を打ち切りと定義し、生存時間解析を実施する。
%FVC、Modified Norris Scale スコア、ALSAQ40 スコア、握力、ピンチ力、MMT(徒手筋力検査)、について、ALSFRS-R スコアと同様な方法で解析を実施する。
ALS 重症度分類に点いては、群ごとに「臨床研究薬投与開始前」から「臨床研究薬増量期終了後、15mg/1 日投与終了2週間後又は中止時」への推移のシフトテーブルを示す。

（3）安全性の評価項目

安全性解析対象集団を解析対象として解析を実施する。
群ごとに有害事象発生率、副作用発現率、重篤な有害事象発現率、重篤な副作用発現率を算出し Fisher の直接確率法を用いて群間比較を行う。

臨床検査、感覚検査（振動覚）の各項目について、群ごと、時期ごとの要約統計量及び「臨床研究薬投与開始前」との差の要約統計量を示す。また、各項目について、群ごとに異常変動率を算出する。

尿検査、感覚検査（しびれ感、ふらつき）については、群ごと、時期ごとに「臨床研究薬投与開始前」を基準とした推移のシフトテーブルを示す。

（4）有意水準

有意水準は5％（両側）とし、信頼区間は両側、信頼係数を 95%とする。なお、本臨床研究計画時の特殊性を考慮し、主要解析における検定の多重性について有意水準の調整を行わない事とする。

14. 研究成果の発表

本臨床研究で得られた研究成果の発表に際しては、被験者の秘密（プライバシー）を保全した上で行うこととする。

15. 参考文献

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6)ドパミンアゴニスト使用上の注意 日本神経学会(H19.5.22)

英文

Study on efficacy and safety of NDDPX08 in ALS patients

Research Organization

Tokai University Hospital

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Revised February 6, 2009 (Version 1.1)
Revised April 9, 2009 (Version 1.2)
Revised April 22, 2009 (Version 1.3)
Revised October 20, 2009 (Version 2)

Confidentiality Policy

This protocol is treated as confidential information disclosed only to the parties involved in this clinical study, as listed below:

- **Institutional Review Board**
- **Study Director**
- **Investigator**
- **Sub-Investigator**
- **Study Contributors**
- **Director, Tokai University School of Medicine**
- **Director, Tokai University Hospital**
- **Units of Tokai University School of Medicine and Tokai University Hospital involved in this clinical study.**

Study Outline

1. Objectives

Amyotrophic lateral sclerosis (ALS) is a motor neuron disease involving selective impairment of motor nerves and presenting with progressive muscular weakness and atrophy. Its etiology remains to be clarified, and no drug adequately effective against this disease is available at present. Thus, it has been desired to develop new methods of treatment for this disease. In our previous studies using a system of cultured cells exposed to oxidative stress, it was shown that NDDPX08 (a compound currently used clinically as a means of treating Parkinson's disease) suppresses loss of nerve cell viability. Furthermore, treatment with NDDPX08 after the onset of ALS was shown to improve motor function and extend the survival period of transgenic mice (mice transfected with the familial ALS type 1 mutant SOD-1 gene, an animal model of ALS).

The present study is designed to evaluate the efficacy of NDDPX08 on motor function and quality of life (QOL) as well as its safety in patients with solitary or familial ALS.

2. Subjects

Patients diagnosed as having ALS and satisfying both requirement 1) and 2) are eligible for this study.

1) Patients in whom ALS is "definite, " "probable" or "probable-laboratory-supported" according to the EL Escorial Modified Airlie House Diagnostic Criteria and the severity is rated at grade 1, 2 or 3 according to the Ministry of Health, Labour and Welfare Criteria for ALS Severity.
2) Patients having given informed consent in writing to participate in the study.

3. Methods

Of the clinical study period lasting for 70-102 weeks, the first 12-week observation period involves treatment with Rilutek (generic name: riluzole) already approved as a drug for treatment of ALS in Japan (100 mg/day). Rilutek is initiated either at or 4 weeks before the start of the observation period. At the end of the observation period, the eligibility of each patient to participate in the study is checked again, and patients rated as eligible begin to receive treatment with a combination of NDDPX08 and Rilutek (combined treatment) according to an escalating dosing schedule (Fig. 1). During the first 2 weeks of combined treatment, the NDDPX08 dose level is set at 1.25 mg/day. Then, the NDDPX08 dose level is increased by 2.5 mg/day at intervals of 2 weeks, reaching 15 mg/day 12 weeks after the start of treatment. The NDDPX08 treatment period is 54-86 weeks. Treatment within the framework of this clinical study is deemed to have been completed at any of the following points of time: (1) beginning of 24-hour use of noninvasive respiration assistive device daily, (2) beginning of the use of an invasive respiration assistive device or (3) death of the patient.

