Check List for 30-day-Clinical Trial Notification Review on an Initial Clinical Trial Notification (Oncology Drugs)

December 10, 2024

I. GENERAL MATTERS (ORGANIZATION FOR CONDUCTING CLINICAL TRIAL, etc.)

1. Contact System and Deadline for Reporting Safety Information (serious adverse event (hereinafter SAE) etc.)

The followings are stated in the Clinical Trial Notification (hereinafter CTN) or attached documents;

☐ Contact system and deadline for reporting from the clinical trial sites to the sponsor (or clinical trial in-country representative, hereinafter CTIR).

☐ Contact system and deadline for reporting from the sponsor (or CTIR) to the other clinical trial sites.

☐ Regarding overseas safety information, contact system and deadline for reporting from the sponsor (or CTIR) to the clinical trial sites in Japan.

☐ If the after-hours emergency contact is an external contractor, the contact system and deadline for reporting safety information from the emergency contact to the sponsor (or CTIR).

2. Medical Device(s) / Equipment Used in the Clinical Trials

☐ Certification/approval number of medical devices(s)/equipment used in the clinical trials is stated in the remark section of the CTN, if a medical device(s)/equipment used in the clinical trial has been certified/approved as a medical device(s)/equipment.

☐ Actions taken in compliance with “Partial amendment of "Handling of Notification of Clinical Trial Plan for Machines and Devices"” (PSB/MDED Notification No.0329-5 dated Mar.29, 2024) No. 4, (2) is stated, if a medical device(s)/equipment used in the clinical trial has NOT been certified/approved as a medical device(s) /equipment. Otherwise, it is stated that appropriate action is to be taken later.

☐ It is stated that the fact that a medical device(s)/equipment which has not been certified/approved is to be used in the clinical trial is mentioned in the protocol (or investigator's brochure) and informed consent document, accordingly, for the information sharing.

II. CLINICAL SAFETY

1. Participants enrolled in Phase 1 Study

☐ Following measures are to be taken, considering the potential toxicities of study drugs and the rationale to include the patients who can benefit from standard therapy in terms of the prolongation of life or alleviation of the symptoms.

- In the dose escalation part, patients with a malignant tumor who are not expected to respond to standard therapies, or for whom have no standard therapy option is available are selected as study population.
- After the recommended doses has been decided; it should be explained followings at least, when enrolling patients who can benefit from standard therapy options.
  - The study drug is expected to have equivalent or more efficacy than the standard therapy.
  - Scientific or ethical rationale for combining the study drug and established therapy, if the study drug is being developed as a combination therapy.

☐ If the study drug is being developed in combination with a standard therapy, it is stated in the informed consent document that the participant may not be able to receive standard therapy, if he/she experiences dose limiting toxicity (hereinafter DLT) and/or SAE.

2. Starting Dose and Administration

The attached documents contain the following information:

☐ Appropriate starting dose for human has been determined based on the non-clinical studies (pharmacology study, pharmacokinetic study, and toxicity study). If the clinical trial has been started overseas prior to the clinical trial in Japan, appropriate starting dose and dosage has been determined based on the onset of DLT in the overseas clinical trials, external and internal racial extrinsic and intrinsic ethnic factors etc., and the rationale is explained.

☐ In the multi-regional clinical trials in which Japanese participants are enrolled competitively, if enrollment of non-Japanese patients participants has been started and safety information has been available, starting dose and dosage presumed for Japanese participants are specifically stated.

3. First in Human Study

☐ The interval between the initial administration to the first and the second participants has been determined. In addition, the rationale for the determination that the safety of the participants is ensured with the interval is explained.

☐ When repeated dose study is conducted without prior single-dose study, the rationale of the decision that it is acceptable to start the repeated dose study is explained.

4. Clinical Trials with Concomitant Administration

The attached documents contain the following information:

☐ It is explained that, based on the results of overseas clinical studies of monotherapy etc., concomitant administration unlikely cause significant increase of toxicity due to overlap in the

toxicity profile etc., and that safety problems are unlikely to occur in combination therapy.

☐ Concomitant administration is conducted within the dosage for which it is judged as tolerable with monotherapy.

5. Measures to ensure the safety during tolerability evaluation period.

☐ Participants are to be hospitalized during the tolerability evaluation period.

or

☐ If the participants are monitored under outpatient setting during the tolerability evaluation period, the attached documents explain followings; situation where participants can be managed on an outpatient basis (e.g., The degree of adverse events judged to be amenable to outpatient management), preparation to receive the participant in a hospital in case of emergency, and measures to ensure the safety of participants under outpatient setting.

