

Project to Promote the Development of Innovative Pharmaceuticals, Medical Devices, and
Regenerative Medical Products (Ministry of Health, Labour, and Welfare)
Regulatory Science Research for the Establishment of Criteria for Clinical Evaluation of Drugs for
Alzheimer's Disease

Issues to Consider in the Clinical Evaluation and Development of Drugs for Alzheimer's Disease

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[Background]

The Ministry of Health, Labour, and Welfare (MHLW) started the “Project to Promote the Development of Innovative Pharmaceuticals, Medical Devices, and Regenerative Medical Products” in 2012. As a part of this project, in order to establish guidelines for the clinical evaluation of drugs for Alzheimer’s disease (AD), the University of Tokyo Hospital, in collaboration with the Pharmaceuticals and Medical Devices Agency (PMDA), has been performing research for establishing biomarker-based criteria for clinical evaluation of AD drugs as well as a study to develop a disease model to predict the clinical effect of drugs using a modeling simulation technique.

As a part of the MHLW project and in cooperation with PMDA, this interim report summarizes current issues to be considered or resolved in future with respect to the clinical evaluation and development of disease-modifying drugs for AD.

In this project, further investigations are planned to resolve the issues presented in this report.

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I. Introduction

Alzheimer's disease (AD) is characterized by a gradual progression of cognitive impairment, which interferes with the patient's independent activities of daily living (ADL). Therefore, AD has a serious impact on patients as well as their caregivers. In this aging society, AD is becoming a serious and urgent concern from the socio-economic viewpoint. The Japan Health Sciences Foundation has surveyed physicians' satisfaction with treatment outcomes of diseases and degrees of contribution of individual drugs to the treatment on a periodic basis since 1994. According to their report, AD has been ranked low in terms of both the satisfaction level with the treatment outcomes and the contribution of relevant drugs. Currently, symptomatic drugs¹ such as cholinesterase inhibitors and *N*-methyl-D-aspartate (NMDA) receptor inhibitors are commonly prescribed to patients with AD in clinical practice. Although disease modifying drugs² are now being developed, no one has demonstrated clinical efficacy successfully. Based on the assumption that pathophysiological changes associated with AD begin years before the onset of dementia, the early intervention before onset of dementia is considered to be important to use the drug effectively. To conduct a clinical study in such patients, it is essential to use appropriate endpoints as well as inclusion criteria suitable for selecting eligible patients at a target disease stage. It would be particularly difficult to select patients at an early stage of disease as well as to evaluate the efficacy of a drug only through clinical symptoms. Therefore, the use of biomarkers reflecting pathophysiological changes associated with AD is increasingly needed in this field. With a growing number of global clinical studies reflecting the increase in large-scale and long-term studies, establishment of adequate biomarker-based criteria for clinical development is needed for AD drugs.

This report presents issues to be considered or resolved in conducting effective clinical studies of disease-modifying AD drugs. At present, there are still a number of issues to be addressed regarding the conduct of clinical studies. Further investigation and accumulation of evidence are necessary to resolve the issues presented in this report and establish optimal clinical evaluation methods for AD drugs .

Definitions in this document

¹ Symptom-alleviating drugs: Medical agents that improve the clinical symptoms of AD, but cannot inhibit the progression of the disease.

² Disease-modifying drugs: Medical agents that delay neurodegeneration and neuronal cell death by acting on the pathological mechanism of AD and, as a result, inhibit the progression of clinical symptoms.

II. Inclusion Criteria in Clinical Studies

In clinical studies of disease-modifying drugs, establishing appropriate inclusion criteria is necessary to select a homogeneous patient population with a common pathological condition suitable for efficacy and safety evaluation. Attention should be paid to the following issues while designing inclusion criteria for clinical studies on patients with AD dementia (dementia related to pathophysiological changes associated with AD) or mild cognitive impairment (MCI) associated with AD/prodromal AD.