The variables of efficacy and safety, listed below, are evaluated at the beginning of the observation period and at the start, during and the end of combined treatment. Changes in each variable are compared and analyzed (Fig. 2).

【Efficacy variables】 ALSFRS-R, %FVC, Modified Norris Scale, ALSAQ-40, MMT, pinching power, grip, ALS severity grade

【Safety variables】 Adverse events (particularly hallucination, nausea, vomiting, anorexia, etc.), blood pressure, heart rate, laboratory parameters, echocardiography findings

4. Study period and planned number of subjects

Study period: January 1, 2009 through January 31, 2011
Planned number of subjects: 50 cases (total number of patients entering the treatment phase)

5. Participating facilities

Department of Neurology, Tokai University School of Medicine (Main Hospital, Hachioji Hospital, Oiso Hospital)
Department of Neurology, Toho University School of Medicine (Omori Hospital)
Department of Neurology, Kitasato University School of Medicine (East Hospital)

Table of Contents

1. Objectives

On the basis of the findings from our basic studies conducted to date, the present study is undertaken to evaluate the efficacy of orally administered NDDPX08 (a drug currently used clinically for the treatment of Parkinson's disease) on motor function and quality of life (QOL) as well as its safety in patients with solitary or familial amyotrophic lateral sclerosis (ALS).

2. Study organization

1) Study Director

Joh-E Ikeda, Professor, Division of Basic Medicine, Tokai University School of Medicine

2) Researchers

Shigeharu Takagi, Professor, Division of Internal Medicine, Tokai University School of Medicine (Department of Neurology, Tokai University Hospital); in charge of implementing the clinical study and evaluating safety

Fumihito Yoshii, Professor, Division of Internal Medicine, Tokai University School of Medicine (Department of Neurology, Tokai University Hospital); in charge of implementing the clinical study and evaluating safety

Shunya Takizawa, Professor, Division of Internal Medicine, Tokai University School of Medicine (Department of Neurology, Tokai University Hospital); in charge of implementing the clinical study and evaluating safety

Eiichiro Nagata, Lecturer, Division of Internal Medicine, Tokai University School of Medicine (Department of Neurology, Tokai University Hospital); in charge of implementing the clinical study and evaluating safety

Tatsuya Ishikawa, Research Associate, Division of Internal Medicine, Tokai University School of Medicine (Department of Neurology, Tokai University Hospital); in charge of implementing the clinical study and evaluating safety

Yasuhisa Kitagawa, Professor, Division of Internal Medicine, Tokai University School of Medicine (Department of Neurology, Tokai University Hachioji Hospital); in charge of implementing the clinical study and evaluating safety

Kaytsunori Akiyama, Lecturer, Division of Internal Medicine, Tokai University School of Medicine (Department of Neurology, Tokai University Oiso Hospital); in charge of implementing the clinical study and evaluating safety

Yasuo Iwasaki, Professor, Department of Neurology, Toho University Omori Medical Center; in charge of implementing the clinical study and evaluating safety

Mieko Ogino, Lecturer, Department of Neurology, Kitasato University School of Medicine (Department of Neurology, Kitasato University East Hospital); in charge of implementing the clinical study and evaluating safety

3) Study Contributors

Hirohide Takahashi, Associate Professor, Division of Internal Medicine, Tokai University School of Medicine; in charge of evaluating safety

Wakao Takahashi, Associate Professor, Division of Internal Medicine, Tokai University School of Medicine; in charge of evaluating safety

Yuko Onuki, Research Associate, Division of Internal Medicine, Tokai University School of Medicine; in charge of evaluating safety

Kyuichiro Onoue, Lecturer (Part Time), General Institute of Medicine, Tokai University; in charge of evaluating safety

4) Investigator (nominated if Study Director is not a physician)

Fumihito Yoshii, Division of Internal Medicine, Tokai University School of Medicine (Department of Neurology, Tokai University Hospital)

5) Clinical Study Coordinator

Joh-E Ikeda, Neurodegenerative Disease Research Centre, Tokai University Graduate School of Medicine; in charge of coordinating the study and managing the information in collaboration with the participating facilities and CRC

6) Drug Administrator

Kun Ichikawa, Director of Pharmacy, Pharmacy Division, Tokai University Hospital; in charge of adjusting and managing drugs

