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.

July 2, 2020

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Mr. Junji Okada, President and Chief Operating Officer, FUJIFILM Toyama Chemical Co., Ltd.

Dr. Eichi Saitoh, President of Fujita Health University

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Opinion Based on Deaths Mentioned in the "Interim Report of The Favipiravir Observational Study" by Fujita Health University (Regarding Covid-19)

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Purpose of the request

Concerning the use of Avigan (generic name: favipiravir) for the treatment of COVID-19, we request that the Ministry of Health, Labour and Welfare (hereinafter referred to as MHLW), FUJIFILM Toyama Chemical Co., Ltd., Fujita Health University and National Center for Global Health and Medicine (herein after referred to as NCGM) conduct the following:

1_1 suspend the conditional supply of Avigan to those participating in an observational study by Fujita Health University and the "COVID-19 REGISTRY JAPAN (joint study)" by NCGM, and the enrollment of new patients receiving the drug in both

studies.

1_2 closely examine patients who were treated with Avigan and died within the first month of hospitalization after hospitalization (223 patients, 11.6%), as mentioned in an interim report by Fujita Health University's Favipiravir Observational Study Group, and the association between Avigan administration and death. We request that the results of both examinations are published.

1_3 make public the clinical course of death among those above who had minor illnesses (42 patients, 5.1%), without waiting for the results of the examinations described in the previous section.

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 OPINION DATED MAY 1, 2020

On May 1, 2020, we issued a written opinion on Avigan, pointing out the following in summary[1]:

On the one hand, Avigan was unusually approved for stockpiling, even though its efficacy as an anti-influenza virus drug isn't clear. It has also not yet been proven effective against COVID-19.

On the other hand, serious risks such as teratogenicity and fetotoxicity have been identified. Furthermore, the total dose of Avigan administered in Fujita Health University's observational study is more than twice the total dose approved for anti-influenza drugs. This may lead to stronger side effects.

Therefore, we cannot overlook the adverse effects that may occur if this drug is used under excessive expectations without sufficient confirmation of its efficacy.

In addition, Avigan's approval should be based solely on the results of randomized controlled clinical trials.

2 HIGH RATE OF DEATHS AND ETHICAL ISSUES IN FUJITA HEALTH UNIVERSITY'S "OBSERVATIONAL STUDY" OF AVIGAN

2_1 Publication of the Interim Report of the "Observational Study" of Avigan by Fujita

Health University

On May 26, 2020, Fujita Health University's Favipiravir Observational Study Group released an interim report summarizing clinical information on patients treated with Avigan. It's called the "Study of Background Factors and Treatment Effects in COVID-19 Patients Treated with Favipiravir and Other Antiviral Drugs (Observational Study)[2]" (hereinafter referred to as the "Fujita study").

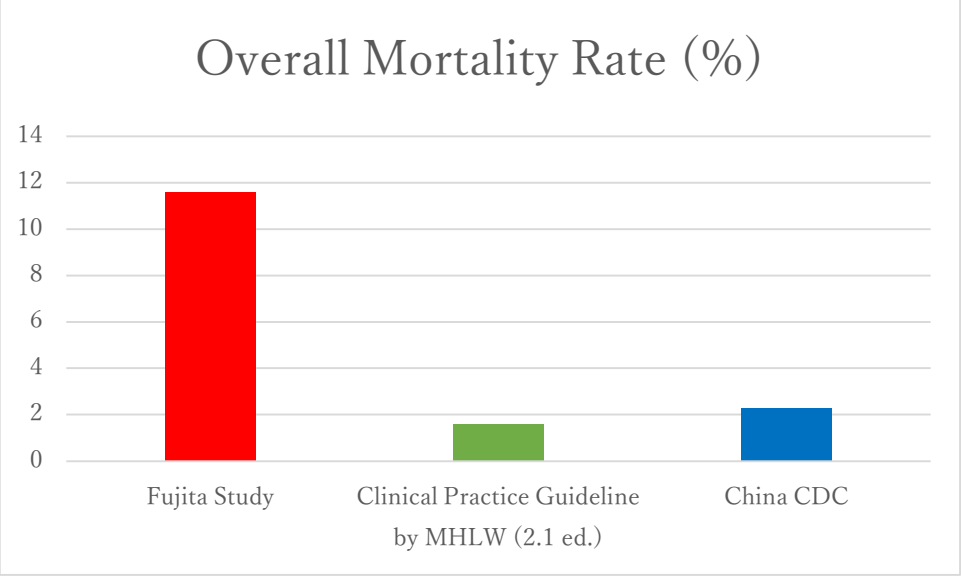
The Discussion section summarizes that "the vast majority of patients with mild and moderate illnesses recovered" when Avigan was administered. Meanwhile, the subtitle of the university's press release stated that "the data from more than 2,000 patients entered into this study showed no new trends in adverse effects[3]."

