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Protocol title [protocol abbreviation]
(Protocol No. **NCCHxxxx**)

SOP on Handling of Safety Information

(Study for the supplemental new drug application)

Version	xx
Prepared By	Name Mmm dd, yyyy
Approved By	Name Mmm dd, yyyy

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1 Purpose

The purpose of these Procedures is to establish procedures for collecting, managing, evaluating, and handling safety information and reporting to local regulatory authorities (Pharmaceuticals and Medical Devices Agency, Japan [PMDA], Ministry of Food and Drug Safety, Korea [MFDS], Taiwan Food and Drug Administration [TFDA], and Ministry of Health, Singapore [MOH]) and specify other necessary information.

Editorial Note: *Add relevant regulatory authority/authorities if the study includes other participating country/countries.*

2 Scope

These Procedures apply to a "Protocol title [protocol abbreviation]" (hereinafter referred to as "the Trial").

3 Definition of Terms

3.1 Adverse Event (AE); See Section X (xxxxx) in the Protocol.

AE is any untoward medical occurrence in a clinical investigation patient administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage.

3.2 Serious Adverse Event (SAE); See Section X (xxxxx) in the Protocol

SAE is any untoward medical occurrence at any dose that:

- results in death;
- is life-threatening (immediate risk of death);
- requires inpatient hospitalization or prolongation of existing hospitalization;
- results in persistent or significant disability/incapacity (substantial disruption of the ability to conduct normal life functions);
- results in congenital anomaly/birth defect.

3.3 Adverse Drug Reaction (ADR)

ADR is any adverse and unintended reaction to the study drug administered irrespective of the dose. Thus, there is at least a reasonable likelihood of a causal relationship between the study drug and the adverse event, and such a relationship cannot be ruled out.

3.4 Unexpected Adverse Drug Reaction (Unknown Adverse Drug Reaction)

Unexpected adverse drug reaction is any adverse reaction for which the nature or severity is not consistent with the applicable study drug information such as an investigator's brochure (including the information that has been reported to each Principal Investigator and local regulatory authorities). However, all known ADRs, for which the seriousness, frequency, and other characteristics are not consistent with the applicable product information, should be handled as unknown ADRs.

A "predictable" point in time should be the date on which the investigator's brochure is prepared or revised or the date on which the report is presented to the regulatory authorities. Therefore, the same AE, of which medical institutions have been notified through written communication since reporting to the regulatory authorities, shall be "predictable" even if the investigator's brochure is not revised.

3.5 Safety Information

The following safety information shall be handled during the Trial:

[Japan]

(1) SAEs Information reported in the Trial

(2) Patient Information from domestic and overseas sites

・ ADR information about the investigational product or any other drugs used overseas whose ingredients are equivalent to those of the investigational product, both of which are supplied by "the study drug provider in the Trial" (hereinafter referred to as "ABC").

- Listing of patients with unknown and serious ADRs (Line listing in Japanese): Output data from the system are provided by ABC every X weeks.
- Listing of patients with unknown and serious ADRs (Line Listings): Output data from the system are provided by ABC every X months.

(3) Reports of Safety Measures

(i) Overseas

Discontinuation of manufacturing, import or sales, or recall or disposal of a drug product used overseas that contains the same active ingredients as the test drug, or measures implemented to prevent occurrence or spread of health hazard associated with such a drug product

(ii) Japan

Measures taken for a drug product used in Japan that contains the same ingredients as the test drug, which has been approved in Japan and investigated in a clinical study intended for" the supplemental new drug application" (hereinafter referred to as "the Application"), and where such measures could affect the content of the clinical study or the Application

(4) Research Reports

(i) ADRs to the investigational product and other drugs or infections associated with their use may cause cancer or other significant diseases/disorders or death.

(ii) There is a remarkable change in the tendency to develop diseases that may be caused by ADRs to the investigational product and other drugs or infections potentially associated with their use, such as incidence, frequency, and conditions for occurrence.

(iii) The investigational product and other drugs are not; (a) indicated for the treatment of the target disease, or, (b) effective for treating it.

