Phase 3, Open-Label, Safety Extension Study of Oral Edaravone (Radicava ORS®) Administered Over 96 Weeks in Patients With ALS (MT-1186-A03)

Angela Genge, MD, FRCP(C)[1]; Gary L. Pattee, MD[2]; Gen Sobue, MD, PhD[3,4]; Masashi Aoki, MD[5]; Hiide Yoshino, MD[6]; Philippe Couratier, MD, PhD[7]; Christian Lunetta, MD[8]; Susanne Petri, MD[9]; Daniel Selness, RN, BA, MBA[10]; Vesna Todorovic, MD, MPhil[11]; Manabu Hirai, MS[10]; Alejandro Salah MD, PhD, MBA, MHA[10]; Stephen Apple, MD[10]; Art Wamil, MD, PhD[10]; Alexander Kalin, MS[10]; Carlayne E. Jackson, MD, FAAN[12]

[1]Montreal Neurological Institute and Hospital, Montreal, Canada; [2]University of Nebraska Medical Center, Lincoln, Nebraska, USA; [3]Nagoya University Graduate School of Medicine, Nagoya, Japan; [4]Aichi Medical University, Aichi, Japan; [5]Tohoku University School of Medicine, Sendai, Miyagi, Japan; [6]Neurology Clinic, Chiba, Japan; [7]CRMR SLA Service de Neurologie, CHU de Limoges, Limoges, France; [8]Istituti Clinici Scientifici Maugeri IRCCS, Neurorehabilitation Unit of Milano, Milan, Italy; [9]Hannover Medical School, Hannover, Germany; [10]Mitsubishi Tanabe Pharma America, Inc., Jersey City, New Jersey, USA; [11]Mitsubishi Tanabe Pharma Europe Ltd., London, UK; [12]University of Texas Health Science Center at San Antonio, San Antonio, Texas, USA

Introduction

- An on/off dosing regimen of Radicava® (edaravone) IV (intravenous) was approved by the US Food and Drug Administration (FDA) in 2017 for the treatment of amyotrophic lateral sclerosis (ALS) after it was shown to slow the rate of physical functional decline in clinical trials[1,2]
- Radicava ORS® (edaravone) oral suspension was FDA-approved for use in patients with ALS in May 2022[1], based on bioequivalence and long-term safety studies
  - Pharmacokinetic (PK) and bioequivalence studies were conducted and demonstrated similar PK profiles between a 105-mg dose of Radicava ORS® and the FDA-approved 60-mg dose of Radicava® IV[3,4]
  - The safety and tolerability of Radicava ORS® in patients with ALS were assessed in a 48-week, global, multicenter, open-label, phase 3 study (MT-1186-A01)[5]
- Here, Study MT-1186-A03, an extension of Study MT-1186-A01, was an open-label, phase 3, 96-week study that further evaluated the long-term safety and tolerability of the FDA-approved on/off dosing regimen of Radicava ORS® in patients with ALS

Objectives

- **Primary**: To assess the long-term safety and tolerability of Radicava ORS® in patients with ALS
- **Exploratory:** To evaluate the efficacy of Radicava ORS® for 96 weeks of treatment or until the drug is commercially available in that country

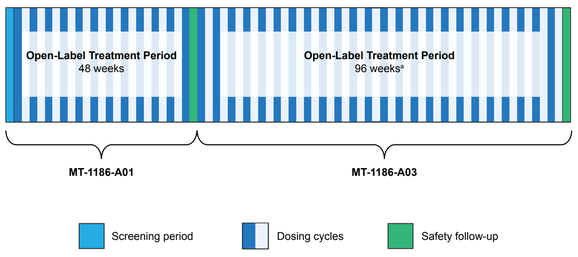
Methods

- Study MT-1186-A03 (NCT04577404) was an open-label, multicenter, 96-week extension study that evaluated the long-term safety and tolerability of the FDA-approved on/off dosing regimen of Radicava ORS® for patients who completed the initial 48 weeks of Study MT-1186-A01
- Patients who successfully completed Study MT-1186-A01 had the option to enroll in Study MT-1186-A03 and continued to receive Radicava ORS® without interruption for an additional 96 weeks

Study Design (Figure 1)

- Day 1 is equal to the week 48 visit of Study MT-1186-A01
- Open-label treatment period up to 96 weeks or until the drug is commercially available in that country
- Long-term safety study
- Safety follow-up period 2 weeks after the last dose

Figure 1. Study Design of MT-1186-A03



[a]Or until the drug is commercially available in that country.