2_2 High mortality rate in patients treated with Avigan

However, it is the mortalities that we should pay attention to.

According to the interim report, of the 1,918 patients whose outcomes were reported within the first month of hospitalization, 223 died, with a mortality rate of 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 (published on June 17, 2020)[4] and the mortality rate of 2.3% that was reported by the China CDC (Chinese Center for Disease Control and Prevention)[5] in 44,672 confirmed cases (as of February 11, 2020). This indicates that Avigan may not be effective and could even be harmful instead.



In particular, concerning Table 3(c) of the report, if we look at what happened to patients with minor illnesses in their first month of hospitalization (these patients did not require oxygen administration), 42 patients were discharged dead, 35 were transferred to another hospital (exacerbation), 160 continue to remain in hospital (survival), 81 were transferred to another hospital (remission), and 512 were discharged (survival). Thus, of the 830 patients with minor illnesses, 42 were discharged dead, resulting in a mortality rate of 5.1%. Furthermore, 35 patients (4.2%) were transferred to another hospital after exacerbation within the first month of hospitalization. It is unknown whether these patients died thereafter. Therefore, this mortality rate is a low estimate.

The mortality rate was at least 5.1% within the first month of hospitalization in mildly ill patients who did not require oxygen. If we compare this figure to a preliminary analysis of a randomized controlled clinical trial that was conducted by the US National Institutes of Health to investigate the effects of Remdesivir[6], it is higher than one death (1.7% mortality rate) that occurred in 60 patients participating in a control (placebo) group who did not require oxygen within 14 days of study enrollment.

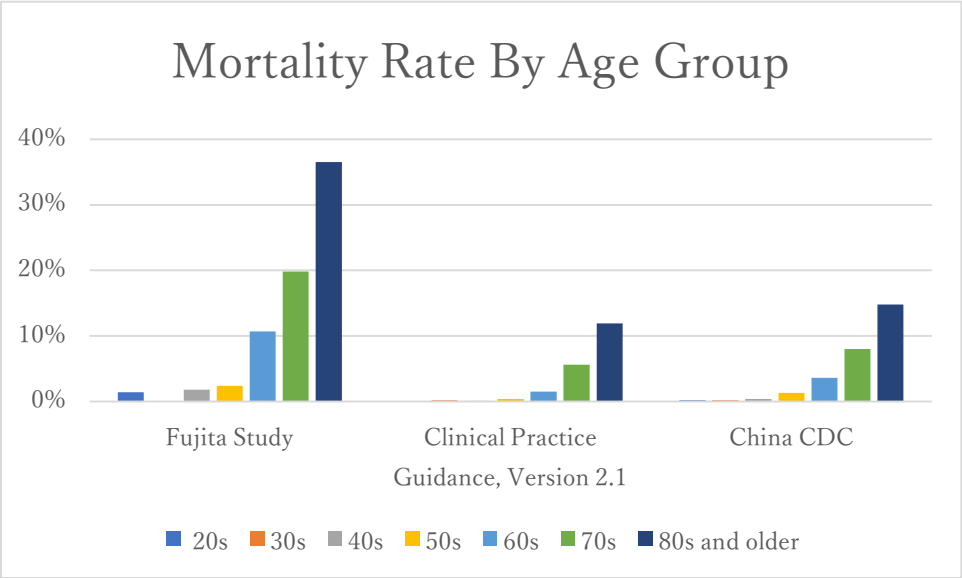
In addition, the mortality rate by age group in the Fujita study was 1.4% (one patient) in their 20s, 0% in their 30s, 1.8% (five patients) in their 40s, 2.4% (11 patients) in their 50s, and 10.7% (42 patients) in their 60s. For adult patients, the mortality rate for all age groups, except those in their 30s, is much higher than the national rates in the nationwide aggregation of the aforementioned Clinical Practice Guidance, Version 2.1 and the data from the China CDC. It should also be noted that in the Fujita study, the mortality rate was as high as 1.4% to 2.4% even in people in their 20s, 40s, and 50s. These people are conventionally considered to have low mortality rates.