7) Participating facilities

Department of Neurology, Tokai University Hospital
Department of Neurology, Tokai University Oiso Hospital
Department of Neurology, Tokai University Hachioji Hospital
Department of Neurology, Toho University Omori Medical Center
Department of Neurology, Kitasato University East Hospital

8) ALS Treatment Plan Evaluation Committee

In charge of supervising and encouraging implementation of this clinical study (a multicenter study) and evaluating and judging the efficacy and safety of NDDPX08 at the end of the study

Chairman

Ichiro Kanazawa, Chief Medical Officer, Grand Steward's Secretariat, Imperial Household Agency; Professor, International University of Health and Welfare Graduate School

Members

Shigeki Katsurahara, Director, National Center of Neurology and Psychiatry
Yasuto Itoyama, Professor, Department of Neurology, Tohoku University School of Medicine
Hajime Sofue, Professor, Department of Neurology, Nagoya University School of Medicine

9) Secretariat for Clinical Study on ALS (FeGALS Office)
Neurodegenerative Disease Research Centre, Department of Frontier Medicine, Tokai University Graduate School, 143 Shimokasuya, Isehara, Kanagawa 259-1193, Japan
TEL: 0463-93-1121(switchboard) Ext. 2568 FAX: 0463-91-4993 (direct)

3. Background

Amyotrophic lateral sclerosis (ALS) is a motor neuron disease involving selective impairment of motor nerves and presenting with progressive muscular weakness and atrophy. Its etiology remains to be clarified, and no drug adequately effective against this disease is available at present. Thus, it has been desired to develop new methods of treatment for this disease. In our previous studies using a system of cultured cells exposed to oxidative stress, it was shown that NDDPX08 (a compound currently used clinically as a means of treating Parkinson's disease) suppresses loss of nerve cell viability. Furthermore, treatment with NDDPX08 after the onset of ALS was shown to improve motor function and extend the survival period of transgenic mice (mice transfected with the familial ALS type 1 mutant SOD-1 gene, an animal model of ALS).

The present study is designed to evaluate the efficacy of orally administered NDDPX08 on the motor function and quality of life (QOL) as well as its safety in patients with solitary or familial ALS. NDDPX08 has been used for 23 years since approval as a drug for the treatment of Parkinson's disease, and adequate data are available on its efficacy and safety when used for such a purpose.

4. Ethical considerations

1) Compliance with ethical guidelines related to clinical studies

This clinical study is carried out in accordance with the ethical principles set forth in the "Ethical Guidelines on Clinical Studies (enforced on April 1, 2005)" prepared by the Ministry of Health, Labour and Welfare (MHLW), the "Rules and Bylaws on Clinical Studies at Hospitals Attached to Tokai University School of Medicine" and the protocol for this study.

2) Ethics Committee

This clinical study needs to be approved in advance by the Institutional Review Board of the Tokai University Hospital.

The Study Director is required to submit a "Report on Status of Clinical Study" to the Institutional Review Board (IRB) at intervals of one year and to follow the view of the IRB as to the appropriateness of further continuing the study (if the study lasts more than one year). Within one month after completion or discontinuation of the study, the Study Director is required to submit a "Report on Completion (Discontinuation) of the Study" to the IRB. Upon the onset of an event of category (a) listed below, the report needs to be submitted within one week after said onset.

The Study Director is required to report any of the following events or cases to the IRB and to follow the view of IRB as to the appropriateness of further continuing the study.

(a) Onset of serious adverse events or the like

(b) Major modification of the protocol for this study
(c) Major modification of the informed consent form or other leaflets
(d) Modification of other documents subjected to IRB check
(e) Other cases judged by the Hospital Director as requiring IRB check

3) Acquisition of informed consent from subjects

Prior to the start of this study, the Investigator or Sub-Investigator informs each candidate patient of the following aspects of the study using the leaflet and obtains consent from the patient to participate in the study issued in writing at his/her own discretion.

The leaflet needs to include the following information:

(1) The research aspect of the treatment involved in the study;
(2) Objectives of the study;
(3) Methods of the study (explorative aspects of the study, patient inclusion criteria, etc.);
(4) Planned duration of participation in the study;
(5) Planned number of subjects of the study;
(6) Predicted clinical advantages, risks and inconveniences (if no clinical advantage is predicted, each patient needs to be so informed);
(7) Availability of other treatment methods for patients and predicted important advantages and risks of such treatment methods;
(8) Treatment which subjects of this study are entitled to receive upon onset of health hazards related to the study;
(9) The capability of each patient to decide whether or not to participate in the study at his/her own discretion; the capability of each patient or his/her proxy consenter to refuse or cancel participation in the study any time; and the policy that refusal or cancellation of participation in the study does not cause any disadvantage for the patient or cause the patient to suffer loss of benefits he/she is reasonably entitled to;
(10) The policy that the patient will be immediately informed of any information possibly affecting the intention of the subject or his/her proxy consenter to remain in the study, after acquisition by the subject or the proxy consenter;
(11) Criteria for rejection of patients from the study;
(12) The policy that the Monitor, Auditors, members of the IRB and domestic/overseas regulatory authority officials may be allowed access to the raw data (medical records, etc.) of the subject, thereby assuring that adequate measures will be taken to protect the privacy of the subject, and that signing of the informed consent form by the patient or the proxy consenter constitutes authorization of access to such data by these parties;
(13) The policy that privacy of the subject will be protected when the results of the study are made public;
(14) Details of the costs to be borne by the subject, if any;
(15) Name, title and contact address of Investigator/Sub-Investigator and Study Contributors (the name, title and contact address of Clinical Study Coordinator, if any);
(16) The unit of the medical facility to be contacted by the subject when he/she desires further information related to the study and his/her rights;
(17) Any responsibilities the subject must fulfill.

4) Supply of information to subjects

If information possibly affecting the intention of the subject or his/her proxy consenter to remain in the study has been obtained, the Investigator is required to furnish the subject or the proxy consenter with such information immediately and to confirm his/her intention to remain in the study. The steps taken on this topic need to be recorded in the medical records.

5) Protection of privacy

The privacy of each subject of this study is protected.

6) Protection and management of personal information

The personal information of the subjects of this study is protected by linkable anonymization. The information of all subjects of this study is managed collectively by the Personal Information Administrator. When the results of the study are published by means of presentation or papers, non-linkable anonymization is used to avoid identification of individual subjects.

Personal Information Administrator: Fumihito Yoshii, Professor, Division of Internal Medicine, Tokai University School of Medicine

5. Selection of subjects

1) Eligible patients

Patients diagnosed as having ALS and satisfying all of the following requirements are eligible for this study.

(1) Patients in whom ALS is "definite," "probable" or "probable-laboratory-supported" according to the EL Escorial Modified Airlie House Diagnostic Criteria (Attachment 1);
(2) Patients having received no treatment with NDDPX08 before;
(3) Patients whose ALS is rated as grade 1, 2 or 3 according to the ALS Severity Criteria (Attachment 2);
(4) Patients with %FVC of 70% or higher;
(5) Patients who developed ALS within 3 years before giving informed consent to participate in this study;
(6) Patients between 20 and 75 years of age at the time of giving informed consent in writing;
(7) Patients having given informed consent to participate in the study in writing (as a rule, the patient's own signature is needed, but the signature may be attached by the proxy consenter if the patient is unable to do so due to hand dysfunction);
(8) Patients with a magnitude of change in ALSFRS-R score (Attachment 3) between -1 and -4 during the pretreatment 12-weeek observation period.

2) Exclusion criteria

Patients falling under any of the following criteria (1) through (10) are excluded from the study.

(1) Patients to whom the diagnosis has not been disclosed;
(2) Patients with a history of allergy to any component of the test drug;
(3) Patients with severe psychiatric symptoms (hallucination, delusion) or dementia;
(4) Patients with severe orthostatic hypotension or other types of hypotension;
(5) Patients with a severe complication(s) such as heart, kidney and/or liver disease;
(6) Patients found by echocardiography to have valvular heart disease (e.g., valve hypertrophy,

restricted range of valve motion, stenosis associated with such abnormalities, etc.) or having a history of such disease (patients with moderate disease of only one valve are eligible for the study);
(7) Pregnant, possibly pregnant or lactating women;
(8) Patients using any other clinical trial drug or having participated in any other clinical trials within 3 months before;
(9) Patients incompetent to give consent to participate in the study;
(10) Other patients judged by the attending physician as inappropriate for the study.

3) Criteria for discontinuation
(1) Onset of serious adverse events or the like;
(2) Cancellation of consent to participate in the study by the patient or his/her proxy consenter;
(3) Cases where the attending physician recommends discontinuation of participation in the study;
(4) Other reasons requiring discontinuation.

【Rationale】
Exclusion criteria (1) through (10) and criteria for discontinuation (1) through (4) are adopted in view of the necessity to implement the study in a safe and ethically acceptable manner and to collect reliable data from the study.