(5) Development Safety Update Report (DSUR)

・ A Development Safety Update Report (DSUR) is an overview of serious ADRs reported through the DSUR form prepared by ABC.

・ A summary of DSURs is provided by ABC once a year.

(6) Investigator's Brochure

・ An investigator's brochure (in English and Japanese) is provided by ABC is begun and the brochure is revised.

・ Investigator's brochure should be submitted to the regulatory authorities according to local regulations.

(7) Information about the quality, efficacy, and safety of the study drug or other important information required for conducting the Trial properly

[Korea, Taiwan, and Singapore] ***Editorial Note:*** *Add other participating country/countries if necessary; hereinafter the same shall apply.*

(1) SAEs Information reported in the Trial

(2) Patient Information from domestic and overseas sites

- ADR information regarding the investigational product or any other drugs used overseas whose ingredients are equivalent to those of the investigational product, both of which are supplied by ABC.
  - ➢ Listing of patients with unknown and serious ADRs (Line Listings): Output data from the system are supplied by ABC every X months.

(3) Development Safety Update Report (DSUR)

- DSUR summarizing the information obtained in the Trial, which was prepared by the Sponsor (National Cancer Center Hospital in these Procedures; hereinafter the same shall apply)
- The Sponsor provides the Principal Investigator with DSUR once a year.
- DSURs should be submitted to the regulatory authorities according to local regulations.

OR

- DSUR is supplied to the Sponsor by the study drug provider in the Trial once a year.
- The Sponsor provides the Principal Investigator with DSUR once a year.
- DSURs should be submitted to the regulatory authorities according to local regulations.

(4) Investigator's Brochure

- ABC provides an investigator's brochure (in English) to the Principal Investigator when the Trial is begun and the brochure is revised.
- Investigator's brochure should be submitted to the regulatory authorities according to local regulations.

(5) Information regarding the quality, efficacy, and safety of the study drug or other important information required for conducting the Trial properly

3.6 Serious Adverse Event Report (SAE Report)

Serious Adverse Event Report is a report which is described the details of SAEs reported in the Trial and the medical assessment (e.g., causality, seriousness, and predictability) of the reporter. In the Trial, a "Serious Adverse Event Report Form" is used for reporting to the Sponsor by investigators. "Standardized Form for New Trial Request ([Med] Forms 12-1 and 12-2)" is used in Japan. The applicable forms should be used according to local regulations in Korea, Taiwan, and Singapore.

3.7 AEs Confirmation Letter [applicable only for Japan]

AEs Confirmation Letter is a report that summarizes the Coordinating Investigator's and Principal investigators' medical judgement and medical consideration (reporter's opinions and future action) of the safety information collected (hereinafter referred to as "Confirmation Letter,")

4 Role and Responsibilities for Handling of Safety Information and Other Information

4.1 Non-industry-sponsored Investigator [applicable only for Japan]

See the protocol supplement.

(Responsibilities)

As "non-industry-sponsored investigators," Japanese Principal Investigators shall be responsible for the following:

- After having become aware of the occurrence of SAEs at their study centers, the Japanese principal Investigators shall provide treatment to subjects, ensure their safety, and report the matter immediately to the director of the study center and the Coordinating Committee/Sponsor regardless of their causal relationship. When the reported SAEs meet the requirements specified in Article 273 of the Enforcement Regulations of the PMD Act, PMDA shall be provided with a report through the Coordinating Committee.
- After having collected information regarding SAEs related to the Trial that occur in other study centers and upon finding that they meet the requirements specified in Article 273, Paragraph 1 of the Enforcement Regulations of the PMD Act, the Japanese Principal Investigators shall report them to PMDA through the director of the study center and the Coordinating Committee.
- After having received domestic and overseas SAE reports and upon ascertaining the reported SAEs as meeting the requirements specified in Article 273 of the Enforcement Regulations of the PMD Act, the Japanese Principal Investigators shall report them to PMDA through the director of the study center and Coordinating Committee. If they can confirm that the SAEs have been reported by ABC or are scheduled to be reported within a time frame prescribed by law according to PFSB-ELD Notification No. 0701-21, they do not have to report them.
- After having received domestic and overseas research reports and safety measure information and upon finding that they meet the requirements specified in Article 273 of the Enforcement Regulations of the PMD Act, the Japanese Principal Investigators shall report to PMDA through the director of the study center and Coordinating Committee. If they can confirm that the safety measure information and the research reports have been reported by ABC or are scheduled to be reported within a timeframe prescribed by law according to PFSB-ELD Notification No. 0701-21, they do not have to report them.
- For information regarding the quality, efficacy, and safety of the study drug or other important information required for the proper conduct of the trial, the Japanese Principal Investigators must also collect such information from ABC and evaluate and utilize the information.
- After having become aware of information regarding the quality, efficacy, and safety of the study drug or other important information required for the proper conduct of the trial, the Japanese Principal Investigators shall amend the protocol and revise written information/informed consent forms if necessary.
- Japanese Principal Investigators shall make a periodic report according to provisions of Article 273, Paragraph 3 of the Enforcement Regulations of the PMD Act.