6. Inclusion/Exclusion Criteria

☐ Appropriate inclusion/exclusion criteria are established, taking into account the adverse events expected from the mode of action, toxicity test study results, and clinical study results of similar drugs, etc.

☐ When enrolling patients who may have a history of hepatitis B virus infection, and the administration of study drugs may cause an immunosuppressive effect, safety measures such as testing at screening and monitoring are established in compliance with the "Guidelines for Hepatitis B Caused by Immunosuppression/Chemotherapy" (The Japanese Society of Hepatology).

☐ If the study drug may cause interstitial lung disease (hereinafter ILD), exclusion criteria include a history of ILD or significant pulmonary comorbidities.

☐ Patients with a history of hypersensitivity to the drug substance contained in the study drug are excluded.

7. Evaluation of Tolerability

☐ Definition of DLT is specified so that tolerability can be evaluated objectively.

☐ It is stated how the tolerability should be evaluated in the participants for whom the dosage of the study drug was reduced, interrupted, or postponed (discontinued) during the tolerability evaluation period.

☐ To ensure that DLT is not underestimated, the adverse events should be assessed as DLT if they lead to drug interruption or dose reduction beyond a certain level, and hematologic toxicity lead to the use of hematopoietic factor preparations.

☐ When participating in a multi-regional clinical trial, the method for evaluating tolerability in

Japanese participants at the recommended dose is stated.

☐ When a dose-escalation study design based on statistical considerations is used, the explanation includes that the operating characteristics of the dose-escalation study design has been evaluated with simulation study and that safety can be ensured based on the results, after referring to "Statistical Considerations When Planning Phase I Clinical Trials in Oncology - From the Safety Perspective（Early Consideration）＜https://www.pmda.go.jp/files/000272426.pdf＞". The sponsor should confirm that the explanation refers to the followings:

- Rules for dose escalation, definition of maximum tolerated dose (hereinafter MTD), stopping rules of tolerability evaluation (maximum number of participants overall and at each dose level, etc.
- Following results of simulation study with the scenarios that the true DLT rate at the lowest dose level slightly exceeds the threshold for excessive toxicity.
  - Proportion of each dose level to be selected as the MTD
  - Average number of participants enrolled at each dose
  - Average number of participants with DLT at each dose
  - Proportion of the trial termination,

8. Handling of Participants who had Adverse Events

☐ Criteria for the resumption of administration of the study drug and the dose at resumption have been established.

9. Concomitant Drugs

☐ It is stated whether the study drug can be administered concomitantly with other anti-cancer drugs.

☐ When a drug is concomitantly used for an indication that has not been approved in Japan, such as hematopoietic factor preparations used for anemia associated with cancer chemotherapy, it is stated that the indication is not approved in Japan.

☐ It is stipulated whether the concomitant use and intake of drugs, foods, and supplements that may affect the pharmacokinetics of the study drug are allowed or restricted.

☐ The informed consent document states that participants should consult with the investigator if they take drugs other than the study drug or supplements.

10. Requirements regarding Contraception, Pregnancy, and Breastfeeding

☐ The specific period for which contraception is required during the study and after the last dose of study drug is stated.

☐ Participants who require contraception (women of childbearing potential etc.) are defined.

☐ Specific contraceptive methods and whether drugs/devices used for it are certified/approved in Japan are stated.

☐ It is clearly stated that patients who are pregnant or who may be pregnant are excluded. In addition, pregnancy test is specified.

☐ Actions to be taken in the event that a participant or partner becomes pregnant are stated. (e.g., discontinuation of study drug, reporting to the investigator, and the follow-up)

☐ It is stated that breastfeeding patients are excluded. It is also stated whether such patients can be enrolled if they suspend breastfeeding and if so, specific period until breastfeeding is resumed.

11. Sufficiency of Non-Clinical Studies Conducted prior to Clinical Studies

☐ In accordance with the non-clinical study guidelines/guidance (ICH S9, S6, M3, etc.), non-clinical studies sufficient for starting the clinical study have been conducted appropriately.