Comparison of mortality rates between the Fujita Study Interim Report and other statistics (by age group)

Age group	Fujita Study	Clinical Practice Guidance, Version 2.1*	ChinaCDC
20s	1.4%	0%	0.2%
30s	0%	0.2%	0.2%
40s	1.8%	0.1%	0.4%
50s	2.4%	0.4%	1.3%
60s	10.7%	1.5%	3.6%
70s	19.8%	5.6%	8.0%
80s and older	36.5%**	11.9%	14.8%
Total	11.6%	1.6%	2.3%

* According to the MHLW's "Trends in Domestic Outbreaks of COVID-19," as of 18:00 on April 16, 2020, which is considered to be when this nationwide total was calculated, of the 9,027 infected persons, 5,693 were symptomatic and 539 were asymptomatic, excluding the 2,795 persons whose symptoms were still being confirmed.

** In Table 4(c) of the interim report above, those in their 80s, 90s and older are separated, but we calculated the total.



According to a review report that was issued when Avigan was approved as an anti-influenza drug, a study on animals was conducted in which the highly pathogenic avian

influenza virus was transmitted to cynomolgus monkeys. There were no deaths in the placebo group. However, in the Avigan group, one out of three animals died in the high- and low-dose groups respectively, bringing a total of two deaths. Deaths have also been observed in rats and dogs. Furthermore, when the no-observed-adverse-effect-level (NOAEL) in the repeat-dose toxicity study was compared with the clinical dose in adults, it was approximately 0.58 to 0.87 times higher in rats, 0.23 to 0.27 times higher in dogs and 0.9 to 1.3 times higher in monkeys, which were lower than or similar to the clinical doses[7,8].

In light of the above, and without careful examination, it is inappropriate to assume that the high mortality rate of patients in the Fujita study is due to differences in patient background such as their older age, the way the data were collected and the large number of patients with underlying diseases, and to deny the possibility that the deaths were due to Avigan's side effects or that Avigan aggravated the symptoms.

2.3 Issues in light of Clinical Trials Act and ethical guidelines

2.3.1

The Study Group explains that the Fujita study is an "observational study."

The research protocol for the Fujita study[9] describes the type of research as an observational study and states that there is no presence or absence of intervention. It explains that "although favipiravir and others are off-label, the decision to administer them will not be included in the study because the decision to administer them has already been made at each participating medical facility based on medical necessity." In addition, it says, "since information from the medical records of patients who receive the drug will be used, the presence or absence of intervention will be judged as none." Furthermore, it also states that because the Fujita study is an observational study, it does not fall under Section 13 of the research protocol, “Response to the provision of medical care after the implementation of the research, and handling of adverse events when they occur."

It is claimed that since the Fujita study is an observational study, each participating medical institution is responsible for explaining the off-label use of Avigan and the subsequent occurrence of adverse events to patients, and that the Fujita study is not subject to the Clinical Trials Act.

2.3.2

However, it is questionable whether we can say that the Fujita study is an "observational study" and not subject to the Clinical Trials Act.

