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

(Interim Summary)

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(Draft of English version)

[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 the lowest in terms of both treatment satisfaction and relevant drug contribution. Currently, symptomatic drugs[1] 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 drugs[2] 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 .

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[1] Medical agents that improve the clinical symptoms of AD, but cannot inhibit the progression of the disease.

[2] 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 in designing inclusion criteria for clinical studies in patients with AD dementia[3] or mild cognitive impairment (MCI) due to AD[4].

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 $A\beta$ in the brain, such as a decreased level of amyloid beta$_{42}$ ($A\beta_{42}$) 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).

When conducting clinical studies of disease-modifying drugs that target molecules involved in pathophysiological process of AD, such as $A\beta$ and tau, excluding patients with non-AD dementia precisely from the study population is necessary. For this purpose, it is necessary to consider using the above-mentioned biomarkers as part of the inclusion criteria. 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,"

2.   MCI due to 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

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[3] Dementia that arises as a consequence of the AD pathophysiological process.
[4] Mild cognitive impairment that arises as a consequence of the AD pathophysiological process.

MCI. The condition of MCI associated with AD is expressed as "MCI due to AD" and "prodromal AD," for which research criteria using biomarkers have been published by the NIA-AA and Dubois et al., respectively. Although the criteria for "MCI due to AD" and "prodromal AD" are similar, a consensus has not been reached regarding the term that should be officially used. In this report, for descriptive purposes, the term MCI due to AD is used to indicate MCI whose underlying pathophysiology is AD.

In clinical studies of disease-modifying drugs targeting the pathophysiology of AD, appropriate selection of patients with MCI due to AD as a study population is necessary. However, assessment of clinical symptoms is not enough to exclude patients with other causes of MCI. 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 in subjects with MCI due to AD who are highly likely to develop dementia. To include such patients, inclusion criteria should be specified using cognitive tests and biomarkers suitable for diagnosing MCI due to AD.

Currently, studies are being performed to specify the appropriate biomarkers and cognitive tests for the accurate prediction of AD progression, as well as criteria for assessing positive/negative or cut-off values of 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 design using biomarkers.

Because diagnostic criteria for MCI due to AD has not been sufficiently established, inclusion criteria of a clinical trial specified based on currently available information may differ from the diagnostic criteria that will be established in the future. Some of these differences may lead the results of the clinical study to be insufficient as the evidence for 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 Aβ 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.

・ 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 the way that include patients who are positive for any of one biomarker used, not for all of them, the study should be designed so that any difference in demographics or efficacy/safety of a drug can be identified among populations included based on different biomarkers. 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.

・ APOE ε4 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 ε4 carriers compared to non- carriers. Obtaining

information on APOE genotypes including APOE ε2 is desirable so that it can be used for subgroup analyses. However, due caution should be taken when handling genetic information including the disclosure of genetic information to study subjects.

· With respect to procedures for using an unapproved diagnostic agent such as PET ligand in a clinical study, having a consultation with PMDA and MHLW before initiating the study is recommended.

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 "guideline on medicinal products for the treatment of Alzheimer's disease and other dementias," (EMEA Guideline, London, 24 July 2008, CPMP/EWP/553/95 Rev.1) in Europe requires evaluating 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 at a limited scale and a limited period, one of cognition, ADL, and overall clinical response could be specified as the primary endpoint while specifying the others as secondary endpoints.

Assessment scales for respective endpoints should be the ones that have been verified in terms of validity and reliability and which can reflect the clinical symptoms and severity of AD dementia with sufficient sensitivity to detect drug efficacy. In cases where a Japanese version of an assessment scale originally developed in overseas is used, due attention should be paid to differences in language and cultural background as well as comparability of the details and degrees of difficulty between Japanese tests and foreign ones.

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.

Use of as many rating scales as possible for secondary endpoint is recommended so that drug efficacy can be evaluated from various perspectives.

2. MCI due to AD

Up to the present, there have been no established efficacy endpoints to evaluate patients with MCI due to AD. 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 due to AD, 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 which assesses both cognition and function, such as the Clinical Dementia Rating–Sum of Boxes (CDR-SB), 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 due to AD. However, in using such a scale, the clinical meaningfulness of changes in score should be demonstrated based on their association with existing rating scales, AD progression, and the onset of AD dementia, etc. In examining the clinical meaningfulness of changes in the score, using data from longitudinal studies such as Alzheimer's Disease Neuroimaging Initiative (ADNI) seems helpful.

In patients with MCI due to AD who have only mild impairment in cognition and ADL, showing

merely statistically significant changes compared to placebo in such clinical rating scales is insufficient for explaining the clinical meaningfulness of the drug. The outcomes of secondary endpoint using biomarkers might be able to explain the disease modifying effect and the clinical meaningfulness of the drug (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.

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. Because many of AD patients are elderly, investigation of tolerability, safety, and pharmacokinetics in the elderly should also be considered. However, phase I studies of immunotherapy targeting molecule such as Aβ or tau could be performed in target patients if subject safety is sufficiently ensured.

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 considered appropriate that relationships between pharmacokinetics and pharmacodynamics effect of biomarkers are examined in early phase II study in order to investigate doses in an exploratory manner. 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 dose response based on clinical symptoms have been evaluated in a phase II study conducted overseas, it would be difficult to presume clinical efficacy in Japanese patients from a comparison of pharmacokinetic effects or pharmacodynamic effects based on changes in biomarker between Japan and overseas at present. Therefore, even in such a case, a Japanese phase II study should be performed in principle to investigate the differences and similarities of dose-response based on clinical symptoms between Japan and overseas 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. Phase III studies are designed as placebo-control, double-blind, 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.

To prove the disease-modifying effect, it is appropriate to demonstrate that the drug has an improving effect on clinical symptoms and also that the drug inhibits pathophysiological progression of AD using biomarkers in a randomized parallel-group study. Meanwhile, the FDA has suggested the use of "randomized start design" or "randomized withdrawal design" for a clinical study to prove the disease-modifying effect.

Primary endpoints in phase III studies (confirmatory studies) should be specified by reference to "III. Efficacy Endpoints."

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 existing clinical study in which a sufficient number of patients have been treated for at least 1 year with a study drug at its dosage intended for clinical use, a study to investigate long-term safety of the drug is not necessarily separately conducted.

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 shown with reproducibility 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

In principle, the efficacy of a study drug for MCI due to AD 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 due to AD, however, the results of a confirmatory study in AD dementia, in addition to the results of a clinical study in MCI due to AD, 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 due to AD and AD dementia in a complementary manner is explainable (such as when it is successfully explained based on sufficient evidences that the patient populations in both studies have AD-associated pathophysiological changes and that a high percentage of patients with MCI due to AD 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). In clinical development of a drug intended only for patients with MCI due to AD, if a confirmatory study is performed at a large scale and for a long period and if clinically meaningful efficacy is clearly shown in the study (such as when the primary endpoint is specified as "onset of AD dementia"), consideration should be taken whether or not it is necessary to demonstrate the superiority of the study drug over placebo in another clinical studies.

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