4.2 Sponsor

(1) Sponsor/Study Chair

See the protocol supplement.

(Responsibilities)

- The Sponsor/Study Chair should report all serious and unexpected ADRs immediately to all concerned Principal Investigators/study centers, and regulatory authorities.
- The Sponsor/Study Chair should comply with the applicable regulatory requirements and ICH Guideline E2A.
- According to the applicable regulatory requirements, the Sponsor/Study Chair should submit all updated safety information and reports of safety measures to the regulatory authorities.

(2) Pharmacovigilance (List contact information of Unblinded Safety Information representative, etc., if necessary)

See the protocol supplement.

(Responsibilities)

- The Unblinded Safety Information representative shall manage unblinded safety information appropriately.
- The Unblinded Safety Information representative shall obtain unblinded safety information and report to regulatory authorities, when necessary.

(3) Coordinating Committee [applicable only for Japan]

See the supplement to the protocol

(Responsibilities)

- The Coordinating Committee shall report safety information related to the conduct of the whole trial(s) for the investigational product to the Japanese Principal Investigators and provide advice.
- The Coordinating Committee shall report the safety information obtained to the Japanese Principal Investigators without delay. The Committee shall also report SAEs that occur in the Trial to ABC without delay.
- When necessary, the Coordinating Committee shall summarize opinions from all the Japanese Principal Investigators and report them to PMDA using a report form specified in Section 5.2 (Report Forms for ADRs and Other Events).
- According to "Procedures for Efficacy and Safety Evaluation Board," the Coordinating Committee shall report unknown and serious AEs to the Efficacy and Safety Evaluation Board (E-DMC) and shall be able to consult the Board about trial continuation, change, or discontinuation.
- For SAEs and other events that occur.
- during the Trial, the Coordinating Committee shall prepare a report form for the regulatory authorities (CIOMS form) based on the reports from the Principal Investigator.

(4) Coordinating Committee Secretariat [applicable only for Japan]/project manager

Provided in the supplement to the protocol

(Responsibilities)

- Coordinating Committee Secretariat or the project manager shall help the Sponsor or the Coordinating Committee in communicating safety information to the Principal Investigator, Coordinating Committee, ABC, and monitor(s) at each study center without delay and report such information properly to the regulatory authorities.
- Coordinating Committee Secretariat or the project manager is responsible for managing the reports provided by each study center or by the study drug provider and those submitted to PMDA.

4.3 Contract Research Organization (CRO)

See the protocol supplement.

(Responsibilities)

- For SAEs, the CRO shall prepare, on the basis of reports from the Principal Investigator, a report for the regulatory authorities in Korea, Taiwan, and Singapore.
- The CRO shall make safety information reports and submit a notification to the regulatory authorities in Korea, Taiwan, and Singapore in accordance with local regulations.

- The CRO is responsible for managing safety information reports and other safety related documents submitted to the regulatory authorities in Korea, Taiwan, and Singapore.

4.4 External Data Monitoring Committee (E-DMC)

See the protocol supplement.

(Responsibilities)

- When the Study Chair or Coordinating Committee consults with the External Data Monitoring Committee regarding SAEs and other events that occur in the trial, the External Data Monitoring Committee shall recommend the continuation, change, or discontinuation of the trial.