The Act defines the term "clinical trials" as research to clarify the efficacy or safety of pharmaceuticals by the use of such pharmaceuticals in humans (Article 2). Enforcement Regulations on the Act exempt "research that uses medical information or samples as a result of providing the most appropriate medical care for the patient, *without controlling the presence, absence or degree of examination*, *medication or other medical treatment for diagnosis, or treatment* for research purposes. (Emphasis added.)" This is an "observational study" as defined by the said regulations, and to be exempt from the Clinical Trials Act, "the study must not control the presence, absence or degree of medical treatment."

In this regard, since the Fujita study's purpose is to "estimate the effect of drugs" such as Avigan and others against COVID-19 (study protocol), it is clearly subject to the Clinical Trials Act.

In which case, can it be said that it "does not control the presence, absence or degree of medical treatment"? The MHLW's Headquarters for the Promotion of Countermeasures to COVID-19 issued a Notification on May 15, 2020, entitled "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 (Part 3)". In its attachment, it says, "The use of Avigan for new coronavirus infections is only possible when medical institutions participate in an observational study conducted by a research team, the participating patient agrees, and the use of Avigan is required at the discretion of a physician. Therefore, *in order to use Avigan, the medical institution must participate in the study team*[10]." (Emphasis added.) In other words, as Avigan was approved for stockpiling, and although it is an approved drug, its distribution to the general public is prohibited by the terms of its approval. Therefore, to receive Avigan, one must participate in the Fujita study or a corporate clinical trial or other specific clinical research. This means that participating in the Fujita study is a substantial condition for receiving Avigan. In light of this special conditional relationship, it is difficult to say that the Fujita study does not control whether medication is administered to participating patients.

Therefore, the study does not fall under the category of observational study. It

should essentially be conducted as a specified clinical trial under the category of unapproved uses of approved drugs as stipulated in Article 2 (2), Item 2(b) of the Clinical Trials Act, under a system that provides adequate explanations to protect study participants and is responsible for managing adverse events.

In addition, even if this is called an observational study, the aforementioned special conditional relationship regarding the unapproved use of Avigan cannot be denied. In light of the purpose of the Clinical Trials Act and various guidelines on clinical trials[11,12], the Fujita study should be treated in the same manner as specific clinical research, at least with respect to explanations to protect study participants and being responsible for managing adverse events.

2_4 Summary

As described above, the mortality rate of patients who received Avigan in the Fujita study is clearly higher than the nationwide mortality rate reported by MHLW in its 2.1 edition of the Clinical Practice Guidance for COVID-19 and the mortality rate reported by the China CDC. This raises concerns about the risks of Avigan.

In addition, in light of the Clinical Trials Act and various ethical guidelines, a system should be in place where Fujita Health University is responsible for offering adequate explanations to protect study participants and responding to adverse events. But no action has been taken to address this. Their claiming it is an observational study raises a serious ethical issue.

On the other hand, Avigan's efficacy is not clear. While the urgent nature surrounding COVID-19 and the expectation for therapeutic drugs are understandable, Avigan's continued use within the framework of an observational study will, in fact, undermine patients' interests.

Therefore, we request the following:

2.4.1

Suspend the supply of Avigan, which is conditional upon participation in the Fujita study, and the enrollment of new patients in the study, which is being conducted on patients who have received Avigan under these conditions. Data from patients who have already enrolled should be subject to final analysis in a responsible manner and be published.

In addition, since the cases of Avigan administered in the Fujita study are being

studied in collaboration with the "COVID-19 REGISTRY JAPAN" of NGCM[13], the supply of Avigan to participants and the enrollment of patients receiving Avigan should also be suspended in the registry.

2.4.2

The association between the aforementioned deaths and the administration of Avigan should be scrutinized and the results made public. In particular, the clinical course of death in patients with minor illnesses (42 patients, 5.1%) should be made public, without waiting for the results of an examination into the possibility of death from adverse drug reactions.

2.4.3

The government repeatedly announced its policy of a free supply of Avigan, whose efficacy and safety against COVID-19 had not yet been confirmed. This fueled expectations and allowed its widespread use. It is unacceptable that neither those in charge of the Fujita study nor the government will be held responsible for any deaths after the drug's administration, on the grounds that the Fujita study was an observational study and the decision to administer the drug was made by doctors and patients in the field. Therefore MHLW, FUJIFILM Toyama Chemical Co., Ltd. (based on Article 68-10, Paragraph (1) of Act on Securing Quality, Efficacy and Safety of Products Including Pharmaceuticals and Medical Devices, etc.) and Fujita Health University should take responsibility for the above measures.

