Phase 3b Extension Study Evaluating Superiority of Daily vs Approved On/Off Oral Edaravone Dosing in Patients With Amyotrophic Lateral Sclerosis

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BACKGROUND

- Intravenous (IV) edaravone (Radicava®) is a United States (US) Food and Drug Administration (FDA)–approved treatment that has been shown in clinical studies to slow the rate of physical functional decline in patients with amyotrophic lateral sclerosis (ALS)[1,2]
- Subsequently, oral edaravone (Radicava ORS®) was approved by the US FDA for use in patients with ALS in May 2022, gained approval in late 2022 in Canada and Japan, and was approved in Switzerland in May 2023
- Approval was based, in part, on pharmacokinetic (PK) and bioequivalence studies which demonstrated that a 105-mg dose of oral edaravone had a similar PK profile to the existing 60-mg dosage of IV edaravone[3,4]
- Study MT-1186-A02 is an FDA postmarketing commitment; it is a multicenter, phase 3b study that is evaluating and comparing whether daily dosing displays superior efficacy vs the approved on/off dosing regimen of oral edaravone, in addition to evaluating the safety and tolerability of these dosing regimens, in patients with ALS based on the change in the revised ALS Functional Rating Scale (ALSFRS-R) score over 48 weeks
- Study MT-1186-A04, an extension study following Study MT-1186-A02, is evaluating whether daily dosing displays superior efficacy vs the approved on/off dosing regimen of oral edaravone, in addition to evaluating the safety and tolerability of these dosing regimens, for an additional 48 weeks

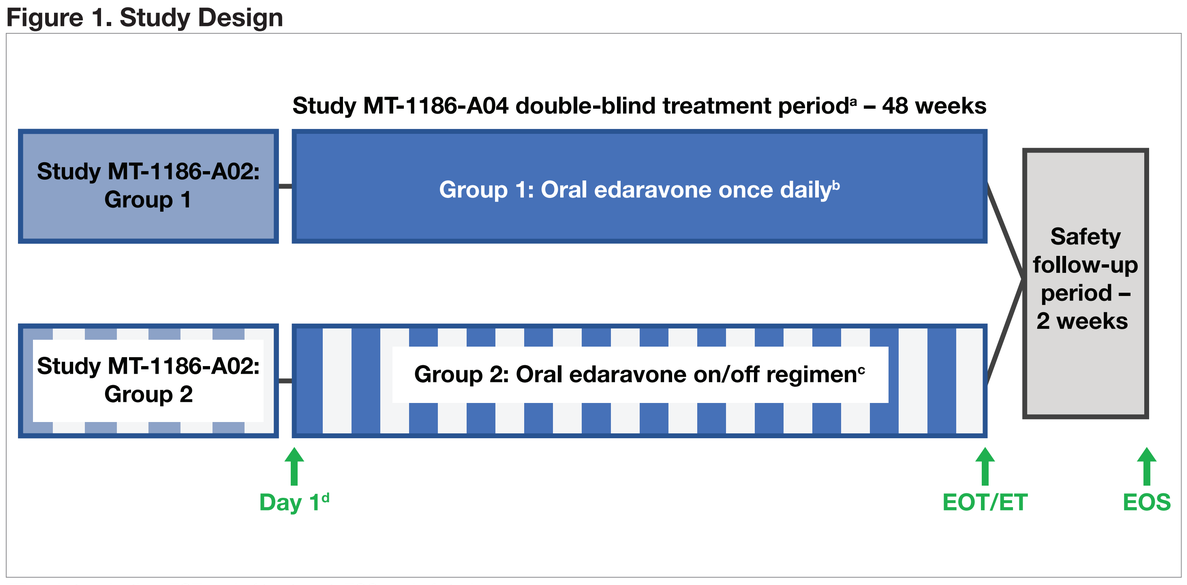
OBJECTIVES

- Study MT-1186-A04 (NCT05151471) is evaluating whether daily dosing displays superior efficacy vs the approved on/off dosing regimen of oral edaravone, in addition to evaluating the safety and tolerability of these dosing regimens, for an additional 48 weeks following the end of Study MT-1186-A02 in patients with ALS, comprising a total duration of up to 96 weeks