1. AD dementia

As a diagnostic criteria for AD, the “Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision” (DSM-IV-TR), published by American Psychiatric Association, and the “National Institute of Neurological and Communicative Disorders and Stroke AD and Related Disorders Association (NINCDS-ADRDA) criteria” have been widely used. However, these diagnostic criteria provide little consideration to underlying pathophysiological processes, and the criteria give only vague differentiation between AD and other cause of dementia. Taking these issues into account, the National Institute of Aging and the Alzheimer’s Association (NIA-AA) revised the NINCDS-ADRDA criteria in 2011 including the core clinical criteria and biomarkers reflecting pathophysiological process associated with AD. The revised criteria describes about biomarkers reflecting deposition of A β in the brain, such as a decreased level of amyloid beta₄₂ (A β ₄₂) in cerebrospinal fluid (CSF) and amyloid imaging by positron emission tomography (PET) ; and biomarkers reflecting neurodegeneration, such as increased CSF-tau or phosphorylated tau, atrophy of the medial-temporal lobe/hippocampus identified by magnetic resonance imaging (MRI), and decreased metabolism in the temporal-parietal lobe/precuneus identified by fluorodeoxy glucose-PET (FDG-PET). Furthermore, according to the International Working Group (IWG)-2 criteria published by Dubois et al. in 2014, the diagnosis of AD requires at least one of the following criteria to be satisfied: (1) Reduction of the A β ₄₂ level and elevation of the level of tau or phosphorylated tau in the CSF, (2) accumulation of amyloid confirmed by PET imaging, and (3) mutation of the gene(s) (PSEN1, PSEN2 or APP) responsible for familial AD.

When conducting clinical studies of disease-modifying drugs that target molecules involved in pathophysiological process of AD, such as A β and tau, excluding patients with non-AD dementia precisely from the study population is necessary. For this purpose, it is essential to utilize biomarkers that would reflect the pathophysiological changes associated with AD. It is therefore necessary to consider adopting A β deposition or biomarkers reflecting neurodegeneration, mentioned above, as inclusion criteria, although consensus has not yet been reached over which diagnostic criteria/biomarkers should be adopted. However, at present, there are various issues to be addressed regarding the use of biomarkers in clinical studies as presented in the section, “II. 3. Use of

Biomarkers.”

The severity of the disease in the subjects enrolled in the clinical study should be evaluated in an integrated manner on the basis of multiple tests. Tests and indicators of evaluation which may be adopted include the Mini-Mental State Exam (MMSE), Alzheimer’s Disease Assessment Scale – Cognitive Subscale (ADAS-cog), Clinical Dementia Rating (CDR), etc. Other indicators deemed as being more appropriate, if any, may also be adopted.

2. MCI due to AD/ Prodromal AD

Since intervention with disease-modifying drugs from an early stage of AD before the onset of dementia is thought to be more effective, several clinical trials have been conducted in patients with MCI. The disease states of AD before the onset of dementia is expressed as “MCI due to AD” and “prodromal AD”; diagnostic criteria for these states based on biomarkers have been published by the NIA-AA and Dubois et al., respectively, so as to enable identification of patients having pathophysiological changes associated with AD. On the other hand, no consensus has yet been reached in regard to which of “MCI due to AD” or “prodromal AD” should be used as a criterion, or whether it should be recommended using any of these terms or criteria. When a drug targeting MCI due to AD/prodromal AD (MCI/pAD) is evaluated, it would be necessary for patients to be treated with the drug have an accurate diagnosis in terms of the presence/absence of AD-associated changes and the risk of onset of dementia, and for the potential clinical efficacy of the drug to be clearly demonstrated by the clinical study results. However, as mentioned below, further discussion is needed about which diagnostic criteria should be adopted and what methods should ideally be used for the efficacy evaluation.

In clinical studies of disease-modifying drugs, appropriate selection of patients with AD-associated changes as the study population is necessary. However, assessment of clinical symptoms is not sufficient for appropriate exclusion of patients with cognitive impairment of other causes. Furthermore, the risk of developing dementia vary depending on individual patients, and there may be some patients who never develop dementia in their lives in spite of having AD pathophysiological changes. Considering that no drug is free from risks, it is important to administer a study drug only to those subjects with cognitive impairment caused by AD who are highly likely to progress to dementia. For this purpose, the inclusion criteria should be specified using appropriate cognitive test results, evidence of A β deposition, biomarkers reflecting neurodegeneration, etc.

