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

We oppose the emergency approval of Shionogi's COVID-19 drug Xocoba

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1 Introduction

On November 22nd, 2022, a joint meeting of two advisory panels of experts at the Ministry of Health, Labour and Welfare (hereinafter referred to as the "MHLW") will discuss whether to grant emergency approval for Xocova Tablets 125 mg (generic name: encitrelvir fumarate, hereinafter "the drug") for the treatment of COVID-19.

This issue was also discussed at a joint meeting held on July 20th of this year. At the meeting, because the Phase II study failed to show significant differences in the primary endpoint of 12 clinical symptoms compared to the placebo group, it was deemed insufficient to meet the "presumption of efficacy" criterion, a requirement for emergency approval. Accordingly, emergency approval was not granted.

However, Shionogi has since requested emergency approval again. It claims that the preliminary results of the Phase III part of the Phase II/III clinical trial, in which the primary endpoint of the clinical trial was reduced to five symptoms instead of 12, showed a significant difference versus the placebo group[1].

We published an opinion opposing the emergency approval of this drug in June of this year[2]. Again, we strongly oppose the emergency approval of this drug after the change to the primary endpoints.

We think that granting emergency approval to the drug at this point in time, as described

below, is an act that violates the main principles of clinical trials and regulatory approval, distorts the nature of the emergency approval system and jeopardizes the system's future.

2 Problems in approving post-hoc multiple analysis

2.1 At the July joint meeting, Shionogi claimed that there was already a significant difference versus the placebo group in the improvement of five symptoms (runny or stuffy nose, sore throat, cough, feeling hot or feverish, and shortness of breath (dyspnea)) characteristic of the Omicron strain.

2.2 However, Yasuhiro Fujiwara, the Chief Executive of the Pharmaceuticals and Medical Devices Agency, harshly criticized this assertion as follows:[3]

"This method is a post-hoc analysis, and Shionogi has been doing it again and again. In terms of biostatistics, it may be better for Dr. Yamaguchi or Dr. Sato to explain this later, but it is often the case that significant results are obtained by chance after many, many analyses. For example, if the p value is 0.05, it is self-evident that one out of every 20 times the result is wrong. When conducting statistical analysis so repeatedly, it is necessary, for example, to set the p-value for significance very small, as the secretariat put it earlier, as adjustment for multiplicity. As I understand it, Shionogi, without having done so, claims that it is enough because a significant difference was found somewhere in the results after repeated analyses."

2.3 However, according to a September 28, 2022 press release from Shionogi titled "Shionogi Announces Achievement of the Primary Endpoint for Ensitrelvir Fumaric Acid (S-217622) in the Phase 3 part of the Phase 2/3 Clinical Trial in Asia", in the Phase III part of a Phase II/III study of this drug, the primary endpoint in the study was "selected in consultation with medical experts and regulatory authorities including the Ministry of Health, Labor and Welfare (MHLW), the Pharmaceuticals and Medical Devices Agency (PMDA) in Japan and the U.S. Food and Drug Administration (FDA), based on their scientific and medical validity". The study then set the five symptoms (stuffy or runny nose, sore throat, cough, feeling hot or feverish, and low energy or tiredness) as the new primary endpoints. These were similar to the five symptoms (four of the five symptoms were the same -- stuffy or runny nose, sore throat, cough, feeling hot or feverish, and shortness of breath (difficulty breathing)) whose selection was criticized as an invalid claim of significant differences at the July joint meeting above. Shionogi claims that the drug achieved "favorable results," by demonstrating a significant reduction versus placebo in the time to resolution of these five symptoms.

If this is true, it means that after the study was criticized as a post-hoc multiple analysis, Shionogi used a forbidden technique in clinical trials to prove efficacy by changing the primary endpoint to one that was likely to reach statistical significance in the middle of the trial, and that the Japanese and US regulatory authorities cooperated in the use of such a technique.

It is difficult to understand why this kind of thing is allowed.

3 It's questionable whether the significant difference is clinically meaningful.

According to the above press release, the median time to resolution of the five symptoms set as primary endpoints was 167.9 hours in those treated with the drug. This was approximately 24 hours shorter than the 192.2 hours in the placebo group, and a statistically significant improvement in symptoms was confirmed (p=0.04).

However, the Omicron strain is alleged to have a lower severity and fatality rate than the Wuhan strain, and this drug only shortens the time to resolution of five symptoms of the Omicron strain (stuffy or runny nose, sore throat, cough, feeling hot or feverish, and low energy or tiredness) by about 24 hours. It is questionable whether the drug has sufficient clinical meaning for approval under the emergency approval system, which is a serious exception to the approval system.

4 Application criteria under the emergency approval system are not met

4.1 There is no urgency

The Emergency Approval System requires that "drugs to which the emergency approval system applies shall be those that need to be used urgently to prevent the spread of diseases that may seriously affect the lives and health of citizens and other health hazards." (Legal grounds are as follows: Article 14-2(2) Paragraph 1, Item 1 of the Pharmaceuticals and Medical Devices Law).

As it is a serious exception to the approval system, the urgency criterion envisions cases where the public's health is seriously threatened by an "emergency situation" such as a pandemic, nuclear accident, or bioterrorism. It must be strictly construed.

This means that in the case of a pandemic, there must be a high degree of urgency, such as the rapid spread of a highly lethal virus or other infectious agent, the declaration of a state of emergency, or emergency measures have been taken, and medical services are on the verge of collapse. Or, due to the spread of disease overseas and the difficulty in identifying the infection route, a rapid spread of the

disease in Japan and a threat to normal medical services are strongly anticipated.