6. Study period and planned number of subjects

Study period: January 1, 2009 through January 31, 2011
Planned number of subjects: 50 cases (total number of patients entering the treatment phase)

【Rationale】
In view of the explorative nature of this study, the minimum number of subjects sufficient to yield statistically significant differences, taking into account feasibility at the participating facilities, is adopted.

7. Registration

The Study Director registers patients as subjects of this study after confirming that they satisfy the inclusion criteria, fall under none of the exclusion criteria and plan to receive treatment with NDDPX08 for a period of at least 54 weeks during the study period.
Stated concretely, the following steps are taken for registration.

Temporary registration: The Researcher at a participating facility enters the information about the start of the observation period for each patient satisfying the above-mentioned criteria and having given informed consent in Form 1 (Temporary Registration Form; entry by CRC acceptable) and dispatches it by FAX to the FeGALS Office (Secretariat for Clinical Study on ALS). The FeGALS Office enters the patients in the Registration Control List in order of the time of arrival of the Temporary Registration Form (Form 1).
Formal registration: A Researcher at a participating facility evaluates each patient at the end of the observation period and checks whether or not the patient satisfies the requirements, using the Formal Registration Form (Form 2). The Researcher then enters necessary information into Form 2 and dispatches it by FAX to the FeGALS Office. The FeGALS Office assigns a drug allocation code to each

patient, using a table of random numbers, after receipt of the Formal Registration Form. The drug allocation code assigned is sent by FAX to the CRC in charge at the corresponding participating facility, using the Drug Allocation Notification Form (Form 3). In addition, the FeGALS Office enters the information about the start of treatment for each patient in the Registration Control List. The CRC receiving the Drug Allocation Notification Form requests the Researcher to prescribe the drug for the patient concerned, without notifying the Researcher of the drug allocation code for the patient. (The prescription ordering system at each participating facility needs to be arranged appropriately to ensure blinding of the drug/placebo prescribed for each subject of this study).

8. Methods

1) Multicenter double-blind study procedure

【Drug treatment】

Efficacy and safety are evaluated through analysis of changes in each variable measured at the start of the observation period and before and after the start of treatment with NDDPX08 or placebo.

For patients who begin to receive Rilutek treatment at the start or 4 weeks before the start of the observation period, the 12-week treatment with Rilutek alone (100 mg/day) during the observation period is followed by combined treatment (Rilutek + NDDPX08). The NDDPX08 dose level begins at 1.25 mg/day and is increased in steps to 15 mg/day during the 12-week treatment period according to the dose escalation schedule given on the next page (Fig. 1). If any serious adverse reaction arises following a dose increase to 10 mg/day and it is judged to be difficult to maintain this dose level, the dose level of 7.5 mg/day is regarded as the maintenance dose level. If alleviation of symptoms is noted during dose escalation steps, the dose level producing alleviation of symptoms is used as the maintenance dose level.

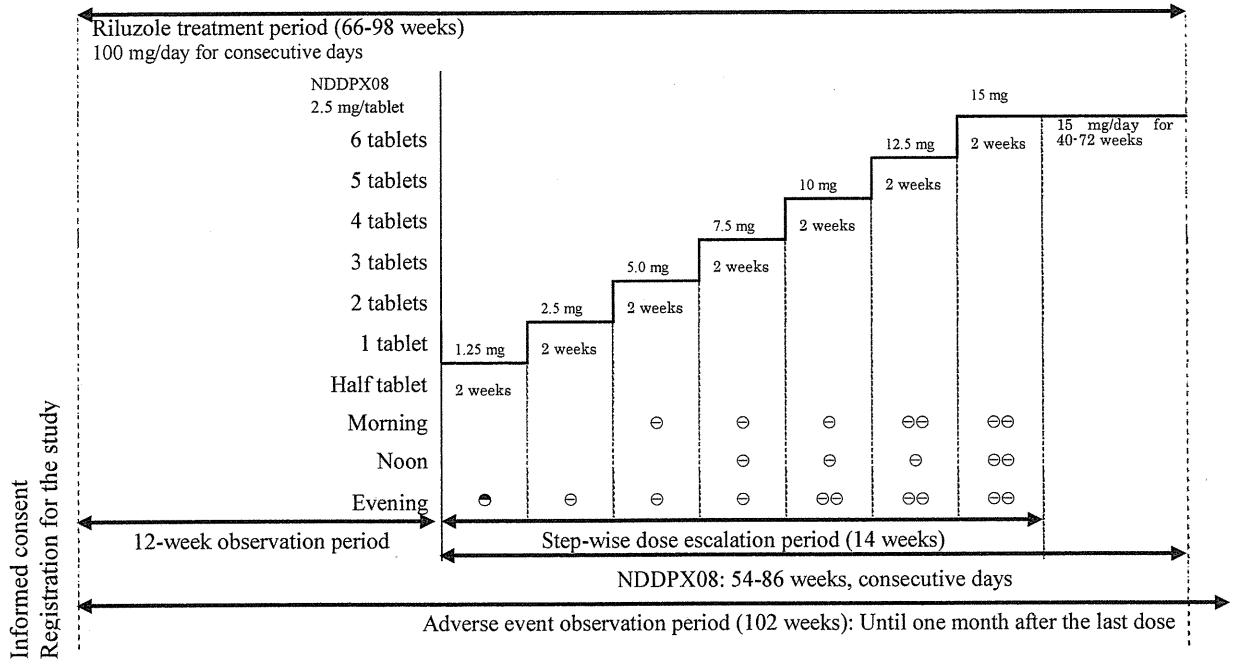
The total NDDPX08 treatment period is 58-90 weeks (including the 4 weeks during which the dose level is reduced in steps). Follow-up of adverse events is continued until 1 month after the end of NDDPX08 treatment.