Currently, studies are being performed to determine combinations of biomarkers and cognitive test results that would accurately predict the risk of progression to AD dementia, as well as to determine criteria for assessing positive/negative results or cutoff values of the biomarkers. At present, a number of issues are still to be addressed regarding the use of biomarkers (see “II. 3. Use of Biomarkers”). Therefore, the latest relevant information should be taken into account when planning a study using

biomarkers.

When evaluating the severity in individual cases with MCI/pAD, it is entirely possible that evaluation by the MMSE and ADAS-cog, which have conventionally been used for assessing patients with AD dementia, fails to detect cognitive impairment because of the ceiling effect, and it is necessary to explore other indicators suitable for evaluation of the severity of MCI/pAD.

Furthermore, because diagnostic criteria for MCI/pAD have not yet been clearly established, the inclusion criteria set for a current clinical trial may differ from the diagnostic criteria that will be established in the future. In such cases, it is necessary that the results of the current clinical study sufficiently explain the efficacy and safety of the study drug in patients satisfying the latest diagnostic criteria at the time of review of application for approval of the drug or in patients expected to be treated with the drug after it is approved. However, these issues may lead to the judgment that the results of the clinical study are insufficient as evidence for granting drug approval.

3. Use of Biomarkers

Attention should be paid to the following issues with respect to the use of biomarkers for inclusion criteria for AD dementia or MCI due to AD.

- Concerning CSF biomarkers (e.g., CSF A β and tau ; hereinafter the same meaning shall apply) and imaging biomarkers (e.g., amyloid imaging, MRI, FDG-PET), standard measurement methods have not been established as shown in the facts that there is variability in results among laboratories or evaluators even when the same method is used. To control such assessment variability, it is recommended at present to use the central laboratory measurement, using biomarker samples that are collected, stored, or captured at each facility by common procedures. Storing a part of the samples for CSF biomarkers will be useful, so that the samples can be re-evaluated in the future when standard measurement methods are established. At present, adoption of measurement methods used in past large-scale studies, such as the ADNI is recommended; however, it is also acceptable to use other measurement methods, if appropriate rationales exist for their use.
- In cases where a biomarker is used in combination with other biomarkers, as seen in the concomitant use of CSF biomarkers and amyloid imaging, it is necessary that deciding in advance how to handle patients in whom one biomarker is positive while the other one is negative in consideration of relationships or differences between the biomarkers. If inclusion criteria are specified in such a manner that patients who are positive for any one of the biomarkers adopted, not necessarily all of them, can be included, it is desirable to collect a certain number of subjects positive for each biomarker, so that any influence on the results arising from differences in the demographics or efficacy/safety of a drug among the populations included based on different biomarkers can be evaluated. Obtaining as much information as possible at the time of enrollment

regarding biomarkers that are not used for inclusion criteria is useful, which may be used for post hoc subgroup analyses. This information can play an important role in the evaluation of individual or ethnic differences in efficacy and safety.

