

Administrative Notice

December 25, 2023

To: Division of Pharmaceutical Affairs,
Prefectural Health Department (Bureau)

From: Pharmaceutical Evaluation Division,
Pharmaceutical Safety Bureau,
Ministry of Health, Labour and Welfare

Q&A for basic principles for conducting phase 1 studies in Japanese prior to initiating multi-regional clinical trials including Japan for drugs in which early clinical development is preceding outside Japan

Questions and answers have been compiled as shown in the Appendix in association with the issuance of the "Basic principles for conducting phase 1 studies in Japanese prior to initiating multi-regional clinical trials including Japan for drugs in which early clinical development is preceding outside Japan (PMSB/PED Notification No. 1225 (2), Director, Pharmaceutical Evaluation Division, Pharmaceutical Safety Bureau, Ministry of Health, Labour and Welfare, dated December 25, 2023). We ask you to understand this compilation and to cooperate in informing related parties under your jurisdiction of this matter.

* This English version of the Japanese Administrative Notice is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

Appendix

Q&A for basic principles for conducting phase 1 studies in Japanese prior to initiating multi-regional clinical trials including Japan for drugs in which early clinical development is preceding outside Japan

Q1 What points should be considered to determine whether the safety of Japanese participants is clinically acceptable and manageable in the multi-regional clinical trial (MRCT) in which Japan will participate?

(Answer)

The risks of the study drug should be comprehensively examined, mainly taking into account the points described in the following 1) and 2), to confirm that there is a possibility that the risk for Japanese participants is greater than that for non-Japanese participants, and then determine whether the safety of Japanese participants in the MRCT is clinically acceptable and manageable in the proposed dosing regimen.

However, the points to consider should be selected according to the characteristics of each study drug, and other aspects may need to be considered depending on the study drug.

1) Safety of study drug

- The results of non-clinical studies suggest no significant risk (findings leading to death or not-recovered) with an unclear mechanism of onset at the dose used in the MRCT.
- The maximum dose used in the MRCT has a sufficient safety margin, and no clinically significant risks have been identified in the preceding foreign clinical trial(s) in which the safety has been assessed which sufficiently covers the clinical exposure expected in Japanese participants in the MRCT.
- There are clear approaches and monitoring methods for mitigating potential risks and the potential risks are manageable by defining appropriate measures/monitoring in the MRCT.
- No clinically significant risks that increased in incidence or severity dose-dependently have been identified in the preceding foreign clinical trial(s)
- When there are similar drugs (e.g., the same active substance, the same mechanism of action, biosimilar drugs, etc.) which can be used as a reference in the safety evaluation, no clinically significant risk of the study drug is

anticipated from the safety data of those drugs.

2) Effect of ethnic factors on study drug

- Ethnic differences in pharmacokinetics are unlikely based on comprehensive considerations of the following points:
 - The pharmacokinetics of the study drug is linear.
 - The drug is poorly metabolized or multiple metabolic pathways are involved.
 - It has not been reported that there are ethnic differences in the genetic polymorphisms of metabolic enzymes or transporters involved, or that the prevalence of polymorphisms with increased blood concentration of the study drug is higher in Japanese than in non-Japanese.
 - The pharmacokinetics of the drug is not significantly affected by BMI and body weight.
 - No significant impact of ethnic factors on the pharmacokinetics of the study drug is estimated based on an appropriate population pharmacokinetic analysis, etc.
- The drug has characteristics that make the safety and PK unlikely to be affected by ethnic factors (e.g., antibodies, peptides, endogenous substances, drugs that are poorly absorbed into systemic circulation and that act locally, etc.)
- There is no significant impact of ethnic factors such as race, region, body weight on the safety or pharmacokinetics based on previous clinical trial(s) in which the drug has been administered in multiple races/regions, or participants covering a wide range of body weight.
- When there are similar drugs (e.g., the same active substance, the same mechanism of action, biosimilar drugs, etc.) which can be used as a reference in a safety evaluation, no clinically significant ethnic differences in the safety are observed with those drugs, and the same is anticipated for the study drug.

Q2: What additional measures can be taken to ensure the safety of Japanese participants in the MRCT?

(Answer)

Safety measures differ depending on the characteristics of each study drug. The appropriate measures should be selected based on prior information about the drug, the design of the study, and how additional safety measures could affect the safety evaluation. For example, the following measures can be taken, and other safety measures may be more appropriate in certain cases.

- Set up a cohort to evaluate the safety (including pharmacokinetics, if necessary) of a small number of Japanese participants prior to the main part of the study.
- Until the safety evaluation is completed for a certain number of Japanese participants, administer the drug to a small number of Japanese participants (e.g., one participant at a time) with appropriate intervals between each administration.
- Increase the frequency of visits and monitoring during the early stage of administration.
- During the initial stage of administration, Japanese participants will either be hospitalized or observed at the study site for a certain period of time.
- Until the safety evaluation is completed for a certain number of Japanese participants, execute safety monitoring with special attention to Japanese participants in an organization composed of third parties, such as an independent data monitoring committee.