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Mr. Shigeyuki Goto, Minister of Health, Labour and Welfare

Opinion against emergency approval of Shionogi's COVID-19 drug

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Purpose of the request

We oppose the approval of a drug candidate (Xocova Tablets 125mg) applied for under the emergency approval system by Shionogi to treat COVID-19.

Reasons for the request

1. Introduction

On June 22nd, 2022, the Ministry of Health, Labour and Welfare (hereinafter "MHLW") will hold an advisory panel meeting to discuss Shionogi's application for the approval of Xocova Tablets 125 mg (generic name: encitrelvir fumarate, hereinafter "the drug") for the treatment of COVID-19[1].

This oral drug was developed to allegedly suppress the growth of SARS-CoV-2 by selectively inhibiting 3CL protease, an enzyme essential for viral growth[2].

It was applied for approval in February of this year under the conditional early approval system. However, the application was switched to a new emergency approval system, which was created in May.

2. Application criteria under the emergency approval system

The emergency approval system is an exceptional system that grants approval in an emergency, without waiting for the results of Phase III confirmatory clinical trials.

Its application criteria are urgency, no alternatives, presumption of efficacy, and safety (Legal grounds are as follows: Article 14-2(2) Paragraph 1, Item 1 of the Pharmaceuticals and Medical Devices Law and a Notification issued by the director of the Pharmaceutical Evaluation Division of MLHW on May 20, 2022[3]).

Of these criteria, at least two -- urgency and presumption of efficacy -- have not been met. The reasons are described below.

3. Presumption of efficacy

3.1 Presumption of efficacy in the emergency approval system is based on the assumption that, in an emergency, when there is no time to wait for the results of Phase III trials, it can be presumed that the efficacy demonstrated in Phase II will also be proven in Phase III trials.

3.2 On April 24th, 2022, results of the Phase b part (one of the Phase II/III studies conducted by Shionogi) were posted on Shionogi's website[4]. According to these, of the antiviral effect, a rapid clearance of SARS-CoV-2 was demonstrated. On day four of treatment (following the third dose), the proportion of patients with a positive viral titer decreased by approximately 90% compared to placebo. Meanwhile, infectious virus shedding was shortened by 1-2 days versus placebo, and a significant reduction in viral RNA on days 2, 4, 6 and 9 was shown compared to placebo. Viral RNA levels were reduced to less than one-tenth versus the placebo group.

However, concerning improvements in the main clinical symptoms, there was no significant difference in the primary endpoint of a total score of 12 COVID-19 symptoms between treatment arms compared to the placebo group. Although Shionogi states that an improvement in composite score of five “respiratory and feverish” symptoms, characteristic of omicron strain infection, was shown, this is only a secondary analysis. Furthermore, as the analysis of five “respiratory and feverish” symptoms is, in particular, a post-hoc analysis, its results should not be over-interpreted. Rather, it is better to focus on the fact that the pre-planned primary endpoints have not been achieved.

3.3 Since the primary endpoint regarding clinical symptoms was not met in the Phase II study, it is difficult to assume that this endpoint will be met in the Phase III study.

Although antiviral efficacy has been demonstrated, what is important for drug approval is the primary endpoint of clinical symptom improvement. The fact that this endpoint was not achieved in Phase II should not be underestimated. In this regard, at the session of the House of Representatives Committee on Health, Labor

and Welfare of the 208th Diet on April 12, 2022, where the emergency approval system was discussed, representative Toru Miyamoto asked whether emergency approval could be granted in cases where the virus titer has decreased but clinical symptoms haven't improved. In response, Mr. Tsuguya Fukui, an expert witness, who, as chair of the Committee on the Pharmaceutical and Medical Device System, discussed and established the new emergency approval system, and published a report on how pharmaceutical approval should be in emergency situations, said, "Even if the virus titer is reduced, if the important outcome for patients does not change at all, clinically it cannot be said that the drug has been effective.[5]"

Therefore, unless new data have been submitted to MHLW since then to support the presumption that the primary clinical endpoint has been met, efficacy cannot be presumed for a drug that has failed to meet its primary endpoint of improvement in clinical symptoms in the Phase II study.

4. Urgency

4.1 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).

It approves drugs without efficacy being demonstrated through confirmatory clinical trials and is a serious exception to the approval system. Therefore, 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.

The aforementioned MHLW notification 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."

4.2 In this regard, the declaration of a state of emergency and emergency measures

have already been lifted even in Tokyo, where the outbreak of infection was remarkable. Even tourists from abroad are now allowed to enter the country, albeit with some restrictions. The decline in the number of infections and the trend toward an end to them have been consistent. Taking June 18, 2022 as an example, the daily number of deaths and serious illnesses nationwide was 20 and 39 respectively, and the hospital bed occupancy rate remains low[6].

Therefore, the situation is not urgent enough to invoke the emergency approval system. In this regard, it should be said that the urgency criterion has not been met.

5. Safety

In animal studies, this drug has been found to be teratogenic, causing skeletal morphology abnormalities in fetuses[7]. There are also concerns about the risk in humans. Since the drug has not yet been tested in Phase III, caution must be exercised in the safety evaluation and risk-benefit assessment.

6. Conclusion

Various issues concerning the emergency approval system were discussed in the 208th session of the Diet. In establishing the system, 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[8,9].

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. During this process, the company's president even made a top sales pitch to a former cabinet member. These go so far as to raise the question of whether the company is disregarding the purpose of the exceptional systems of the Pharmaceuticals and Medical Devices Law.

The emergency approval system is a serious exception to the approval system. Approving this drug for the first time under the emergency approval system would jeopardize the new system's future.

For these reasons, we oppose the approval of this drug under the emergency approval system.

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[1] Advisory Panel Meeting on June 22, 2022
https://www.mhlw.go.jp/stf/newpage_26115.html

[2] Shionogi's Release on April 24, 2022
https://www.shionogi.com/global/en/news/2022/04/20220424.html

[3] MLHW Director's Notification issued on May 20, 2022
https://www.mhlw.go.jp/content/11120000/000940766.pdf

[4] Note 2, above.

[5] Statement of Expert Witness Fukui, 208th Diet, Session of the House of Representatives Committee on Health, Labor and Welfare, No. 12, April 12, 2022.
https://kokkai.ndl.go.jp/#/detailPDF?minId=120804260X01220220412&page=15&spkNum=70&current=-1

[6] NHK's special site COVID-19
https://www3.nhk.or.jp/news/special/coronavirus/data-all/

[7] Shionogi's release: Notice Regarding the Media Coverage about S-217622, a Therapeutic Drug for COVID-19
https://www.shionogi.com/global/en/news/2022/04/e-20220413.html

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

[9] Supplementary resolution of the House of Councillors
https://www.sangiin.go.jp/japanese/gianjoho/ketsugi/current/f069_051201.pdf