- Cut-off values, if used for inclusion criteria, should be specified appropriately based on information obtained from similar clinical studies or research reports in consideration of the target population (including disease stage and race) and evaluation methods. At present, because only a limited number of reports are available on Japanese subjects, it is still unclear whether there is any difference in biomarkers between Japanese and non-Japanese individuals. In cases where Japan participates in a global clinical study planned based on the research primarily in non-Japanese populations, it is necessary that examining in advance whether there are any ethnic differences associated with biomarkers to be used.
- In cases where biomarkers are used for selecting patients for clinical studies, use of the same biomarkers in clinical practice after obtaining marketing approval may be required to select appropriate patients to be treated. Therefore, investigating if biomarkers used in clinical studies are also usable in the clinical practice is necessary. If, for example, amyloid imaging is used for inclusion criteria, target patients for a study drug would be unable to be selected in clinical practice if PET ligand and its synthesis device have not been approved when the drug are approved. In the development of a drug requiring the use of a biomarker for inclusion criteria, therefore, consideration should also be given to the development status of measurement methods of the said biomarker. In addition, the selection of patients in clinical practice or the feasibility of clinical studies may be affected by issues such as the following: facilities that handle amyloid imaging are limited; the cost of amyloid imaging might be expensive; and CSF biomarkers require invasive procedures. To deepen scientific understanding of the disease and to establish a better therapeutic method, however, it seems permissible to measure a biomarker, which currently is not usable in clinical practice, in a clinical study as long as it does not cause intolerable burden on study subjects.
- If only patients positive for certain biomarkers are expected to receive treatment with the drug during clinical practice, it is recommended that cases negative for the biomarker also be included in the clinical trial of the drug so that the validity of confining the use of the drug only to cases positive for the biomarkers or validity of the cutoff levels of such biomarkers, etc., can be assessed. However, this recommendation does not apply to cases where the drug is considered to be unlikely to be effective in biomarker-negative cases or where there is concern about the safety of the drug.
- Whether there is need to measure the level of each of the biomarkers that had been adopted as an inclusion criterion for the study while selecting patients to be treated with this drug during clinical practice should be judged on the basis of the purpose of the biomarker (for diagnosis of the disease,

prediction of the prognosis, prediction of the responses to treatment, etc.), the risk/benefits of the drug, and the healthcare environments at the time of review of the application for approval. If the drug is not expected to manifest efficacy in patients negative for some particular biomarkers and its use involves a high safety risk, checking for such biomarkers before treatment with the drug may be indispensable.

- APOE ϵ 4 is known as a risk gene for the onset and progression of AD. Some drugs are suggested to have increased risk of adverse effects in APOE ϵ 4 carriers compared to non-carriers. Obtaining information on APOE genotypes including APOE ϵ 2 is desirable so that it can be used for subgroup analyses. However, due caution should be exercised when handling genetic information and biomarker-related information, including the disclosure of such information to the study subjects.

Based on the above, which biomarkers are to be used in clinical studies should be closely examined.

III. Efficacy Endpoints Used in Clinical Studies

The following issues should be considered when specifying efficacy endpoints for clinical studies in patients with AD dementia or MCI due to AD.

1. AD dementia

As efficacy endpoints for drugs for AD dementia, the first draft of the “guidelines for the clinical evaluation of antidementia drugs” (November 8, 1990; FDA) in the US requires cognitive (core symptoms of AD) and global assessment as the primary efficacy endpoints. Meanwhile, the “Draft Guideline on the clinical investigation of medicines for the treatment of Alzheimer’s Disease and Other Dementias” (EMA Guideline, London, 28 Jan 2016 EMA/CHMP/539931/2014) in Europe requires evaluation of cognition and ADL as the primary endpoints, and global assessment as a secondary endpoint.

A global consensus has been reached that the efficacy for patients with AD dementia should be assessed by evaluating cognition as well as ADL or overall clinical response. In Japan, also it is necessary to specify co-primary endpoints consisting of cognition and ADL or overall clinical response to demonstrate efficacy in confirmatory studies of drugs for AD dementia. Meanwhile, in exploratory studies that are conducted on a limited scale and/or for a limited period, it seems acceptable to set any one of evaluations of cognition, ADL or overall clinical response as the primary endpoint, and of the others as the secondary endpoints.

The indicators or scales for evaluation of the respective endpoints should be ones whose validity and reliability have been verified, and which can reflect the clinical symptoms and severity of AD dementia with sufficient sensitivity as to allow detection of the drug efficacy. In cases where a Japanese

version of an assessment scale originally developed overseas is used, due attention should be paid to differences in the language and cultural backgrounds, as well as to equivalence of the test details and degree of difficulty in testing between the Japanese and foreign versions. Scales often used in previous clinical trials include the ADAS-cog/Severe Impairment Battery (SIB) (cognitive function), Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (ADCS-ADL) / Disability Assessment for Dementia (DAD) (activities of daily living), and Clinician's Interview-Based Impression of Changes plus caregiver input (CIBIC-plus) / Alzheimer's disease cooperative study - clinical global impression of change (ADCS-CDIS) / Clinical Dementia Rating - Sum of Boxes (CDR-SB) (overall clinical evaluation). On the other hand, in patients with mild AD dementia, evaluation with these scales might be hampered by a ceiling effect, necessitating the selection of other appropriate primary endpoints depending on the severity of the disease in the patients studied.