METHODS

- Study MT-1186-A04, an extension study following Study MT-1186-A02, is an ongoing, multicenter, phase 3b, double-blind, parallel group, randomized study that is evaluating whether daily dosing displays superior efficacy vs the approved on/off dosing regimen of oral edaravone, in addition to evaluating the safety and tolerability of these dosing regimens (**Figure 1**)
  - **Group 1** will have oral edaravone administered once daily for each 28-day cycle
  - **Group 2** will have oral edaravone administered for 10 days followed by placebo for 18 days in each 28-day cycle
  - Dosing in both groups will continue up to 48 weeks during the double-blind treatment period
  - End of treatment (EOT) assessments will occur at week 48
  - For patients who complete the double-blind treatment period, a safety follow-up telephone visit will occur 2 weeks after the last dose, at week 50

Figure 1. Study Design



ET, early termination; EOT, end of treatment; EOS, end of study.
[a]The dose of oral edaravone should be taken following an overnight fast and at least 1 to 2 hours before the morning meal. [b]Oral edaravone 105 mg administered once daily for 28 days for 12 cycles (approximately n=150). [c]Oral edaravone 105 mg administered for 10 days, followed by placebo for 18 days in each 28-day cycle for 12 cycles (approximately n=150). [d]Day 1 is equal to the week 48 visit of Study MT-1186-A02.

- Patients (approximately n=300, n=150 per treatment group) who have completed Study MT-1186-A02 and who meet Study MT-1186-A04 eligibility criteria will continue in the same previously assigned treatment group/regimen from Study MT-1186-A02
- Week 48 study procedures from Study MT-1186-A02 will be used as the screening/entry criteria for Study MT-1186-A04
- Concomitant use of riluzole is permitted throughout the course of the study when the dose and regimen remain unchanged from the screening visit evaluation of ALSFRS-R in Study MT-1186-A02 through the EOT or early termination of Study MT-1186-A04. Dose reduction, dose interruption, or discontinuation due to the onset of adverse events (AEs), progression of dysphagia, or gastrostomy while on oral edaravone 105 mg are allowed
- The use of sodium phenylbutyrate-taurursodiol (PB-TURSO) is permitted for patients if it becomes commercially available via prescription in their respective country. PB-TURSO should be taken at least 1 hour after oral edaravone dosing
- Patients will be allowed to change from oral administration to percutaneous endoscopic gastrostomy (PEG)/radiologically inserted gastrostomy (RIG) tube administration during the study

Inclusion Criteria

- Patients must provide a signed and dated informed consent form to participate in the study
- Patients must be able (in the judgment of the Investigator) to understand the nature of the study and all risks involved with participation in the study
- Patients must be willing to cooperate and comply with all protocol restrictions and requirements
- Patients must have successfully completed all Study MT-1186-A02 visits and have been compliant with study drug

Exclusion Criteria (Partial List)

- Patients of childbearing potential unwilling to use an acceptable method of contraception from the day 1/screening visit until 3 months after the last dose of study medication. Patients who are sexually active who do not agree to use contraception during the study period
- Patients who are pregnant (as confirmed with a positive pregnancy test) or lactating at the day 1/screening visit
- Patients who have a significant risk of suicide. Patients with any suicidal behavior or suicidal ideation of type 4 (active suicidal ideation with some intent to act, without a specific plan) or type 5 (active suicidal ideation with specific plan and intent) based on the Columbia-Suicide Severity Rating Scale at week 48 of Study MT-1186-A02
- Patients who are not eligible to continue in the study, as judged by the Investigator in conjunction with the MTDA medical monitor
- Patients who are unable to take their medications orally or through a PEG/RIG tube