【Allocation of placebo】

Placebo (lactose) is administered to 10 of the 50 subjects planned to be enrolled in the study. Patients registered as subjects of this study at 3 hospitals of Tokai University, Kitasato University East Hospital and Toho University Omori Medical Center are combined and numbered 1 through 50 in order of the time of registration.

Allocation of NDDPX08 is performed by the Tokai University Secretariat for Clinical Study on ALS (FeGALS Office), using a table of random numbers. The information on drug allocation is maintained securely as confidential information.

Fig. 1 Flow chart of the clinical study (drug treatment method): NDDPX08 dose escalation schedule



【Dispensing】

The placebo (lactose: 250 mg and 500 mg) and NDDPX08 2.5 mg tablet used for this study are in powder form. Each NDDPX08 2.5 mg tablet weighs 140 mg. To minimize the amount of drug remaining in the pack after use (to minimize errors in drug dose levels), the 140 mg powder equivalent to one NDDPX08 2.5 mg tablet is combined with 110 mg lactose to a total weight of 250 mg. If half of an NDDPX08 2.5 mg tablet (=1.25 mg tablet) is administered at a time, the powdered drug is combined with 180 mg lactose to a total weight of 250 mg. If two NDDPX08 2.5 mg tablets are administered at a time, the powdered drug (280 mg) is combined with 220 mg lactose to a total weight of 500 mg. Each active drug (powder equivalent to 1.25 mg, 2.5 mg and 5.0 mg of the active ingredient) and each placebo (powdered lactose 250 mg and 500 mg, equal in amount to the powdered active drug) are packed and stored shielded from light.

The placebo and active drug in powder form are prepared at the pharmacy of each participating facility (Tokai University Hachioji/Oiso Hospital, Kitasato University East Hospital, Toho University Omori Medical Center). The drug/placebo (NDDPX08 2.5 mg tablet, lactose) and materials (packing paper, light-shielding and other materials needed for dispensing of powder preparations) are supplied by the FeGALS Office. The manuals for powder dispensing, identification and control of the active drug and placebo, etc. are supplied by the Pharmacy of the Tokai University Hospital and the FeGALS Office CRC.

【Distinction between active drug and placebo】

A drug code No. (NDDPX08-TSM-specific 6-digit alphanumeric) is printed on the paper pack for NDDPX08. The times for drug intake (morning, noon and evening) and the amount of drug contained (1.25 mg, 2.5 mg and 5.0 mg) are printed on each pack. A drug code No. (NDDPX08-TSM-specific 6-digit alphanumeric) is also printed on the paper pack for the placebo (lactose). The times for drug intake

(morning, noon and evening) and the amount of drug contained (1.25 mg, 2.5 mg and 5.0 mg) are printed on each pack. The active drug (NDDPX08) and its placebo are prepared at the pharmacy of each participating facility and subsequently stored and managed strictly. The Investigator delivers either the active drug or the placebo to each subject.

The drug code No. is composed of the test drug code (NDDPX08), the code for each participating facility (Tokai University Hospital = TSM, Tokai University Hachioji Hospital = TSH, Tokai University Oiso Hospital = TSO, Kitasato University East Hospital = KHH, Toho University Omori Medical Center = TMC) and the active drug/placebo code (identifiable specific 6-digit alphanumeric).