Evaluation may be affected by deficient skills of evaluators or a deficient amount of information provided from informant. Such potential problems should be addressed in advance through appropriate measures such as giving training to evaluators and establishing criteria that enable informants to obtain a sufficient amount of subject information.

It is desirable to use multiple indicators or scales for evaluation of the secondary endpoints, as far as possible, so that efficacy and safety of a drug may be evaluated from diverse points of view.

2. MCI due to AD

Until date, there are no established efficacy endpoints for patients with MCI/pAD. Currently, the following endpoints are considered usable. Whichever endpoint is chosen, the endpoint should clearly show the clinical meaningfulness of performing early intervention for AD patients at a pre-dementia stage.

In clinical studies in patients with MCI due to AD, it is appropriate to use “onset of AD dementia” (time to a diagnosis of dementia, or incidence of dementia) as a primary endpoint. Considering that AD is characterized by a gradual decline in cognition and ability to perform ADL, however, time of the onset of AD dementia assessed may vary depending on evaluators. To eliminate potential differences in assessment of the onset of AD dementia among evaluators, appropriate measures should be taken in advance, such as giving them sufficient training. In case where time to a diagnosis of dementia is used as efficacy endpoint, appropriate frequency of evaluation and tests should be specified so that frequency of evaluation and tests would affect the efficacy result. The central evaluation method by multiple experts is recommended to confirm the appropriateness of assessment, after collecting relevant information such as detailed clinical courses and the results of neuropsychological tests (including information/explanation based on which assessment is made if the evaluator's subjective view is reflected in rating).

As an efficacy endpoint for MCI/pAD, the draft of the “Guidance for Industry, Alzheimer's

Disease: Developing Drugs for the Treatment of Early Stage Disease” (Draft Guidance, February 2013, FDA) in the US mentions that it is appropriate to use a single composite scale that can assess both cognition and ADL, such as CDR-SB, as a single primary efficacy outcome measure. Also the “Draft Guideline on the clinical investigation of medicines for the treatment of Alzheimer’s Disease and Other Dementias” (EMA Guideline, London, 28 Jan 2016 EMA/CHMP/539931/2014) in Europe refers to the possibility of using a composite scale that would allow assessment of the influence on both cognition and ADL as a single primary efficacy outcome measure. In clinical studies in patients with MCI due to AD who have only mild impairment in ADL or overall clinical response, it would be difficult to use rating scales that assess ADL and overall clinical response as the primary endpoints, like AD dementia. Therefore, the use of a composite scale to assess both cognition and function as a single primary endpoint may also be acceptable in Japan. In addition to using CDR-SB, it may also be possible to develop a new rating scale suitable for the assessment of patients with MCI/pAD. However, in using such a scale, the clinical meaningfulness of changes in the scores should be demonstrated based on their association with the progression of AD, with the results of evaluation using existing rating scales, and the onset of AD dementia, etc. In explaining the clinical meaningfulness of changes in the scores, it may also be helpful to analyze the changes in the scores in relation to the progression of AD using the data from appropriate longitudinal studies or the like. As far as secondary endpoints are concerned, it would be desirable for the effectiveness to also be demonstrated by evaluation of the length of time until onset of AD dementia, percentage of patients developing AD dementia, and the existing indicators.

At the stage of MCI/pAD, the disturbance in cognition and ADL is mild. Information useful for explaining the drug efficacy at this stage may be obtained not only by demonstrating statistically significant changes in the above-mentioned clinical indicators in the drug-treated group as compared to the placebo group, but also demonstrating definite influence of the drug on the disease progression through evaluation of biomarkers that are believed to reflect neurodegeneration as secondary endpoints (see “III. 3. Use of Biomarkers”).