12. Anticipated Adverse Events Predicted from Non-Clinical Studies and Overseas Clinical Trials etc.

☐ Appropriate test items/schedules are established, taking into consideration anticipated adverse events can be caused by the study drug or its combination therapy, that are expected from non-clinical studies, overseas clinical trials, etc., and the incidence of adverse events in similar drugs if there are any similar drugs.

☐ If ILD can be induced, screening and appropriate test items/schedules for early detection have been established.

☐ The anticipated side effects of the study drug or its combination therapy are stated in the informed consent document for the participants (or his/her legal representative) in an easily understandable manner.

☐ When the study drug is administered for a long period before the long-term repeated dose toxicity studies have been conducted (or not yet completed), or when the drug is administered to women before reproductive and developmental toxicity studies have been conducted (or not yet completed), it is stated in the informed consent document that only limited safety information is available.

13. Clinical Trials where Pharmacogenomic Data is to be Obtained/Used

☐ If blood or tissue samples are taken in the clinical trial, the method, amount, timing, and the purpose are stated.

☐ Personal information related to blood or tissue samples is appropriately protected.

☐ Arrangement for storage and disposal of blood or tissue samples is stated.

☐ The procedure to disclose the genetic test results to a participant is stated. If the results are not to be disclosed, it is stated as such, with the reason.

☐ The procedures to be taken in the event of the refusal of consent at the time of enrollment or the withdrawal of consent during the clinical trial concerning the use of blood or tissue samples are stated. (Such as suitability for the participation in the clinical trial, disposal of samples, etc.)

14. Clinical Trials in which Genetic Testing, etc. is to be Done

☐ If the diagnostic reagent/device to be used in the clinical trials for genetic testing, etc. is not certified/approved as an in vitro diagnostic (hereinafter IVD) or a medical device, it is stated that the genetic testing etc. has not been certified/approved and that false positives/negatives can occur.

☐ It is stated that the results of genetic testing, etc. and information on blood or tissue samples may also be used for the development of IVDs or medical devices.

15. Other Matters regarding Informed Consent Document

The followings are stated in informed consent documents;

☐ The purposes of a study in tolerability evaluation period (e.g., Cycle 1) and also that of a study the following continued administration (e.g., Cycle 2 and onwards), separately.

☐ Action to be taken when the participants failed to take the study drug (missed dose, etc.), or erroneous administration/intake occurs, such as overdosing.

☐ Emergency contact during off-hours. (e.g., nighttime and holidays)

☐ When the participant visits a medical institution other than the clinical trial site to seek medical attention during the period of his/her participation in the clinical trial, the participant needs to inform the physician of his/her participation in the clinical trial.

III. ATTACHED DOCUMENTS

1. CTN

☐ If the field for the co-investigator(s) is/are unfilled, it is stated that appropriate procedure is to be taken as soon as the co-investigator(s) is/are determined.

☐ If the clinical trial is applicable to either of the followings, appropriate description is provided in the columns for "Other information on the investigational drug" and "Other information regarding this notification" in the CTN, in compliance with relevant notifications (*)

(1) Multi-regional clinical trial

(2) Clinical trial in which genomic testing is to be done

(3) Clinical trial using a drug product regulated by The Cartagena Act

(4) Clinical trial using an agent which is expected to be designated as a Biological product defined in the PMD Act

(5) Microdose clinical trial

(6) Description of medical device/equipment used in the clinical trial

(7) Clinical trial involving a companion diagnostics/device

(8) Combination products

(* “Partial amendment of "Handling of Clinical Trial Notification etc. by Sponsor"” (PSB/PED Notification No.0329-2 dated Mar. 29, 2024), "Points to be noted regarding New Drug Application of Companion Diagnostic Drugs and Related Drugs" (PFSB/ELD Notification No.0701-10 dated July 1, 2013), "Amendment of "Handling of Application of Combination Product" (PSEHB/PED Notification No.1122-4 dated November 22, 2016).

2. Protocol and Investigator's Brochure

□ If protocol and/or investigator's brochure both in Japanese and English is submitted to clinical trial sites in Japan, it is stated which version is to prevail for use at the clinical trial sites in Japan. In case the English version prevails, it is stated that a sponsor ensures the contents and details of the Japanese and the English version are identical.

3. Quality Information

□ For a formulation other than low-molecular weight compound, a document regarding quality which is prepared in compliance with "Revised Q&A regarding the clinical trial notification and conducting drug clinical trials" (PSEHB/PED, Administrative Notice, dated Feb. 7, 2022) (Q&A 27) is attached to the CTN.