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.

September 13, 2021

Norihisa Tamura, Minister of Health, Labour and Welfare

Yukio Yuzawa, President, Fujita Health University

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Third Opinion Requesting the Immediate Suspension of the Avigan "Observational Study" in Light of the High Mortality Rate of Patients Treated with Avigan

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Purpose of the request

We request the following concerning Avigan (generic name: Favipiravir).

1. The Ministry of Health, Labour and Welfare (hereinafter referred to as MHLW) and FUJIFILM Toyama Chemical Co., Ltd. should immediately discontinue the conditional supply of Avigan to those participating in an observational study by Fujita Health University. Fujita Health University should also immediately stop the enrollment of new patients receiving the drug.
2. MHLW should not approve Avigan for the treatment of COVID-19 without proof of efficacy through rigorous randomized controlled clinical trials and an appropriate assessment of the balance between risks and benefits.

Reasons for the request

1 OUR PREVIOUS OPINIONS

We have published two opinions on Avigan.

1.1 Our Opinion Dated May 1, 2020[1]

We issued the first opinion in May 2020, in light of the fact that MHLW had issued a notification in April 2020 permitting the conditional use of Avigan for the treatment of COVID-19 to those participating in an observational study by Fujita Health University. The 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").

The opinion pointed out that Avigan was unusually approved for stockpiling despite its failure to demonstrate robust efficacy as an anti-influenza drug, that it had yet to show efficacy against COVID-19, that serious risks such as teratogenicity and fetotoxicity had been identified, and that additional unknown side effects might emerge. The opinion contained requests for actions such as the careful use of Avigan.

1.2 Our Opinion Dated July 2, 2020[2]

The second opinion was released in July, in response to the interim report of the Fujita study. The report was published by the Favipiravir Observational Study Group of Fujita Health University in May 2020.

Our opinion pointed out that according to the interim report, the mortality rate of patients treated with Avigan within approximately the first month of hospitalization was as high as 11.6%. This is clearly higher than the nationwide mortality rate of 1.6% that MHLW reported in its 2.1 edition of the Clinical Practice Guidance for COVID-19, which raised concerns about the risks of Avigan. Our opinion also pointed out that there was a serious ethical issue, such as the possibility of violating the Clinical Trials Act or the Clinical Research Guidelines, because Fujita Health University does not have a system in place to provide adequate explanations to protect study participants and manage adverse events. Thus, we requested the suspension of the conditional supply of Avigan to those participating in the Fujita study and the "COVID-19 REGISTRY JAPAN" by the National Center for Global Health and Medicine (NCGM), and the enrollment of new patients receiving the drug in both studies.

We also pointed out that Avigan should not be approved for the treatment of COVID-19 without proof of efficacy through rigorous randomized controlled clinical trials and an appropriate assessment of the balance between risks and benefits.

2 FAVIPIRAVIR OBSERVATIONAL STUDY INTERIM REPORT 3 -- HIGHER MORTALITY RATE IN PATIENTS RECEIVING AVIGAN --

Subsequently, on April 19, 2021, the third interim report of the Fujita study (as of February 28, 2021, hereafter referred to as "Fujita Report 3"[3]) was published.

According to the report, the mortality rate for the 10,659 patients with known outcomes within a month from hospitalization was 3.6%, 13.2%, and 27.6% for moderate and severe diseases, respectively.

However, a paper published in September 2020, based on data from a registry study enrolling hospitalized patients with COVID-19 in Japan[4], showed that the mortality rate of 2,632 hospitalized patients was 0.4% for mild, 14.6% for moderate, and 33.5% for severe diseases. Compared to this, the mortality rate for patients in Fujita Report 3 is extremely high for minor diseases*.

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.

According to Fujita Report 3, the mortality rate was 1.1% for patients under 60 years old, 12.7% for patients over 60 years old, and 8.0% for patients of all ages. Compared

* The use of Avigan is conditional on participation in the Fujita study, and some of the "Registry Study on COVID-19" at the NCGM included patients treated with Avigan. Thus, a comparison of the two studies may have reduced the risk of Avigan. This point is also pointed out in the registry study paper.

with the mortality rate of 12,599 hospitalized patients nationwide, which was 0.3% for patients under 60 years old, 10.7% for patients over 60 years old, and 4.2% for all ages, as reported in the "Mortality rate of COVID-19 by age group using COVID-19 registry data" in the January 2021 issue of the National Institute of Infectious Diseases (NIID) Infectious Agents Surveillance Report (IASR)[5], the mortality rate of patients under 60 years of age in the Fujita study was more than three times higher and nearly double for all ages.

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%

3 AVIGAN TAKEN BY A PREGNANT WOMAN

In addition, a "Notice of Precautions for Administration to Patients with Reproductive Potential" dated June 8, 2021, prepared by FUJIFILM TOYAMA CHEMICAL Co., was distributed to medical institutions using Avigan. It explains the reason for its distribution: "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."