3. Use of Biomarkers

Relationships between clinical symptoms and changes in biomarkers in the natural course of AD are investigated in observational studies such as ADNI. As results, it was suggested that the treatment effect of a study drug may be evaluated in a smaller-scale clinical study when using biomarker as efficacy endpoints compared to when using only clinical symptoms. In clinical studies, it is desirable to evaluate biomarkers as much as possible as secondary endpoints of exploratory or confirmatory studies to confirm that a study drug has an effect on its target and to investigate relationships between the clinical efficacy of the drug and changes in biomarker values. In case global development strategy is performed, it is desirable to obtain biomarker data at an early stage of development both in Japan

and overseas and using the data to examine ethnic differences in efficacy, safety, dose, and regimen.

Meanwhile, since relationships between changes in biomarkers and clinical effect by drug intervention have not been clarified, it is still unclear what biomarker change reflects inhibition of the progression of AD and improvement of clinical symptoms. At present, therefore, it is unknown which biomarker should be chosen as an efficacy endpoint to demonstrate inhibition of the progression of AD. Under this circumstance, it is not appropriate to use any biomarker as a surrogate endpoint for clinical evaluation in confirmatory studies. Use of biomarkers as efficacy indicators requires further investigation based on result of ADNI, and drug intervention studies, etc. For the reasons given above, it is now recommended that evaluation of biomarkers be conducted, as far as possible, within the framework of explorative evaluation.

IV. Issues to Be Considered Regarding Clinical Studies at Each Stage of Development

1. Phase I Study

Phase I studies are performed at the first stage of clinical development by administering a study drug in human to investigate tolerability, safety, and pharmacokinetics, based on information obtained from non-clinical studies. Pharmacodynamics may also be investigated using biomarkers.

In principle, phase I studies are performed in healthy adult subjects and because many of AD patients are elderly, investigation of tolerability, safety, and pharmacokinetics in the elderly should also be considered. However, if phase I studies of immunotherapy target molecules such as A β or tau, it is also acceptable to perform the studies in AD patients indicated for the drug after sufficiently ensuring the safety of subjects based on the safety profile of each test drug.

2. Phase II Study

Phase II studies in patients are to be started after evaluating the results of non-clinical and phase I studies. Phase II studies can be divided into early phase II studies, in which the efficacy and safety of a study drug in patients are investigated in an exploratory manner, and late phase II studies, in which dose-response relationship is clarified and the dose/regimen of the study drug is determined to perform phase III studies.

Late phase II studies for the investigation of dose response relationship are usually designed as placebo-control, randomized, double-blind, parallel-group studies, in which it is recommended that at least two doses of a study drug are investigated.

Primary endpoint in phase II studies is specified by reference to “III. Efficacy Endpoints.” It is acceptable for relationships between the pharmacokinetics and pharmacodynamics to be examined through analysis of biomarkers to explore the appropriate dose levels in early phase II studies. However, since there are no biomarkers that can be used as surrogate endpoints for clinical symptom evaluation, it would be difficult to select appropriate doses based only on changes in biomarker. Late

phase II studies performed to determine a dose to be used in phase III studies, therefore, are required to investigate dose-response based on clinical symptoms in principle.

Even if the dose-response based on the clinical symptoms has been evaluated in a phase II study conducted overseas, it would be difficult, at present, to presume equivalent clinical efficacy in Japanese patients from a comparison of the pharmacokinetic effects or the pharmacodynamic effects based on the changes in biomarkers between Japanese and overseas populations, because no biomarker that allows accurate estimation of the influence on the clinical symptoms has been established yet. Therefore, even in such a case, a phase II study should be carried out, as a rule, in Japanese subjects (dose determination study) as a domestic study or an multi regional clinical trials, to investigate the differences and similarities of the dose-response based on clinical symptoms between Japanese and overseas populations before moving on to a phase III study (confirmatory study).