3 AVIGAN CANNOT BE APPROVED BASED ON THE FUJITA STUDY

3.1 Prime Minister Abe's press conference and the notification issued by two Directors of MHLW dated May 12, 2020

At a press conference on May 4, 2020[14] and in the plenary sitting of the House of Councillors held on May 15[15], Prime Minister Abe expressed his view that submitting clinical trial results is not required for Avigan’s regulatory approval review, and that the drug's efficacy may be confirmed through the results of observational and clinical studies.

On May 12, 2020, the MHLW issued a notification (the so-called "Two Directors' Notification") in the name of the heads of two organizations that review and approve

pharmaceuticals and medical devices [16]. It states that there may be reasonable reasons for not submitting data related to clinical studies under certain conditions.

以上

3.2 The need for comparative clinical trials

However, the provision that it is not necessary to submit clinical trial data and other materials on study results is a serious exception to the approval system. It should not be applied to COVID-19, whose clinical course can be observed in a relatively short period of time and clinical trial participants can be recruited during the epidemic period.

In principle, a pharmaceutical product's efficacy should be judged by statistically significant differences in randomized controlled clinical trials with appropriate endpoints.

As we pointed out in our written opinion dated May 1, 2020, Avigan originally drew attention as a potential drug for the treatment of COVID-19 because it is said to selectively inhibit viral RNA polymerase to prevent viral replication. It was expected to be applicable to SARS-CoV-2, which has the same RNA virus as the influenza virus. However, its robust efficacy against seasonal influenza, that should have been obtained by its mechanism of action, was not observed (i.e., no clinical effects were observed in humans, although the viral load was decreased)[17]. Thus, its clinical efficacy against COVID-19 may be similar. In addition, in the case of COVID-19, it is said that 80% of cases pass as a minor illness or with no symptoms, and many people recover spontaneously[18]. Therefore, even if the patient is cured, proof by the principle method of confirming statistical significance in a randomized controlled clinical trial is still necessary to determine that the cure is not spontaneous and is, instead, due to Avigan.

There are concerns not only about the serious side effects of this drug, such as teratogenicity and fetotoxicity, which have already been identified, but also about the risk of death in patients with mild illnesses as mentioned above. Therefore, the risks should be carefully examined, and whether the efficacy of the drug outweighs the risks should be verified.

While expectations for the development of therapeutic drugs for the treatment of COVID-19 are fully understandable, drugs whose efficacy and safety have not been scientifically proven should not be approved prematurely. This could result in fatal adverse drug reactions.

A hasty response lacking scientific evidence not only jeopardizes the very

foundation of the approval system, but also causes unnecessary confusion in the medical field. This is contrary to public interest. [19,20,21]

Therefore, Avigan should not be approved for the treatment of COVID-19 without proof of efficacy based on the results of rigorous randomized controlled clinical trials and an appropriate assessment of the between risks and benefits.

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2 Favipiravir Observational Study Group: Preliminary Report of the Favipiravir Observational Study in Japan.
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4 MHLW: The Clinical Practice Guidance for (or Guide to the Treatment of?) COVID-19, 2.1 edition
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7 Review Report (March 24, 2014), p.63
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10 MHLW: Outline of observational study on Avigan (generic name: favipiravir) for the treatment of coronavirus infection and provision of drugs for use in the study
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11 https://www.wma.net/policies-post/wma-declaration-of-helsinki-ethical-principles-for-medical-research-involving-human-subjects/

12 MEXT & MHLW: Ethical Guidelines for Medical and Health Research Involving Human Subjectshttps://www.mhlw.go.jp/file/06-Seisakujouhou-10600000-Daijinkanboukouseikagakuka/0000153339.pdf

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[17] Ibid., 2.

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