4.5 Study Drug Provider

See the protocol supplement.

(Responsibilities)

- ABC shall provide the Coordinating Committee with the investigator's brochures and copies of domestic and overseas listings of patients with unknown and serious ADRs, research reports, reports of safety measures, and the summary of DSURs. ABC shall also receive safety information about the Trial reported by the Principal Investigator.
  The description of the safety information supplied by ABC, the time at which the information is obtained, and the method of collecting the information are explained in "6. Reporting Procedures." The safety information shall be collected via e-mail, and other means should be considered depending on the nature of the information provided.

4.6 Monitors

See the protocol supplement.

(Responsibilities)

- The monitor(s) should make an effort to verify information about SAEs and other events that occur during the Trial and are reported from the Principal Investigator, sub-investigator, and trial collaborator through monitoring activities. The monitor(s) shall also ensure that these events are properly reported to IRB or the director of the relevant study center, Sponsor or Coordinating Committee, and others if required.
- The monitor(s) shall perform monitoring activities to ensure that various safety information reports from the Sponsor or the Coordinating Committee are properly managed and stored and help with the management and retention of the reports.

5 Reporting of ADRs and Other Events to Local Regulatory Authorities

5.1 Method of Reporting and Other Procedures

When Sponsor or the Coordinating Committee considers that it is necessary to report ADRs and other events to local regulatory authorities, the Coordinating Committee or CRO shall prepare a report according to the notifications/regulations listed below. If the notifications/regulations are revised or updated, the report should conform those revisions or updates.

[Japan]

(1) "Clinical Safety Data Management: Definitions and Standards for Expedited Reporting" (PAB-ED No. 227 dated March 20, 1995)
(2) "Reporting of Adverse Drug Reactions Occurring in Clinical Trials to Pharmaceuticals and Medical Devices Agency (PMDA)" (PFSB Notification No. 0330001 dated March 30, 2004)
(3) Enforcement of Ministerial Ordinance on Partial Amendments to the Enforcement Regulations of the PMD Act Regarding Reporting of Adverse Drug Reactions and Other Events Related to Clinical Trials of Drugs (PFSB Notification No. 1228001 dated December 28, 2005)
(4) Points to Bear in Mind About Reporting of Adverse Drug Reactions and Other Events Occurring in Clinical Trials (PFSB-ELD Notification No. 0426001 dated April 26, 2006)
(5) Development Safety Update Report (DSURs) (PFSB-ELD Notification No. 1228-1 dated December 28, 2012)
(6) Considerations for Enforcement of Ministerial Ordinance on Partial Amendments to the Enforcement Regulations of Pharmaceutical Affairs Law (PFSB-ELD Notification No. 1228-11 dated December 28, 2012)
(7) Reporting of Adverse Drug Reactions and Other Events Occurring in Clinical Trials by Non-industry-sponsored Investigators (PFSB-ELD Notification No. 0701-21 dated July 1, 2013)

[Korea]

(1) Korean GCP, amended in 2013 (hereinafter called "KGCP")
(2) Korea MFDS guideline of SUSAR reporting

[Taiwan]

(1) Taiwan GCP, amended in 2005 (hereinafter called "TGCP")
(2) Taiwan National Adverse Drug Reactions Reporting System Q&A
(https://adr.fda.gov.tw/Manager/Pages/PB010014.aspx)

[Singapore]

(1) Singapore GCP, amended in 1999 (hereinafter called "SGCP")
(2) Safety Reporting Requirements for Clinical Drug Trials in June 2011

[Japan]

For a report prepared by the Coordinating Committee, the Coordinating Committee shall submit the report, together with a reference sheet (Addendum 1 in 5.2 [2]), to PMDA on behalf of the Principal Investigator by the deadline. The Coordinating Committee shall receive the reference sheet from PMDA, which enters the date of receipt and receipt number on the sheet, and check the receipt number. The Coordinating Committee is responsible for the management and retention of the receipt number of the reference sheet sent back from PMDA.