3. Phase III Study (Confirmatory Study)

Phase III studies (confirmatory studies) are conducted to verify the efficacy of a study drug, of which safety, efficacy and recommended dose have been estimated in phase II studies. It is appropriate to design phase III studies as placebo-controlled, double-blind, randomized, parallel-group studies. In some cases, such as where it is difficult to select a single recommended dose/regimen from the results of phase II studies, more than one dose/regimen may be specified in a phase III study. Primary endpoints should be set with reference to “III. Efficacy endpoints.”

When evaluating the disease-modifying effects of drugs, it is appropriate to demonstrate that the drug improves the clinical symptoms, and also to evaluate suppression of the pathophysiological progression of AD by the drug using biomarkers in a randomized parallel-group study. Meanwhile, in the draft guideline on the clinical evaluation of early-stage AD, the FDA has suggested the use of a “randomized start design” or “randomized withdrawal design” for clinical studies conducted to demonstrate the disease-modifying effects of drugs. However, before such a study design is adopted, consultation with the PMDA is recommended, because discussion is needed about the evaluation methods, evaluation period, etc.

In case of conducting global study, see the section, “IV. 5. Clinical Data Package.” for the clinical data package needed for application in Japan.

4. Phase III Study (Long-term Study)

Since AD drugs are generally administered for a long period, the long-term study should be planned to evaluate safety of the patients treated with a study drug for at least 1 year at dosage intended for clinical use. The number of patients should be determined in reference to ICH E1 guideline. If data are available from an existing clinical study in which a sufficient number of patients had received treatment for at least 1 year with the study drug at the dose level and dosing method recommended for

clinical use, a separate study to investigate the long-term safety of the drug is not indispensable.

In cases where a study drug targets MCI due to AD as well as AD dementia, the number of subjects should be large enough to evaluate safety of the study drug at each disease stage. If a long-term study is planned in the way that combining data of AD dementia and MCI due to AD to fulfill required sample size, appropriateness of the use of the data from each patients in a complementary manner should be rationally explained [see “5 (2) MCI due to AD”].

The main purpose of a long-term study is to evaluate the safety and efficacy of a study drug administered for a long period at its recommended dose and regimen. Therefore, it is appropriate to conduct a long-term study at a stage where a recommended dose/regimen is estimated.

5. Clinical Data Package

(1) AD dementia

In principle, the efficacy of a study drug must be reproducibly shown in Japanese subjects based on the results of multiple randomized parallel-group studies. Furthermore, as stated in the section, “III. Efficacy Endpoints,” a confirmatory study in patients with AD dementia should demonstrate the efficacy of a study drug through measurements of co-primary endpoints. There are a number of development strategies such as domestic development in Japan, bridging strategy, and participation in a global clinical study. Thinking about how the requirements presented above can be met is important to devise a development strategy. Concepts of clinical data packages in representative development methods are presented below. However, data packages required in respective drugs should be discussed individually in consideration of the latest findings and the profiles of the drugs.

1) Domestic Development in Japan

On the condition that the superiority of a study drug over placebo has been demonstrated in the primary endpoint(s) specified in phase II studies, superiority of the study drug over placebo needs to be demonstrated in both primary endpoints shown in the section, “III. Efficacy Endpoints,” in phase III studies.

2) Bridging Strategy

In cases where confirmatory study has been conducted overseas and bridging strategy is performed in Japan to extrapolate the results of the overseas confirmatory study, conducting a bridging study is necessary, which is comparable to a relevant overseas study to demonstrate the similarities of the results of the Japanese and overseas studies in terms of efficacy, safety, and dose-response. To show ethnic similarities, analyzing study results from various perspectives including biomarker are effective. However, at present, it is required, in principle, to show ethnic similarities of dose response by evaluating clinical symptoms. An overseas bridging study should be a study in which dose response

has been evaluated using more than one dose and the superiority of a study drug over placebo has been demonstrated in co-primary endpoints presented in the section, “III. Efficacy Endpoints.” A bridging study performed in Japan should also meet pre-specified requirements for bridging such as showing the superiority of a study drug over placebo in co-primary endpoints that are the same as those in an overseas bridging study, and showing similarities of dose response.