Dosing

Radicava ORS® Dosing:

- Patients received a 105-mg dose of Radicava ORS® administered in treatment cycles identical to the FDA-approved on/off dosing schedule
- Treatment cycles were 28 days with patients being administered a 105-mg dose once daily for 10 out of 14 days, followed by a 14-day drug-free period, for up to 96 weeks of treatment or until the drug is commercially available in that country
- Patients received Radicava ORS® following an overnight fast, followed by continued fasting for at least 1 to 2 hours before the next meal

Key Inclusion and Exclusion Criteria of MT-1186-A03

Inclusion Criteria

MT-1186-A01

- Males and females aged 18 to 75 years
- Definite, probable, probable laboratory-supported, or possible ALS according to El Escorial revised Airlie House diagnostic criteria
- Baseline forced vital capacity (FVC) ≥70% of predicted
- Disease duration ≤3 years
- Ability to function independently

MT-1186-A03

- Patients who provided a signed and dated Informed Consent Form to participate in the study
- Patients who successfully completed all Study MT-1186-A01 visits and had been compliant with the study drug

Exclusion Criteria

- Patients who were able to bear children and who did not have a negative pregnancy test
- Women who were nursing or who did not agree to use a highly effective form of contraception from Visit 1 until 3 months after the last dose of study medication
- Patients who had a significant risk of suicide
- Patients with any suicidal behavior or suicidal ideation of type 4[a] or type 5[b] on the Columbia-Suicide Severity Rating Scale (C-SSRS) at Visit 1
- Patients who were not eligible to continue in the study, as judged by the Investigator
- Patients who were unable to take their medications orally or through a percutaneous endoscopic gastrostomy/radiologically inserted gastrostomy (PEG/RIG) tube

[a]Active suicidal ideation with some intent to act, without a specific plan.
[b]Active suicidal ideation with specific plan and intent.

Study Endpoints

Primary Safety Endpoints	Exploratory Efficacy Endpoints
• Adverse events – Any TEAE – Any serious TEAE (TESAEs) – Any TEAE related to study drug – Any TEAE leading to study drug discontinuation – Any TEAE leading to death • Physical examination • Body weight • 12-lead ECG parameters • Vital signs • Laboratory safety assessments • C-SSRS	• Change in ALSFRS-R score from baseline to each visit • Time (days) to death, tracheostomy, or PAMV

ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; C-SSRS, Columbia-Suicide Severity Rating Scale; ECG, electrocardiogram; PAMV, permanent assisted mechanical ventilation; TEAE, treatment-emergent adverse event.