According to Article 273, Enforcement Regulations of Law on Securing Quality, Efficacy, and Safety of Pharmaceuticals, Medical Devices, Regenerative and Cellular Therapy Products, Gene Therapy Products, and Cosmetics (hereinafter referred to as "PMD Act"), reports should be submitted by the deadline for reporting shown in Table 1 in Japan. The starting point of the SAE reported in the Trial is the day on which the Principal Investigator of the relevant study center obtains SAE information, and the starting point of other reports is the day on which individual Principal Investigators obtain the information (the day shall be Day 0).

(Table 1) Information to be reported to PMDA and deadline for reporting

Data source: Article 273 of the Enforcement Regulations of the PMD Act

Information to Be Reported	Predictability	Seriousness	Deadline for Reporting
Serious ADRs	Unexpected	Death or leading to death	7 days
		Other serious events	15 days
	Expected	Death or leading to death	15 days
Research reports (domestic and overseas)	Research reports (indicating that ADRs to the investigational product or treatment-related infections may cause cancer, other significant diseases/disorders, or death, that there is a remarkable change in the tendency to develop diseases such as the incidence, frequency, and conditions for occurrence, and that the investigational product is not indicated for the treatment of the target disease or it is not effective for treating it).		15 days
Reports of safety measures (domestic and overseas)	Overseas and domestic safety measures (commercially available products for which clinical trials for the Application are conducted) are measures taken to discontinue the manufacturing, importing, or marketing of drugs, recall or dispose of such drugs, and avoid a hygiene hazard or increased risk of the hazard.		15 days

[Korea, Taiwan, and Singapore]

The CRO shall report to the local regulatory authorities according to local regulations. The CRO is responsible for the documentation and the retention of the submitted reports.

The starting point of the SAE reported in the Trial is the day on which the Principal Investigator of the relevant study center obtains SAE information, and the starting point of other reports is the day on which individual Principal Investigators obtain the information (the day shall be Day 0).

According to Chapter 8 in K-GCP, the CRO should make a report by the deadline shown in Table 2 in Korea.

(Table 2) Information to be reported to MFDS and the deadline for reporting

Information to Be Reported	Seriousness	Deadline for Reporting
All unknown serious ADRs	Leading to death or life-threatening	7 days In this case, a detailed report must be submitted additionally within 8 days of the first report.
	Other serious events	15 days

According to Article 106 of T-GCP, the CRO should make a report by the deadline shown in Table 3 in Taiwan.

(Table 3) Information to be reported to TFDA and the deadline for reporting

Information to Be Reported	Seriousness	Deadline for Reporting
All unknown serious ADRs	Leading to death or life-threatening	7 days In this case, detailed documents should be submitted within 15 days of becoming aware of detailed reports.
	Other serious events	15 days

According to Article 5.17.1 of S-GCP, the CRO should make a report by the deadline shown in Table 4 in Singapore.

(Table 4) Information to be reported to MOH and the deadline for reporting

Information to Be Reported	Seriousness	Deadline for Reporting
All unknown serious ADRs	Leading to death or life-threatening	7 days
	Other serious events	15 days

5.2 Report Forms for ADRs and Other Events

[Japan]

Forms used for reporting ADRs and other events to PMDA shall be stipulated by the notifications listed below. Abbreviations for individual forms are described in parentheses, and these abbreviations should be used to indicate each form.

(1) Forms specified in the Reporting of Adverse Drug Reactions Occurring in Clinical Trials to Pharmaceuticals and Medical Devices Agency (PMDA) (PFSB Notification No. 0330001 dated March 30, 2004_PFSB Notification No. 1215003 revised on December 15, 2005)

(i) Attachments 7 and 8, Case Report Forms of ADRs and Infections Related to the Study Drug: “Forms 7 and 8”

(ii) Attachments 9 and 10, Research Reports of the Study Drug: “Forms 9 and 10”

(iii) Attachments 11 and 12, Reports of Safety Measures Such as Discontinuation, Recall, and Disposal of the Study Drug in Foreign Countries: “Forms 11 and 12”

(2) Forms specified in the Reporting of Adverse Drug Reactions and Other Events Occurring in Clinical Trials by Non-industry Sponsored Investigators (PFSB-ELD Notification No. 0701-21 dated July 1, 2013)

Addendum 1 Reference Sheet of ADRs and Other Events Reported in Clinical Trials: “Reference sheet”

[Korea, Taiwan, and Singapore]

The applicable forms should be used according to local regulations.

