

Administrative Notice
October 27, 2014

To: Prefectural Health Department (Bureau)

Evaluation and Licensing Division,
Pharmaceutical and Food Safety Bureau,
Ministry of Health, Labour and Welfare

Basic Principles for Conducting Phase I Trials in the Japanese Population
Prior to Global Clinical Trials

As one of the key factors toward timely patient access to new drugs, the “Basic principles on Global Clinical Trials” (PFSB/ELD Notification No. 0928010, Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 28, 2007) and the “Basic Principles on Global Clinical Trials (Reference Cases)” (Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau, Ministry of Health, Labour and Welfare, dated September 5, 2012) have been issued from the perspective of promoting Japan’s active participation in global clinical trials.

Based on the accumulated knowledge up to now, the “Basic Principles for Conducting Phase I Trials in the Japanese Population Prior to Global Clinical Trials” has been compiled as attached. We ask you to inform manufacturers and sellers placed under your administration to utilize this for their business operations.

*1st publication : 20/11/2014 Revised : 15/1/2015

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.

(Attachment)

Basic Principles for Conducting Phase I Trials in the Japanese Population Prior to Global Clinical Trials

In the current situation where drug developments are becoming globalized, active participation in global clinical trials is a valuable opportunity for Japan to promote clinical development without falling behind developments overseas and to accumulate appropriate evidence in the Japanese population; therefore it is important to establish development plans so as not to lose this opportunity. In order to do this, with consideration of the timing of conducting a global clinical trial, tolerability data of the test drug in the Japanese population should be ensured before participating in the global trial, and there should be sufficient consideration about accumulating related information and data, including about conducting phase I trials in the Japanese population. Meanwhile, when considering whether or not Japan should participate in a global clinical trial, there are in fact many cases in which human data in a foreign population has already been obtained to some extent in drug developments lead by foreign countries. Based on the accumulated knowledge up to now, there may be cases where Japanese phase I trials are not necessarily required prior to Japan's participation in global clinical trials if safety in the Japanese population that will be included in the global clinical trial is ensured by foreign data.

If phase I trial data in the Japanese population have not been obtained, Japan's participation in phase II or phase III global clinical trials should be comprehensively judged based on the consideration of the following main points. Regarding individual cases, consultation is recommended with the Pharmaceuticals and Medical Devices Agency (hereinafter referred to as PMDA) after considering the details stated in this document.

1. Principles

The main purpose of conducting a phase I trial is to evaluate tolerability and pharmacokinetics of the test drug in humans. Therefore, if at the point of initiating global clinical trial tolerability in human has not been sufficiently confirmed or the safety risk is thought to be high in the Japanese population, a phase I trial should be required to be conducted in the Japanese before participating in the global clinical trial.

On the other hand, if tolerability of the test drug has been confirmed in human and ethnic

factors are thought to have little effect on the safety of the test drug, a phase I study may not be required in the Japanese population prior to participation in a global clinical trial. Whether or not a phase I trial is necessary in the Japanese will be comprehensively judged after considering both the possibility for a large-scale comparative study to accumulate a sufficient sample size of Japanese subjects as well as safety in the Japanese, taking into account the property of the test drug.

In general, if Japan participates in a global clinical trial regardless of whether or not to conduct a prior phase I trial in the Japanese population, it is beneficial to include a sufficient number of Japanese cases in that trial and to conduct pharmacokinetics measurements and safety monitoring accordingly.

If a phase I trial in the Japanese population is considered necessary prior to participation in global clinical trial, refer to the “Basic principles on Global Clinical Trials” (PFSB/ELD Notification No. 0928010, Director of Evaluation and Licensing Division, Pharmaceutical and Food Safety Bureau Ministry of Health, Labour and Welfare, dated September 28, 2007) for individual judgment on how to conduct the phase I trial. Even if a phase I trial is not conducted in the Japanese population prior to participation in global clinical trial, human pharmacology study in the Japanese should in principle be conducted concurrently with the global clinical trial because pharmacology study is used in evaluating pharmacokinetic profile, comparing pharmacokinetics among ethnic groups, and investigating appropriate doses.

2. Main points to be considered about whether or not to conduct a phase I trial in the Japanese population

Prior to participation in phase II and III global clinical trials, the following main points should be considered for whether or not to conduct a phase I trial in the Japanese population. However, because the points to be considered differ among individual drugs under development, consideration is not necessarily required on all of the following points and may rather require consideration on points other than those stated below.