【Blinding protocol】

At the end of the 12-week observation period, the Investigator judges the eligibility of each temporarily registered patient in the treatment phase of the study. If rated as eligible, the patient is registered via FAX (formal registration), and the FeGALS Office assigns a drug allocation code No. (selected from a table of random numbers) to this patient on the basis of the formal registration form. Then, FeGALS dispatches the Drug Allocation Notification Form by FAX to the CRC of the participating facility concerned. The CRC receiving the Drug Allocation Notification Form transmits the information about the drug allocation code No. to the Pharmacy (or sends the drug allocation notification form directly by FAX). Each party involved checks the information and the CRC requests that the attending physician issues a drug prescription while keeping the physician uninformed as to the drug allocation code (i.e., whether the prescription is an active drug or a placebo). The Pharmacy delivers the drug of the corresponding drug allocation code No. to the patient after receiving the prescription issued by the attending physician. The CRC of each participating facility gives adequate accounts to the subject or his/her family as to the procedures for drug storage, drug intake and re-collection of the drug package used or kept unsealed.

The CRC of each participating facility re-collects the drug packages brought by the patient during hospital visits to check the status of compliance with dosing instructions. After temporary storage by this CRC, the re-collected drug package is handed to the CRC of the Tokai University ALS Clinical Study Group during the patient's visit.

The FeGALS Office stores all re-collected drug packages. Prior to statistical analysis of efficacy by an outside contractor, the drug remaining in the re-collected packages and the unused drug package (extracted at random) are subjected to identification by an outside testing facility and comparison to the drug allocation codes.

Prior to statistical analysis of the data on each subject, the FeGALS Office submits the medication (active drug/placebo) information as well as that about the drug remaining in the packages and the unused drug packages to the ALS Treatment Plan Evaluation Committee.

【Placebo allocation】

The placebo is allocated by dynamic allocation. Dynamic allocation involves the following two factors.

Factor 1: ALS severity grade (1, 2 and 3)

Factor 2: Age (60 years)

【Cooperation among CRCs of multiple participating facilities】

This clinical study on ALS is carried out at multiple facilities (Tokai University, Kitasato University and Toho University). To ensure smooth implementation of the clinical study, universal validity of the efficacy evaluation criteria and objectivity of evaluation, CRCs (clinical research coordinators) are incorporated in accordance with the clinical study protocol. The CRCs at all participating facilities

cooperate with each other to facilitate monitoring of the clinical study protocol, management of information on temporary and formal registration of subjects, management of patient visits, tests and drug intakes, monitoring of evaluations, management of evaluation-related information and smooth linkage among the attending physicians, evaluators (neurologists) and pharmacies. To this end, the CRC (University CRCs Cooperation) Secretariat is organized within the FeGALS Office, and the Tokai University CRC is nominated as the head of the CRC Secretariat. The CRCs of all participating facilities share the information about the hospital visit schedule, tests, questionnaire survey, medication protocol, etc. for each subject. The CRC Secretariat carries out intensive management of these pieces of personal information and maintains strict custody of such information. A CRC worksheet and CRF of uniform design are employed for this study (Cf. CRF list and sample forms attached). The CRC Secretariat delivers the CRC worksheet and CRF of uniform design to the CRC of each participating facility.

【ALS Treatment Plan Evaluation Committee】

The ALS Treatment Plan Evaluation Committee is organized as an outside unit of this study to ensure the reliability and subjectivity of study implementation and evaluation. The duties assigned to this committee are adjustment and encouragement of the study and evaluation and judgment of the safety and efficacy of NDDPX08 in patients with ALS at the end of the clinical study.

【Prohibited concomitant drugs】

Whether or not a concomitant drug or other drugs during the study period are approved is judged in accordance with the criteria given below. Concomitant use of the drugs listed below, which can affect evaluation of the efficacy of NDDPX08, is prohibited for the period from 4 weeks before the start of Rilutek until the end of the study period.

(1) Dopamine antagonists: antipsychotics such as metoclopramide and sulpiride
(2) CYP1A2 inhibitors: ciprofloxacin, enoxacin, fluvoxamine, etc.
(3) Estrogen preparations
(4) L-dopa preparations
(5) Dopamine agonists
(6) Anticholinergics
(7) Amantadine hydrochloride
(8) Droxidopa
(9) Selegiline hydrochloride
(10) COMT inhibitors
(11) Mecobalamin
(12) Edaravone

【Other restricted drugs】

(1) It is prohibited to begin treatment with any other drug during the period from 4 weeks before the start of the observation period until the end of the study. Temporary concomitant use of drugs is permitted if aimed at dealing with accidental complications, etc., but the use of such drugs needs to be minimized. (Example: cold medicine, analgesics, wet packs, drugs for pollinosis, etc.)
(2) Concomitant use of drugs is permitted if the drugs begin to be used 4 weeks or more before the start of observation and they are used without changing the dosing method or level. Throughout the study period, the dosing method and level of concomitant drugs must be kept unchanged.
(3) Temporary concomitant use of the antiemetic Nauzelin is permitted.