6 Reporting Procedures

6.1 Reporting Methods

In principle, documents shall be delivered by e-mail. However, other communication means, such as mailing, should be considered depending on the type and amount of information provided.

6.2 SAEs that Occur in the Trial

[Japan]

(1) When an SAE occurs in the medical institution to which the Principal Investigator or sub-investigator belongs, the Principal Investigator or sub-investigator shall prepare a “Serious Adverse Event Report Form” and report to the Coordinating Committee within 24 hours of becoming aware of the occurrence regardless of its causal relationship.

Report to: XXXXX@XXXXX

Unblinded information should be reported to: XXXXX@XXXXX

As a general rule, the Principal Investigator shall be responsible for reporting SAEs and the sub-investigator/trial collaborator is allowed to perform reporting to the Coordinating Committee on behalf of the Principal Investigator. The Principal Investigator shall also prepare "(Med) Forms 12-1 and 12-2" and submit them, together with the report, to the director of the study center. (The original report should be stored in the study center.)

(2) The Coordinating Committee shall report to ABC promptly.

(3) The Coordinating Committee shall make a medical judgment regarding the report from the Principal Investigator, evaluate the necessity of reporting to local regulatory authorities, and prepare a "Confirmation Letter." If it is considered necessary to report to PMDA, the Coordinating Committee shall further document medical considerations. The Coordinating Committee shall provide all Principal Investigators with the "Serious Adverse Event Report Form" and "Confirmation Letter."

(4) On the opinion of the Coordinating Committee, the Principal Investigator shall enter Agree/Disagree immediately on the Principal Investigator's comment column on the "Confirmation Letter," enter the date confirmed, and sign or seal it. The "Confirmation Letter" shall be retained at the study center. When the Principal Investigator disagrees over the Coordinating Committee's opinion, the Principal Investigator shall describe the medical judgment and the medical consideration on the "Confirmation Letter" and report to the Coordinating Committee within 2 calendar days of collecting information.

(5) When the Coordinating Committee concludes that the SAE should be reported to PMDA in the opinion of the Coordinating Investigator and Principal Investigator, the Coordinating Committee shall prepare a "Case Report Form of ADRs and Infections Related to the Study Drug (Form 7)" and a "Case Report of ADRs and Infections Related to the Study Drug (Form 8)" and submit them to PMDA by the deadline shown in (Table 1) after the date on which the Principal Investigator obtains the information in the study center, the location of the SAE. The Coordinating Committee shall provide all Principal Investigators and ABC with a copy of the report. The copy of the report shall be retained at each study center.

(6) Upon obtaining detailed SAE information, the Principal Investigator, who belongs to the study center, i.e., the location of the SAE, shall use an "Serious Adverse Event Report Form" to report to the Coordinating Committee as needed. The Principal Investigator shall also prepare "(Med) Forms 12-1 and 12-2" and submit them, together with the report, to the director of the study center. (The original report should be stored in the study center.)

(7) When obtaining detailed SAE information, the Coordinating Committee shall report to ABC according to the same procedures as those used for an initial report. After reporting to all Principal Investigators and asking for their feedback, the Coordinating Committee shall prepare "Form 7" and "Form 8" (additional report) and submit them to PMDA.

(8) According to the procedures specified by each study center, individual Principal Investigators shall submit all safety information reported to the director of the study center.

[Korea, Taiwan, and Singapore]

(1) When an SAE occurs in the medical institution to which the Principal Investigator or sub-investigator belongs, the Principal Investigator or sub-investigator shall prepare a "Serious Adverse Event Report Form" and report to the Sponsor within 24 hours of becoming aware of the occurrence regardless of its causal relationship.

Report to: XXXXX@XXXXX

Confidential

Unblinded information should be reported to: XXXXX@XXXXX

As a general rule, the Principal Investigator shall be responsible for reporting SAEs and the sub-investigator/trial collaborator is allowed to perform reporting to the Sponsor on behalf of the Principal Investigator.