(1) Characteristic of the drug

a. Whether the characteristics of the drug, such as extended release or nanonized (physical/chemical property, biological activity, etc.), are similar to those of approved drugs.

b. Whether the method of administration is not highly invasive.

(2) Pharmacokinetic properties

- a. Whether the pharmacokinetics of the drug is linear.
- b. Whether multiple metabolic pathways are involved.
- c. Whether there are any ethnic differences in the associated metabolizing enzymes or genetic polymorphism of transporters.
- d. Whether the possibility of ethnic differences in exposure is low.
- e. Whether blood concentration is thought to correlate with efficacy and safety.

(3) Pharmacodynamic properties

- a. Whether the mechanism of action of the active ingredient is not highly innovative.
- b. Whether the pharmacodynamics of drug is linear.
- c. Whether there are any ethnic differences in genetic polymorphism of the target molecule.
- d. Whether the pharmacodynamics is thought to correlate with efficacy and safety judging from the mechanism of action.

(4) Safety

- a. Whether a safety evaluation in the Japanese population is possible using data from preceding clinical trials overseas.
- b. Whether specific safety risks are indicated from existing data (including information of related products).
- c. Whether the scientific mechanism of action has been clearly determined regarding risks that have been specifically observed.
- d. Whether the onset and severity of the adverse events are dose-dependent.
- e. Whether the effect is localized.
- f. Whether there are definite measures or monitoring methods for the expected adverse events.
- g. Whether safety has been confirmed in other dosages and administrations.
- h. Whether sufficient measures are taken to ensure safety of all subjects in the global clinical trial that Japan intends to participate in. Whether measures are appropriate if specific methods in specific areas are necessary for cases where safety risks differ according to ethnic differences.

When considering whether or not to conduct a phase I trial in the Japanese population,

reference information should also be taken into account, for example, whether the target disease is a fatal disease, an orphan disease, or a disease without a similar or alternative treatment.

3. Reference cases regarding the necessity of conducting a phase I trial in the Japanese population

Based on the details mentioned in the above sections 1 and 2, below are example cases for when a phase I trial is necessary in the Japanese population prior to participation in global clinical trial as well as examples for when no conduct of a phase I trial may be accepted. As these are merely examples, consultation with PMDA is recommended for individual cases, with presentation of rational evidence based on scientific evidence.

(1) Cases in which a phase I trial is necessary in the Japanese population

a. In cases where there were serious safety concerns in early clinical trials conducted overseas with no clear understanding of those mechanisms, and where there is no reliable data indicating that those risks in the Japanese population are equal to or less than those in foreign populations.

b. In cases of drugs with new active ingredients that have no similar products whose overseas experience is extremely limited, for example, with no results obtained in phase I repeated dose trials in the foreign population, and whose safety of the dosage and administration in the global clinical trial that Japan intends to participate in is judged to have not been sufficiently ensured in the foreign population.

c. In cases where risks related to blood concentration or safety in the Japanese population is presumed to be remarkably high compared to the risks in the foreign population based on the pharmacokinetics property, foreign clinical trial results, and study results of similar products, and where judging from the clinical trial results in the foreign population, safety is not ensured when dosages intended to be used in the global clinical trial are administered in the Japanese population.

(2) Cases in which no conduct of a phase I trial may be accepted.

a. In cases where immediate participation in a large-scale comparative study or a comparative study for an orphan disease should be considered, taking into account the number of Japanese patients, and where safety of the test drug has been confirmed based

on sufficient dosing experience in a foreign clinical trial, with no remarkable ethnic differences in ethnic factors based on the knowledge obtained.

b. In cases of co-administrations where although toxicity has been observed to a certain extent when each of the test drug and the concomitant drug is administered alone, safety in the Japanese population has been confirmed in each of the single administrations of the test drug and the concomitant drug, and if no significant ethnic differences in safety are observed based on the knowledge obtained so far regarding ethnic factors.

c. In cases of development of new route of administration, new dosage, or new dosage form for drugs approved in Japan in which ethnic differences in clinical effect have not been observed in the approved drug, and the safety risk of the route of administration, dosage, or dosage form under development is considered to be the same or less than the risk of the approved drug.

d. In cases of development for follow-on biologics in which the follow-on biologic has been indicated to be highly similar to the brand-name biopharmaceutical in an appropriate quality study or non-clinical study, and the pharmacokinetics of the brand-name biopharmaceutical is similar between the foreign population and the Japanese population. Note that in the development of follow-on biologics, there may be cases where a clinical pharmacology study (including bioequivalence trial with pharmacokinetics of the brand-name biopharmaceutical) may not be necessary for the Japanese population.