Outline of the Investigation Results about Fatal Case of Clinical Trial Sponsored by Eisai Co., Ltd.

1. Clinical trial outlined

(1) Investigational drug

A drug under development as an antiepileptic by Eisai Co., Ltd. Its mode of action resembles that of perampanel hydrate (brand name: Fycompa) which has already been approved and launched in Japan. Investigational substance code: E2082.

(2) Outline of the trial

The clinical trial is a Phase I, first–in-human trial involving healthy adult males. This trial aims at evaluating the safety, tolerability and pharmacokinetics of the drug.

2. Background and status of the trial

(1) Situation until death of the subject

- The subject who died (hereinafter called “Subject A”) was enrolled in the investigational drug group scheduled to receive repeated dose of the drug at the highest dose (15 mg/day) for 10 days. He began to receive medication as planned.
- Each subject was hospitalized during the study period including treatment period of 10 days and the follow-up period of 3 days. During the treatment period, Subject A experienced mild to moderate sleepiness and dizziness. During the follow-up period, Subject A had mild nausea, sleepiness and dizziness but had no other particular complaints before discharge from the medical institution.
- In the same day of the discharge, Subject A voluntarily visited the medical institution again. At this time, he complained that he had been experiencing visual hallucination, auditory hallucination and insomnia since the first day of the follow-up period. The investigator decided to monitor these symptoms without active intervention, taking into account the subject’s capability of talking and answering questions in a reasonable manner, the stability of his condition and so on. The next morning of the voluntary visit, a police officer informed the investigator that Subject A died by jumping off from a utility pole.

(2) Status of the trial and other subjects

After death of this Subject A, administration of the investigational drug to other subjects has been terminated. The investigator checked the safety of the other subjects enrolled in this trial. Some subjects complained of abnormalities, but there were no serious adverse events.

3. Purposes of the investigation

An investigation was conducted to confirm whether the measures taken before and after this event were appropriate or not under the Ministerial Ordinance on Good Clinical Practice for Drugs (hereinafter called “GCP Ordinance”) from the following viewpoints:

- Were the measures taken by the sponsor and the medical institution appropriate?
  - Did the medical institution deal appropriately with Subject A upon his voluntary

visit to the medical institution after discharge?

- Were the processes of obtaining and documenting informed consent to/from the subjects about the trial appropriate?
- Was the correspondence of the investigator appropriate to conduct a clinical trial? Was the selection of medical institutions, etc. by the sponsor appropriate?

4. Results of the investigation

On-site investigation and other necessary actions were carried out at the medical institution and the sponsor.

The following statements were concluded base on the investigation result considering comments by the experts at the Pharmaceuticals and Medical Devices Agency.

- The causal relationship between the investigational drug and the adverse events experienced by Subject A cannot be ruled out.
- The medical institution provided information about the trial outline and possible adverse reactions when obtaining consent from the subject to the trial and took measures to provide appropriate medical care upon emergency (e.g., setting forth the emergency patient transport plan and its procedure). The sponsor selected the medical institution, taking into consideration the following facts: (1) The institution had sufficient experience with clinical trials; (2) The institution was able to conduct examinations, etc. needed for the trial; (3) The institution had prepared a standard operating procedure in case of subjects' medical emergencies; (4) the physician to be planned to assume the role of Principal Investigator had experience with clinical trials (including phase I clinical trials in the central nervous system (hereinafter called "CNS") area), and so on. Taking these facts into account, No serious deviations from the provisions of GCP Ordinance in the actions taken by the participating medical institution or the sponsor are found. However, there were some points desirable to take more careful considerations in the view of the principles underlying the GCP Ordinance.
  - It would have been more appropriate if the medical institution had arranged immediate referral of Subject A to a psychiatrist when he voluntarily visited to the institution. The medical institution should have conducted a more detailed observation and recording of the subject A during the follow-up period after the end of administration with the investigational drug.
  - At the time of informed consent to the subject, the investigator should have given more detailed precautions in writing about the physical and mental influence of the investigational drug (including the risk related to suicide), and should have explained the subjects to report anything unusual in their physical/mental condition immediately to the institution staff.
  - The investigator should have made a more careful judgment about the actions to be taken when an adverse event which is not covered by his/her specialty was detected.
  - It would have been more appropriate if the sponsor had selected a medical institution sufficiently prepared to provide examination/care by physicians specialized in CNS such as psychiatrists or had appointed a psychiatrist or the like to the principal investigator or sub-investigators of the trial, in view of the risk involved in the investigational drug. In addition, it should have been considered in

advance as to how family members or their equivalents could be involved at the occurrence of adverse events.

5. The future action

Considering the magnitude of this event, the following actions will be necessary when clinical trials to evaluate drug tolerability at early stages of drug development are conducted.

(1) Actions to be taken by the sponsor

- Selection of medical institutions, Principal Investigators and other investigators capable of dealing appropriately with the risk involved in the investigational drug.
- Providing medical institutions with sufficient explanation about adverse events that may develop and potentially result in a serious outcome, and providing the subjects of the trial with such information in writing.
- Confirming that a physician or a medical personnel who are capable to deal with such adverse events participates in the trial, or confirming that good cooperative connection with other medical institutions which can immediately deal with such adverse events is established before the start of the trial.
- In case of a clinical trial on a drug which can cause symptoms related to CNS, selecting medical institutions which is capable of diagnosing adverse events should be considered, and involving family members or their equivalents of each subject should be also considered.

(2) Actions to be taken by medical institution

- Informing the subjects in writing about possible adverse events which may result in a serious outcome, and urging the subjects to report anything unusual in their mental and physical condition immediately to the institution staff.
- Explaining and receiving consent to/from the subjects that: (1) measures to protect the subject (e.g., extension of the hospital stay) may be necessary upon the occurrence of serious adverse events; (2) measures to the subject may involve cooperation of a designated psychiatrist under the Law Related to Mental Health and Welfare of the Person with Mental Disorder depending on the symptoms experienced; and (3) the subject’s family members or their equivalents may be contacted.
- Understanding the possibility for adverse events to develop even after the last administration of the investigational drug depending on the nature of the investigational drug, and monitoring and recording the presence/absence of any adverse event in the subjects after the end of administration with the investigational drug.
- Arranging an appropriate cooperative system in advance (e.g., seeking the opinions from expert physicians with clinical expertise) to deal with the occurrence of events that may potentially result in a serious outcome.