The Principal Investigator shall also submit the report to IRB per IRB requirements. (The original report should be stored in the study center.)

(2) The Sponsor shall report to ABC promptly.

(3) The Sponsor shall make a medical judgment regarding the report from the Principal Investigator, evaluate the necessity of reporting to local regulatory authorities. The Sponsor shall provide the CRO with the "Serious Adverse Event Report Form".

(4) When the Sponsor concludes that the SAE should be reported to the regulatory authorities, the CRO shall report to local regulatory authorities.

(5) Upon obtaining detailed SAE information, the Principal Investigator, belonging to the study center that is the location of the SAE, shall use a "Serious Adverse Event Report Form" to report to the Sponsor as needed. The Sponsor shall report to ABC promptly. The Principal Investigator shall also submit the report to IRB per IRB requirements. (The original report should be stored in the study center.) The CRO shall report to the local regulatory authorities according to the same procedures as those used for an initial report.

6.3 SAEs Reported Inside and Outside a Country in Studies Other than the Trial

[Japan]

(1) ABC shall provide the Coordinating Committee with the listing of patients with unknown and serious ADRs (Line listingin Japanese), which summarizes CIOMS forms prepared on the basis of domestic and overseas information obtained every X weeks and with the listing of patients with unknown and serious ADRs (Line Listings) every X months. When the Coordinating Committee receives the listing of patients with unknown and serious ADRs (Common line listing of individual cases in Japanese and listing of patients with unknown and serious ADRs , the Coordinating Committee shall inform ABC of their receipt by e-mail.

(2) Regarding the information provided by ABC, the Coordinating Committee shall complete the Coordinating Investigator's comment column on the "Confirmation Letter."

(3) The Coordinating Committee shall provide all Principal Investigators with the listing of patients with unknown and serious ADRs and the "Confirmation Letter."

(4) On the opinion of the Coordinating Investigator, the Principal Investigator shall enter Agree/Disagree in the investigator's comment column in the "Confirmation Letter," enter the date confirmed, and sign or seal it. For Disagree, the Principal Investigator shall describe the medical judgment and medical consideration of the "Confirmation Letter" and report to the Coordinating Committee within 2 days of collecting information. The original "Confirmation Letter" shall be stored in each study center.

(5) According to the procedures specified by each study center, the Principal Investigator shall report all collected safety information to the director of the study center.

[Korea, Taiwan, and Singapore]

(1) ABC shall provide the Sponsor with the listing of patients with unknown and serious ADRs (Semi-annual IIR Line Listings) every X months. When the Sponsor receives the listing of patients with unknown and serious ADRs, the Sponsor shall inform ABC of its receipt by e-mail.

(2) The Sponsor shall provide all Principal Investigators with the listing of patients with unknown and serious ADRs.

(3) According to procedures specified by each study center, the Principal Investigator shall report all collected safety information to IRB per IRB requirements.

(4) CRO is responsible to report to local regulatory authorities according to local regulations.

6.4 Domestic and Overseas Research Reports and Reports of Safety Measures

[Japan]

(1) When ABC obtains information corresponding to “research reports” or “reports of safety measures”, ABC shall supply the information to the Coordinating Committee promptly. Upon receiving the “research reports” or “reports of safety measures” by e-mail, the Coordinating Committee shall inform ABC of their receipt, .

(2) The Coordinating Committee shall prepare a “Confirmation Letter” for the research reports and reports of safety measures supplied by ABC. The Coordinating Committee shall provide all Principal Investigators with the research reports or reports of safety measures and the “Confirmation Letter.”

(3) On the opinion of the Coordinating Investigator, the Principal Investigator shall enter Agree/Disagree in the investigator’s comment column in the “Confirmation Letter,” enter the date confirmed, and sign or seal it. For Disagree, the Principal Investigator shall describe the medical judgment and the medical consideration in the “Confirmation Letter” and report it to the Coordinating Committee within 2 days of collecting information.

(4) When collecting information corresponding to “research reports” from reports presented at scientific meetings, literatures, and other sources, the Principal Investigator shall provide the Coordinating Committee with the information promptly.