Results

Patient Disposition

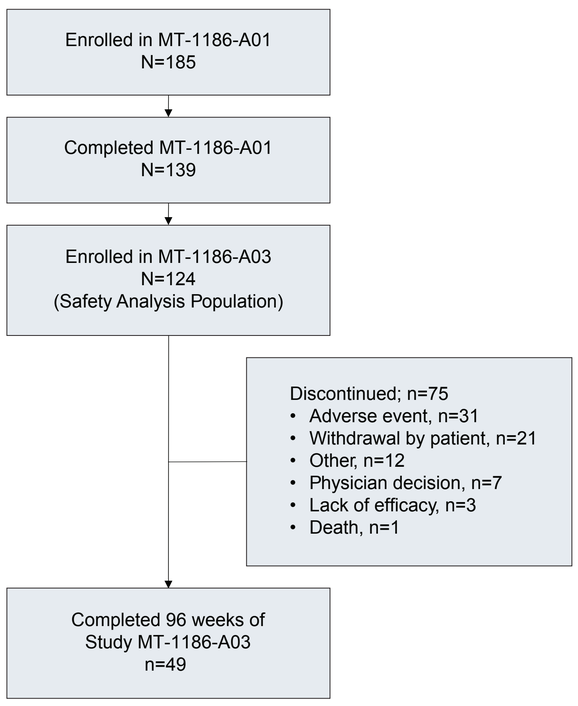
Study MT-1186-A01

- A total of 216 patients were screened in Study MT-1186-A01
- 185 were enrolled and received Radicava ORS®
- 46 patients discontinued (adverse event [n=23], withdrawal by patient [n=17], physician decision [n=1], other [n=5])
- 160 patients completed 24 weeks of therapy and 139 patients completed 48 weeks of therapy

Study MT-1186-A03

- A total of 124 patients were screened in the extension Study MT-1186-A03, all of whom were enrolled (Figure 2)
- 124 patients received Radicava ORS® and were included in the Safety Analysis Population
- 49 patients completed 96 weeks of therapy

Figure 2. Patient Disposition for Studies MT-1186-A01/A03



Demographic and Baseline Characteristics

- Patients' demographic and baseline characteristics are shown in Table 1

Table 1. Demographic and Baseline Characteristics

Baseline Characteristics	Patients N=124
Gender, n (%)	
Male	83 (66.9)
Female	41 (33.1)
Age (years)	
Mean (SD)	59.0 (10.1)
Median (min, max)	59.0 (22, 75)
Body weight (kg)	
Mean (SD)	69.7 (18.6)
Median (min, max)	67.7 (35.2, 125.9)
Country, n (%)[a]	
United States	38 (30.6)
Canada	18 (14.5)
Germany	5 (4.0)
France	8 (6.5)
Italy	5 (4.0)
Japan	50 (40.3)
Region, n (%)[a]	
North America (US, Canada)	56 (45.2)
Western Europe (Germany, France, and Italy)	18 (14.5)
Japan	50 (40.3)
Ethnicity, n (%)[a]	
Hispanic/Latino	2 (1.6)
Not Hispanic/Latino	118 (95.2)
Not reported/Unknown	4 (3.2)

SD, standard deviation; US, United States.
[a]Summarized using MT-1186-A01 data.

Summary of ALS Disease History

- Patients' ALS disease history is shown in Table 2

Table 2. Summary of Patient ALS History

	Patients N=124
Disease duration from onset of symptoms to MT-1186-A01 screening, years	
Mean (SD)	1.6 (0.7)
Median (min, max)	1.6 (0.3, 3.0)
Disease duration from ALS diagnosis to MT-1186-A01 screening, years	
Mean (SD)	0.6 (0.5)
Median (min, max)	0.5 (0.0, 2.3)
ALSFRS-R score at MT-1186-A01 screening	
Mean (SD)	40.8 (4.1)
Median (min, max)	41.0 (25, 48)
Initial symptom, n (%)	
Bulbar onset	28 (22.6)
Limb onset	96 (77.4)
ALS diagnosis, n (%)	
Sporadic	120 (96.8)
Familial	4 (3.2)
El Escorial revised Airlie House diagnostic criteria, n (%)	
Definite ALS	26 (21.0)
Probable ALS	51 (41.1)
Probable laboratory-supported ALS	38 (30.6)
Possible ALS	9 (7.3)
Concomitant use of riluzole, n (%)	
Yes	105 (84.7)
Concomitant use of AMX0035, n (%)	
Yes	9 (7.3)

ALS, amyotrophic lateral sclerosis; ALSFRS-R, ALS Functional Rating Scale-Revised; AMX0035, sodium phenylbutyrate and taurursodiol; SD, standard deviation.