A notification issued by the director of the Pharmaceutical Evaluation Division of MLHW on May 20, 2022[4] also states that, "based on factors such as the rapid increase in the number of infected persons, the difficulty in identifying the route of infection, and the shortages of medical services, consideration will be given to whether the drug is necessary to avoid a serious impact on people's lives and the national economy."
In this regard, currently, although the number of infected people is on the rise, there has not yet been a nationwide shortage of medical services, and no restrictions on activities. In addition, national travel assistance has been implemented, and even tourists from abroad are being accepted. Therefore, we have to say that there isn't enough urgency to recognize the necessity of using this drug to avoid a serious impact on people's lives and the national economy.

4.2 The drug does not meet the “no alternatives” criterion

Since the emergency approval system is an exceptional system, it cannot be applied when other drugs with a similar efficacy have already been approved. It must meet the "no alternatives" criterion.

However, the drug is the third oral antiviral drug following Lagevrio and Paxlovid Pack for the treatment of COVID-19. In addition, as a main protease inhibitor, it is the second following Paxlovid Pack, so alternative drugs do exist.

The aforementioned MHLW notification also states that, "Even if approved drugs, etc. exist, if the candidate product is expected to be extremely useful or safe compared to the approved drugs, etc.", it is possible to interpret this situation as one in which the "no alternatives" criterion is being met. However, while there are several contraindications to the use of this drug, and teratogenic risks have been noted, its effect is only to accelerate the resolution of clinical symptoms, such as a runny or stuffy nose, by about 24 hours, as described above. Therefore, it is impossible to say that the drug is "expected to be extremely useful or safe compared to the approved drugs."

This was also pointed out at the aforementioned July joint meeting by Dr. Kamimura, a panel member from the Japan Medical Association, as follows[5]:

"When I introduced myself earlier, I mentioned that I am an internist. As I am a female doctor, I have many female patients, including young women. In such a situation, contraindicated medications for pregnant women are tricky. When I don't

know if a patient is pregnant or not, I'm too scared to prescribe the drug. There is also already a drug with similar efficacy, Paxlovid Pack. Though it is said to be difficult to swallow because of the size of the tablets, if it has the same efficacy and almost the same mechanism of action, why should I not choose that one? Naturally, in my clinical outpatient practice, I would not want to use Xocova if I was told of this level of difference in efficacy of respiratory symptoms being achieved. I am sorry, but that is how I honestly felt. In addition, considering the fact that it is a strong inhibitor of CYP3A, if it cannot be used for elderly patients with chronic diseases, so the range of its use will be very limited. Until we get clear results from Phase III, I am afraid I cannot touch it."

4.3 The drug should be discussed under the normal approval procedure

The emergency approval system grants approval, in an emergency on the "presumption of efficacy" based on the results of Phase II trials. This is to avoid a serious impact on people's lives and the national economy that could result from waiting for the results of Phase III trials. It requires the submission of the results of Phase III confirmatory clinical trials at a later date.

However, according to the above press release, preliminary results of the Phase III part of the Phase II/III clinical trial, with 1,821 patients enrolled in Japan, South Korea, and Vietnam, have already been obtained for this drug.

We have already mentioned that there is no urgency. If the Phase III study has already been completed, it should be sufficient to have the formal final analysis results submitted before reviewing it under the normal approval procedure. It is not the purpose of the law to review the drug under the emergency approval system after its Phase III study has been completed.

5 Conclusion

Various issues concerning the emergency approval system were discussed in the 208th session of the Diet. Both the House of Representatives and the House of Councillors passed supplementary resolutions from the perspective of preventing undue expansion of applications under the system[6].

However, Shionogi initially submitted its application under the conditional early approval system, an exceptional system for rare diseases for which it is difficult to conduct clinical trials. Then its application was switched to the emergency approval system. Furthermore, during the course of the trial, when they saw that the primary endpoint of improvement of 12 symptoms could not be achieved, they changed the

primary endpoint to another five symptoms similar to the five symptoms that were criticized as a post-hoc analysis. And during this process, there has even been a situation in which it is strongly suspected that the company's president made a top sales pitch to former cabinet member, in violation of the promotion code [7].

This series of actions by Shionogi are in violation of the main principles of clinical trials and regulatory approval, and deviates from the original intent of exceptional approval systems such as the conditional early approval system and the emergency approval system.

The government's response is also problematic. It signed a contract for the purchase of one million doses of the drug once the drug was approved, even before its approval (July 19), though the urgency requirement was supposedly lacking[8].

For these reasons, we oppose the emergency approval of this drug. Such an approval would violate the main principles of clinical trials, distort the essence of the emergency approval system, and jeopardize the system's future.

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[1] Shionogi's press release on September 28, 2022
https://www.shionogi.com/global/en/news/2022/09/20220928.html

[2] Medwatcher Japan: Opinion against emergency approval of Shionogi's COVID-19 drug
URL

[3] Minutes of the Advisory Panel Meeting on July 20, 2022
https://www.mhlw.go.jp/stf/newpage_27328.html

[4] Approval Review Approach in the Emergency Approval System (Notification issued by the director of the Pharmaceutical Evaluation Division of MLHW on May 20, 2022)
https://www.mhlw.go.jp/content/11120000/000940766.pdf

[5] Note 3, above.

[6] Supplementary resolution of the House of Representatives
https://www.shugiin.go.jp/internet/itdb_rchome.nsf/html/rchome/Futai/kourou6C3DDC46184DAAE04925882500304CF5.htm

Supplementary resolution of the House of Councillors
https://www.sangiin.go.jp/japanese/gianjoho/ketsugi/208/f069_051201.pdf

[7] Tweet by Akira Amari, Februrary 4, 2022.
https://twitter.com/akira_amari/status/1489434639555248130

[8] Press conference of Minister of Health, Labour and Welfare, July 22, 2022. https://www.mhlw.go.jp/stf/kaiken/daijin/0000194708_00465.html