3) Participation in a Global Clinical Study

If a drug is being globally developed, it is recommended that Japan participates in a global clinical study from an early stage of development and confirms appropriateness of performing a phase III study as a global study based on the results of the exploratory study, and then participates in a global phase III study. In global clinical development, due attention should be paid to the following.

1. The results of a global phase III study should demonstrate the superiority of a study drug over placebo in the entire study population in co-primary endpoints presented in “III. Efficacy Endpoints,” and then demonstrate the consistency of the results of each endpoint in the Japanese study population and the entire study population. Biomarkers should also be evaluated as much as possible as secondary endpoints and the consistency of results in the Japanese study population and the entire study population should be analyzed.
2. The above 1 should be shown with reproducibility in at least two global phase III studies in which Japan participates. However, even when Japan participates in only one global phase III study, if the efficacy has been clearly demonstrated (such as when the superiority of a study drug over placebo has been demonstrated in appropriate primary endpoints) in a global phase II study in which Japan has participated or domestic study in Japan, the efficacy demonstrated in these study may be used as an evidence of reproducibility.
3. If, in addition to 1, the efficacy of the study drug is clearly and robustly demonstrated, such as when the superiority of the study drug over placebo in the Japanese study population is proven in at least one primary endpoint in a global phase III study, consideration should be taken whether or not a separate clinical study needs to be performed in Japanese patients as an evidence of reproducibility.

(2) MCI due to AD/ Prodormal AD

In principle, the efficacy of a study drug for MCI/pAD needs to be demonstrated with reproducibility based on the results of more than one randomized parallel-group studies, similarly to AD dementia. In cases where a clinical study in AD dementia is planned beside a study in MCI/pAD, however, the results of a confirmatory study in AD dementia, in addition to the results of a clinical study in MCI/pAD, may be allowed to be used as data supporting the reproducibility of efficacy of a study drug, if the appropriateness of using data from clinical studies in MCI/pAD and AD dementia in

a complementary manner is explainable (such as when it is successfully explained based on sufficient evidence that the patient populations in both studies have AD-associated pathophysiological changes and that a high percentage of patients with MCI/pAD progress to AD dementia; and when patients in the respective studies are assessed as the same in terms of a clinically recommended dose, safety profile of a study drug, and risk-benefit balance).

During clinical development of a drug intended only for patients with MCI/pAD, it is plausible to imagine that a confirmatory study is performed at a large scale and for a long period. If this feature is also taken into account, we may anticipate cases where verification of the efficacy through conducting multiple studies is unnecessary on the grounds, for example, that a single confirmatory study involving multiple dose groups has demonstrated clinically significant robust efficacy (e.g., suppression of onset of AD dementia) as well as dose-response relationship.

V. Open issues for the future

Some investigators have proposed that patients with AD-associated pathophysiological changes in whom the cognition is intact or only minimally compromised should be counted as cases of preclinical AD who need early therapeutic intervention. Globally, clinical studies of cases with preclinical AD have been initiated, and therapeutic intervention in such cases before the progression of nerve cell damage may allow more effective suppression of the disease progression. Meanwhile, there is no widely accepted set of diagnostic criteria for preclinical AD that is applicable to clinical practice, and further accumulation of data is desirable concerning MCI/pAD and the risk of progression of this condition to AD dementia.

When drugs for preclinical AD are evaluated, it is essential to carefully select patients who are at a high risk for disease progression, and also necessary to carefully evaluate the safety of long-term treatment. Data endorsing the drug's effect in suppressing the onset of dementia are also needed, but clinical trials aimed at collecting such data involve many unresolved problems, such as a lack of marked changes in the clinical symptoms and the long period of time needed for evaluation of the drug efficacy. It is thus desirable to establish indicators that would enable detection of even slight changes in cognition, and biomarkers that would allow prediction of the clinical responses to treatment.

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