【Concomitant therapy】

The standards given below apply to concomitant therapy or the like during the study period.

(1) Exercise therapy such as rehabilitation

Exercise therapy is applied in a uniform manner as far as possible to all participating facilities. Excessive exercise, which can reduce the muscular strength, is avoided, and the level of exercise is kept equivalent to stretching or the like. Entry into the column "Concomitant therapy" of Form 10 is unnecessary.

(2) Other therapies

No other therapy is permitted, as a rule, except for cases where such therapy is needed to deal with progression of the disease. In cases where such therapy is used, details need to be entered into the column "Concomitant therapy" of Form 10.

2) Efficacy variables

a. Primary efficacy variable

- ALSFRS-R score (Attachment 3)

b. Secondary efficacy variables

- Length of time until death or disease progression to a certain stage (loss of unassisted gait capability, loss of arm function, tracheotomy, attachment of a respirator, tube feeding)
- %FVC
- Modified Norris Scale score (Attachment 4)
- ALSAQ-40 score (Attachment 5)
- MMT (manual muscle test)
- Pinching power
- Grip
- ALS severity grade (Attachment 2)

3) Safety variables

- Adverse events
- Laboratory test
- Echocardiography
- Blood pressure and heart rate

4) Criteria for completion of treatment

For subjects in whom the planned treatment period (54-86 weeks) has been completed or who fall under any of the criteria for completion of combined treatment (death, attachment of an invasive respiration assisting device or beginning of all-day respirator use), the dose level is reduced gradually to zero within one month, to complete treatment with the test drug/placebo.

5) Evaluation of safety and efficacy

Statistical analysis of efficacy data at the end of the study is assigned to an outside contractor. The information about the subjects assigned to the active drug treatment and placebo groups is disclosed at the time of statistical analysis. Statistical analysis as to the efficacy of the test drug is carried out in comparison to the efficacy data from the placebo group, the time course of variables relative to estimates at the end of the 12-week observation period and the natural history of the disease.

The ALS Treatment Plan Evaluation Committee evaluates and judges the safety and efficacy of NDDPX08 in patients with ALS on the basis of the results of the statistical analysis.

Interim evaluation is performed when the number of subjects treated with NDDPX08 for 6 months has reached 25. At that time, statistical analysis of efficacy variables is carried out in comparison to the time course of variables relative to the estimates at the end of the 12-week observation period and the natural history of the disease. At the time of interim evaluation, information as to the subjects assigned to the active drug treatment and placebo groups is not disclosed.

9. Evaluations/tests and their schedules

The evaluations and tests specified below are carried out during the study in accordance with the schedules given in Fig. 2.

Safety is evaluated by the attending physician for each subject. Efficacy is evaluated by one or more neurologists not serving as the attending physician.

Fig. 2 Flow chart of the clinical study (evaluation and survey schedule)

		12-week observation period		NDDPX08 treatment period						Upon discontinuation
				Start	After start				Every other month after 14th week	
		Start	6 weeks		2 weeks	4 weeks	8 weeks	14 weeks		
Informed consent, registration		○		○						
Background	Background variables	●								
	Body weight	●	●	●			●	●	●	
	Complications/disease history	●								
	Concomitant drugs/therapy	●	←	—	—	—	—	—	→	●
Efficacy	ALSFRS-R	●	●	●		●	●	●	●	●
	%FVC	●	●	●			●	●	●	●
	Modified Norris Scale	●	●	●			●	●	●	●
	ALSAQ-4Q	●	●	●			●	●	●	●
	Manual muscle test (MMT)	●	●	●			●	●	●	●
	Pinching power	●	●	●	●	●	●	●	●	●
	Grip	●	●	●	●	●	●	●	●	●
	ALS severity grade	●	●	●			●	●	●	●
Safety	Laboratory tests	●	●	●		●	●	●	●	●
	Echocardiography	●*1								●
	Blood pressure/heart rate	●	●	●	●	●	●	●	●	●
	Adverse events*2	←	—	—	—	—	—	—	—	○ 1 month after last dose

*1: Echocardiography is performed before the observation period.

*2: Presence/absence of adverse events is checked during the period from the start of treatment until one month after the last dose.