Safety Endpoints

- A summary of treatment-emergent adverse events (TEAEs) is shown in Table 3

Table 3. Summary of TEAEs

TEAEs	Patients N=124 n (%)	Most Common AEs, n (%)
Any TEAE	113 (91.1)	Fall – 21 (16.9) Muscular weakness – 18 (14.5) Dyspnea – 17 (13.7)
Any TESAE (serious TEAE)[a]	52 (41.9)	Respiratory failure – 13 (10.5) Pneumonia aspiration – 9 (7.3) Dysphagia – 7 (5.6)
Any TEAE related to study drug	12 (9.7)	Nausea – 2 (1.6)[b]
Any TEAE leading to study drug discontinuation	28 (22.6)	Respiratory failure – 8 (6.5) ALS – 4 (3.2) Respiratory disorder – 3 (2.4)
Any TEAE leading to death	19 (15.3)	Respiratory failure – 7 (5.6) ALS – 5 (4.0) Pneumonia – 2 (1.6)

AE, adverse event; ALS, amyotrophic lateral sclerosis; TEAE, treatment-emergent AE.
[a]One TESAE, phlebitis was related to the study drug.
[b]All other TEAEs related to study drug were reported by one patient each.

Common TEAEs (≥5% of patients)

- In general, these TEAEs are consistent with the disease state (Table 4)
- No common TEAEs reported were related to the study drug

Table 4. Common (Reported by ≥5% of Patients) TEAEs

	Patients N=124 n (%)
Any TEAE, n (%)	113 (91.1)
Fall	21 (16.9)
Muscular weakness	18 (14.5)
Dyspnea	17 (13.7)
Constipation	16 (12.9)
Dysphagia	15 (12.1)
Respiratory failure	14 (11.3)
COVID-19	13 (10.5)
Pneumonia aspiration	10 (8.1)
Insomnia	9 (7.3)
Urinary tract infection	9 (7.3)
Anxiety	8 (6.5)
ALS	7 (5.6)
Dysarthria	7 (5.6)
Nausea	7 (5.6)

ALS, amyotrophic lateral sclerosis; COVID-19, coronavirus disease-2019; TEAE, treatment-emergent adverse event.

Additional safety endpoints

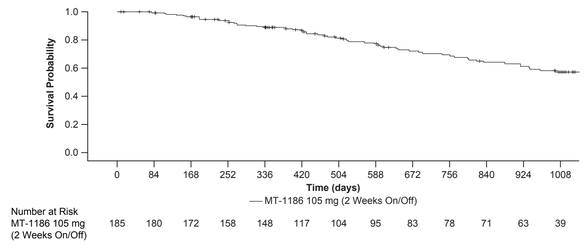
- A total of 25 (20.2%) patients switched from oral to PEG/RIG Radicava ORS® administration (mean time to switching from oral to PEG/RIG was 140.7 days)
- No clear trends were observed in safety laboratory parameters, vital signs, 12-lead electrocardiogram, or physical examinations
- No notable trends in suicidal ideation or behavior were observed during study treatment

Exploratory Efficacy Endpoints

MT-1186-A01/MT-1186-A03 time to death, tracheostomy, or permanent assisted mechanical ventilation (PAMV) (N=185 enrolled in MT-1186-A01)

- There were 185 patients enrolled into Study MT-1186-A01 with 124 patients who continued in Study MT-1186-A03
- Out of the 185 patients enrolled in Study MT-1186-A01 there were 12 and 19 deaths that occurred during the study periods of MT-1186-A01 and MT-1186-A03, respectively
  - Additionally, 16 (8.6%) patients received PAMV, and 11 (5.9%) patients received tracheostomy from the start of Study MT-1186-A01 to the end of Study MT-1186-A03
- 60% of patients were observed at the survival probability (ie, without death, tracheostomy, or PAMV) of 33.6 months (Figure 3)

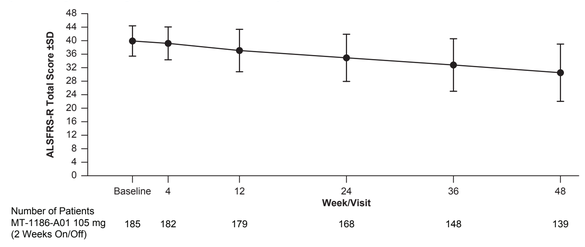
Figure 3. Kaplan-Meier Curve of Time to Death, Tracheostomy, or Permanent Assisted Mechanical Ventilation



ALS Functional Rating Scale-Revised (ALSFRS-R)