Avigan's teratogenicity observed in animal experiments was serious, and we raised concern about it in our opinion papers. The case of this patient shows that a serious problem in terms of safety management could actually occur.

4 CLINICAL TRIALS FAILED TO SHOW AVIGAN'S EFFICACY AGAINST COVID-19

Not only has Avigan's efficacy not been shown; multiple trials have also failed to prove its efficacy.

First, an MHLW's 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[6].

In a placebo-controlled, randomized, double-blind study in Kuwaiti patients with moderate-to-severe COVID-19 (CVD-04-CD-001)[7] (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[8].

5 SUMMARY

FUJIFILM Toyama Chemical Co., Ltd. has newly launched a double-blind clinical trial in Japan and is said to be presenting its results at the end of October[9].

However, the mortality rate of patients treated with Avigan remains high, even in Fujita Report 3, and there is also a risk of teratogenicity. Meanwhile, the ethical issues that conflict with the Clinical Research Act and Clinical Research Guidelines, as pointed out in our written opinion dated July 2, 2020, have not been resolved in any way.The MHLW, in an administrative notification dated April 27, 2021, still states that " MHLW is currently verifying the existing antiviral drugs against COVID-19 by research groups funded by the MHLW Science Research Grants, and so on"[10]. However, it is questionable why Avigan's use in "observational studies" purportedly to verify its efficacy is allowed, despite results from several controlled clinical trials that failed to demonstrate its efficacy.

According to a written answer in the Diet dated February 24, 2021, as of February 1, 2021, Avigan had been administered to approximately 10,000 patients under the name of an observational study[11].

The continued use of an unapproved drug whose efficacy has not been demonstrated, has been shown to have a high mortality rate, has teratogenic risks and is ethically problematic as described above, should not be allowed in light of the Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices and ethical principles.

So we request the following respectively.

1. The Ministry of Health, Labour and Welfare (MHLW) and FUJIFILM Toyama Chemical Co., Ltd. should immediately discontinue the conditional supply of Avigan to those participating in an observational study by Fujita Health University. Fujita Health University should also immediately stop the enrollment of new patients receiving the drug.
2. MHLW should not approve Avigan for the treatment of COVID-19 without proof of

efficacy through rigorous randomized controlled clinical trials and an appropriate assessment of the balance between risks and benefits.

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[1] Medwatcher Japan: Opinion on Avigan (regarding COVID-19)
https://www.yakugai.gr.jp/topics/file/en/20200501%20Opinion%20on%20Avigan%20(regarding%20COVID-19).pdf

[2] 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)
https://www.yakugai.gr.jp/topics/file/en/20200702%20Second%20Opinion%20on%20Avigan%20Based%20on%20Deaths%20Mentioned%20in%20'the%20Interim%20Report%20of%20The%20Favipiravir%20Observational%20Study'%20by%20Fujita%20Health%20University%20(Regarding%20Covid-19).pdf

[3] Favipiravir Observational Study Interim Report 3 （as of February 28, 2021） Favipiravir Observational Study Group, Fujita Health University
https://www.kansensho.or.jp/uploads/files/topics/2019ncov/covid19_favip_210419_eng.pdf

[4] 'Clinical Epidemiology of Hospitalized Patients With Coronavirus Disease 2019 (COVID-19) in Japan: Report of the COVID-19 Registry Japan'
https://academic.oup.com/cid/advance-article/doi/10.1093/cid/ciaa1470/5912544

[5] "Mortality rate of COVID-19 by age group using COVID-19 registry data", National Institute of Infectious Diseases (NIID) Infectious Agents Surveillance Report (IASR), January 2021
https://www.niid.go.jp/niid/ja/diseases/ka/corona-virus/2019-ncov/2488-idsc/iasr-news/10080-491p03.html

[6] Summary of Deliberations on Avigan Tablets 200 mg at the Second Committee on New Drugs of the Pharmaceutical Affairs and Food Sanitation Council (held on December 21, 2020)
https://www.mhlw.go.jp/content/11121000/000719118.pdf

[7] Clinical trial registration for the clinical trial in Kuwait
https://clinicaltrials.gov/ct2/show/NCT04529499?term=CVD-04-CD-001&cond=Covid-19&draw=2&rank=1

[8] Press release on the results of the clinical trial in Kuwait
https://www.drreddys.com/media/928938/2021-01-avigan-trial-update_v1.pdf

[9] Registration of clinical trial by FUJIFILM Toyama Chemical Co., Ltd. (Japan Registry of Clinical Trials)
https://jrct.niph.go.jp/en-latest-detail/jRCT2041210004

[10] The MHLW's Headquarters for the Promotion of Countermeasures to COVID-19: Administrative Notification dated April 27, 2021
https://www.mhlw.go.jp/content/000773800.pdf

[11] Written answer in the Diet in response to the re-questioning on Avigan's approval submitted by Mr. Hitoshi Matsubara, a member of the House of Representatives (February 24, 2021, Cabinet of Ministers, House of Representatives, Q204, No. 45).
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