Endpoints

- Clinical trial endpoints are listed in **Table 1**

Table 1. Clinical Trial Endpoints

Efficacy Endpoints	Safety and Exploratory Efficacy Endpoints
Primary efficacy endpoint • Time from the randomization date in Study MT-1186-A02 to at least a 12-point decrease in ALSFRS-R or death, whichever happens first **Secondary efficacy endpoints** • The CAFS score at all visits from baseline in Study MT-1186-A02 to the end of Study MT-1186-A04 • Change in the Amyotrophic Lateral Sclerosis Assessment Questionnaire 40 score at all visits from baseline in Study MT-1186-A02 to the end of Study MT-1186-A04 • Change in ALSFRS-R score at all visits from baseline in Study MT-1186-A02 to the end of Study MT-1186-A04 • Time from the randomization date in Study MT-1186-A02 to death, tracheostomy, or permanent assisted mechanical ventilation (≥23 hours/day)	**Safety endpoints** • Adverse events, adverse drug reactions, and treatment-emergent adverse events (e.g., grade, incidence, severity) • Physical examination • 12-lead electrocardiogram parameters • Vital signs (heart rate, respiratory rate, sitting systolic and diastolic blood pressure, and axillary, oral, temporal, or tympanic body temperature) • Laboratory safety assessments (e.g., hematology, chemistry, and urinalysis) • Columbia-Suicide Severity Rating Scale **Exploratory efficacy endpoints** • Change in % SVC at all visits from baseline in Study MT-1186-A02 to the end of Study MT-1186-A04 • Change in body weight at all visits from baseline in Study MT-1186-A02 to the end of Study MT-1186-A04 • King's ALS Clinical Stage derived from ALSFRS-R score and death at all visits from baseline in Study MT-1186-A02 to the end of Study MT-1186-A04

ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale – Revised; CAFS, Combined Assessment of Function and Survival; SVC, slow vital capacity.

Statistical Methods

- The primary efficacy endpoint will be analyzed using Kaplan-Meier estimates, 2-sided alpha with a nominal 20% significance level and 80% confidence intervals
- The comparison between Treatment Group 2 vs Treatment Group 1 will be performed using a log rank test with MT-1186-A02 randomization strata of ALSFRS-R rate of decline in score from the MT-1186-A02 screening period (2 levels strata of –1, –2 or –3, –4) and the geographical region (3 levels strata of Europe, America, or Asia Pacific)

RESULTS/DISCUSSION

- An Independent Data Monitoring Committee (IDMC) conducted a pre-planned analysis of Study MT-1186-A02 and concluded that the study met the prespecified futility criteria, and recommended discontinuation of Study MT-1186-A02 and Study MT-1186-A04
- The FDA released MTPA from their postmarketing commitment to conduct Study MT-1186-A02
- While the ALSFRS-R score reduction with daily dosing did not show superior efficacy over the clinical trial patients with on/off dosing, the trajectory of ALSFRS-R scores were similar to the results of the pivotal phase 3 trial for IV edaravone, Study 19 (MCI186-19)
- In Study MT-1186-A02, oral edaravone was well tolerated and no new safety concerns were identified in either arm of the study
- Results from the study will be published once they become available

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DISCLOSURES

- JR is a consultant for Expansion Therapeutics, National Institutes of Health, Department of Defense, F Prime, and The ALS Association. SD and MC have nothing to disclose. LZ has received honoraria for consulting with MTP, Biogen, Amylyx, and Cytokinetics. AC serves on scientific advisory boards for Mitsubishi Tanabe, Roche, Biogen, Denali Pharma, AC Immune, Biogen, Lilly, and Cytokinetics and has received a research grant from Biogen. ACL has served as a scientific consultant for Mitsubishi Tanabe Pharma America, Inc. GS has served as a medical advisor for Mitsubishi Tanabe Pharma Corporation. MD is a medical advisor for the MT-1186-A02 study. DS, AW, AS, and SA are employees of Mitsubishi Tanabe Pharma America, Inc. VT is an employee of Mitsubishi Tanabe Pharma Europe Ltd. MH and TF are employees of Mitsubishi Tanabe Pharma Corporation
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