices Agency (PMDA), which was in charge of the review, explained that Avigan was a "drug to prepare for the spread of highly pathogenic influenza virus infections that are resistant to existing anti-influenza virus drugs" such as Tamiflu. However, a number of panel members pointed out that it was unclear why the drug was effective against highly pathogenic influenza virus infections. The PMDA responded by saying, "The part you pointed out has not yet been clarified," so under normal circumstances, approval would not have been possible. However, the chairman of the panel pushed for approval by saying such things as, "I was thinking of suspending its approval, but I don't know how long I should suspend it for before the data come out" and "It is not for general distribution.[19]"

Two additional clinical trial results were submitted in 2017, but ultimately only one of these was able to show superiority over placebo.[20].

3.2 Failure to prove efficacy against COVID-19

Multiple trials have failed to prove Avigan's efficacy against COVID-19. Even if the clinical trials were to continue, it is easy to assume that the drug's efficacy cannot be demonstrated.

3.2.1 An MHLW advisory board on new drug approval held on December 21, 2020, discussed the results of a randomized, placebo-controlled, single-blind comparative study conducted as a domestic study of Avigan. The discussion was continued because it was difficult to determine Avigan's efficacy clearly.[21]

3.2.2 In a placebo-controlled, randomized, double-blind study in Kuwaiti patients with moderate-to-severe COVID-19 (CVD-04-CD-001)[22] (7 days versus 8 days, $p = > 0.05$), time to resolution of persistent hypoxia, the primary endpoint, did not show a statistically significant difference between Avigan and the placebo. It was announced on January 27, 2021 that the study will be completed[23].

3.2.3 In November 2021, it was announced that a phase III multinational study evaluating Avigan for the early treatment of mild-to-moderate COVID-19 did not achieve statistical significance for the primary endpoint of time to sustained clinical recovery. A total of 1,231 patients from 38 study sites across the United States, Mexico, and Brazil enrolled[24].

4 THE NEED FOR CANCELLATION OF AVIGAN'S APPROVAL AND A SUMMARY REPORT

Anyone who reads the minutes of the Council meeting when Avigan was approved must wonder why the drug was approved. Avigan failed to demonstrate efficacy even against seasonal influenza, and was approved without any scientific evidence to support its efficacy 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". Furthermore, the drug has serious risks, including teratogenicity and fetotoxicity. Therefore, it was not appropriate to approve it, even for stockpiling. Moreover, its use against COVID-19 has further revealed its potential risks. This also demonstrates the limitations of stockpiling a drug when it is not clear what the drug is effective against. Therefore, Avigan's approval should be revoked and its use and stockpiling should be discontinued.

In addition, the unscientific, unethical nature of the politically-driven creation of excessive expectations for such a drug and its use within the framework of an "observational study" are serious. As we have already pointed out, the mortality rate of patients with minor illnesses and patients under 60 years of age is high. There has also been a report of a case in which a patient could not receive the treatment that they should have received because they used a drug without proof of efficacy[25]. In FY2020 alone, the MHLW spent 1.59 billion yen to purchase Avigan[26]. Furthermore, FUJIFILM Toyama Chemical received over 1,407.4 million yen from the MHLW to support clinical trials[27] and 4,068 million yen in subsidies from the Ministry of Economy, Trade and Industry to expand its manufacturing facilities[28].

The MHLW should not leave things up to FUJIFILM Toyama Chemical and Fujita Medical University. Instead, it should provide a summary report to explain to the public how to prevent any recurrence, based on its responsibility for issuing a notice with no scientific basis.

Therefore, we request as stated in the purpose of the request.

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[2] MHLW: Review Report (March 4, 2014)
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[3] Prime Minister of Japan and His Cabinet: Press Conference by the Prime Minister Regarding the Declaration of a State of Emergency, April 7, 2020
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[4] MHLW Headquarters for the Promotion of Countermeasures to COVID-19: Notification on April 27, 2020, "Request for Public Awareness of the Outline of the Observational Study on Favipiravir for the Treatment of Novel Coronavirus Infections and the Provision of Pharmaceuticals for Use in the Study", etc.
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[6] Medwatcher Japan: Second Opinion on Avigan Based on Deaths Mentioned in 'the Interim Report of The Favipiravir Observational Study' by Fujita Health University (Regarding Covid-19) (July 2, 2020)

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[8] MHLW: Review Report, Note 2 above.

[9] MHLW: "Minutes of the Second Division of the Pharmaceutical Affairs and Food Sanitation Council" (February 3, 2014).
https://www.mhlw.go.jp/stf/shingi/0000056624.html

[10] FUJIFILM Toyama Chemical Co., Ltd. "Description of teratogenicity in non-clinical studies (for healthcare professionals) [Possible teratogenicity of Avigan Tablets]"
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[11] FUJIFILM Toyama Chemical Co., Ltd. "Risk Management Plan for Avigan Tablets 200 mg"
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[12] FUJIFILM Toyama Chemical Co., Ltd. "Package insert of Avigan Tablets 200 mg" (revised in April 2019 (7th edition))
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[13] MHLW: Review Report, Note 2 above.

[14] FUJIFILM Toyama Chemical Co., Ltd. "Risk Management Plan for Avigan Tablets 200 mg", Note 11 above.

[15] Favipiravir Observational Study Group, Fujita Health University: Favipiravir Observational Study Interim Report 3 （as of February 28, 2021）
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[19] MHLW: "Minutes of the Second Division of the Pharmaceutical Affairs and Food Sanitation Council", Note 9, above.

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