(5) The Coordinating Committee shall prepare a “Confirmation Letter” for the research reports and reports of safety measures supplied by the Principal Investigator. The Coordinating Committee shall provide all Principal Investigators with the research reports or reports of safety measures and the “Confirmation Letter.” If it is considered necessary to report to PMDA, the Coordinating Committee shall prepare a “Research Report (Forms 9 and 10)” and submit it by the deadline shown in (Table 1) (if the report overlaps with the report from ABC, it shall not be reported to PMDA). The Coordinating Committee shall provide all Principal Investigators and ABC with a copy of the report.

(6) According to the procedures specified by each study center, individual Principal Investigators shall submit all information reported to the director of the study center.

6.5 Other Safety Information

[Japan]

On becoming aware of the study drug information falling under Section 3.5 (5) (Development Safety Update Report (DSUR)), the Principal Investigator shall report it to the Coordinating Committee according to reporting procedures in Section 6.2 (SAEs that occur in the Trial). The coordinating investigator shall provide all Principal Investigators with the information obtained, at the right moment, through the Coordinating Committee.

7 Preparation of Development Safety Update Reports (DSURs)

[Japan]

(1) A summary of DSURs provided by ABC shall be handled according to procedures in Section 6.3 (6.3 SAEs Reported Inside and Outside a Country in Studies Other than the Trial).

[Korea, Taiwan, and Singapore]

(1) A summary of DSURs provided by ABC shall be handled according to procedures in Section 6.3 (SAEs Reported Inside and Outside a Country in Studies Other than the Trial).

OR

(1) The Sponsor shall prepare a DSUR related to the Trial once every year, reckoned from the date of initial submission of the Trial notification.

(2) CRO shall submit a DSUR to the local regulatory authorities within 2 months of data lock. The Sponsor shall provide a summary of the DSUR and a copy of the DSUR, respectively, to the Principal Investigator and ABC.

8 Reporting of Trial Discontinuation, Suspension, or Resumption

If the Trial is discontinued or suspended due to safety issues or the Coordinating Committee/Sponsor collects information from the Principal Investigator and others about the resumption of the trial, the Coordinating Committee/sponsor should immediately provide the information to all Principal Investigators and ABC.

9 Protocol Amendments/Revisions of the Written Information/Informed Consent Forms

If new important information (information regarding the quality, efficacy, and safety of the study drug and other important information required for the proper conduct of the trial) becomes available, the Coordinating Committee/Sponsor shall examine the necessity of amending the protocol and revising the written information/informed consent forms. If necessary, the Coordinating Committee/Sponsor may also consult with the E-DMC.

When amendments or revisions are considered necessary, the the Coordinating Committee/Sponsor should amend the protocol or revise these documents promptly.

10 Provision of Information to Subjects and Re-consent

The Principal Investigator shall promptly inform the subjects (including those who have completed study treatment as needed) whenever new safety information becomes available and is considered important in that it may affect the subjects' willingness to continue participation in the trial. For subjects who are under treatment with the study drug, the Principal Investigator shall affirm their willingness to continue to participate in the trial. When the written

information/informed consent forms are revised, the Principal Investigator shall provide an explanation again using the revised written information/informed consent forms and obtain written re-consent from the subject themselves.

11 Handling of Mandatory Reporting Period

The mandatory reporting period for ADRs and others related to clinical trials conducted by the Sponsor and non-industry-sponsored investigators shall begin, in principle, on the date of initial submission of the trial notification (CTN or IND) and end on the submission date of the trial completion notification, trial discontinuation notification, or development discontinuation notification by ABC. The information provision period for ABC shall also be handled in a similar manner.

12 Retention of Trial Documentation

According to the "SOP on Storage of Records" specified separately, the Sponsor and the Japanese Principal Investigators shall store the prepared documents and records.
Non-Japan Principal Investigators shall store the prepared documents and records for a period stipulated in clinical study agreement with investigator/institution.

13 Appendices

14 Enactment and Revision History

Version Number	Date of Revision	Revision Details
XX	Mmm dd, yyyy	First version