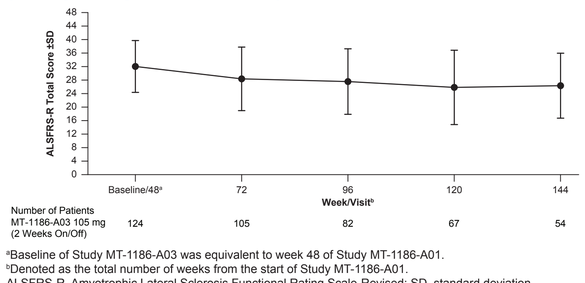
- MT-1186-A01 mean (standard deviation [SD]) ALSFRS-R score was 40.0 ± 4.5 points at baseline (n=185) and 30.6 ± 8.5 points at 48 weeks (n=139) (Figure 4)
  - The mean change from baseline to 48 weeks was −9.9 points (n=139)
- MT-1186-A03 mean (SD) ALSFRS-R score was 31.8 ± 7.6 points at baseline/48 weeks (n=124) and 26.2 ± 9.5 points at 144 weeks from the start of MT-1186-A01 (n=54) (Figure 5)
  - The mean change from baseline/48 weeks to 144 weeks was −8.8 points (n=54)

Figure 4. Study MT-1186-A01 ALSFRS-R Score by Visit (Safety Analysis Population)



ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; SD, standard deviation.

Figure 5. Study MT-1186-A03 ALSFRS-R Score by Visit (Safety Analysis Population)



[a]Baseline of Study MT-1186-A03 was equivalent to week 48 of Study MT-1186-A01.
[b]Denoted as the total number of weeks from the start of Study MT-1186-A01.
ALSFRS-R, Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; SD, standard deviation.

Conclusions

- In general, Radicava ORS® (105 mg, on/off regimen) was well tolerated during Study MT-1186-A03, which was an extension of Study MT-1186-A01
- No new safety concerns were identified during this study
- The most frequently reported TEAEs, TESAEs, and TEAEs leading to death were associated with ALS disease progression or were study drug-unrelated, non-specific symptoms
- ALSFRS-R total score decreased by 8.8 points on average over the 96-week study period from a mean baseline value of 31.8 points
  - This indicates an ALSFRS-R rate of decline of 0.40 points/month[a] during Study MT-1186-A03, suggesting potential improved efficacy when compared to the ALSFRS-R rate of decline of 1.02 points/month in the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) database[6], although the interpretation may be limited by certain confounding factors
- Out of the 185 patients enrolled in Study MT-1186-A01, there were 12 and 19 deaths that occurred during the study periods of MT-1186-A01 and MT-1186-A03, respectively
  - Additionally, 16 (8.6%) patients received PAMV, and 11 (5.9%) patients received tracheostomy from the start of Study MT-1186-A01 to the end of Study MT-1186-A03
- The median survival time to death, tracheostomy, or PAMV at the 50% survival probability timepoint could not be calculated due to the low number of events (56 events [30.3% for 185 patients enrolled into Study MT-1186-A01])

[a]0.40 points/month=8.8 points (descriptive mean) divided by the 22-month (96-week) duration of Study MT-1186-A03.

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Disclosures

- **AG** and **GL** have served as a consultants for Mitsubishi Tanabe Pharma, Inc.; **GS** and **MA** have served as a medical advisors for Mitsubishi Tanabe Pharma Corporation. **HY** has served as medical advisor for Mitsubishi Tanabe Pharma Corporation. **PC** has served as a consultant for Biogen and as an editor for Elsevier. **CL** has served as a scientific consultant for Mitsubishi Tanabe Pharma Europe, Cytokinetics, Neuraltus, and Italfarmaco. **SP** has served as a scientific consultant for Cytokinetics, Biogen, and Roche, and received speaker's honoraria from Biogen, Roche, and Italfarmaco. **VT** is an employee of Mitsubishi Tanabe Pharma Europe Ltd. **DS**, **MH, AS, SA, AW,** and **AK** are employees of Mitsubishi Tanabe Pharma America, Inc. **CEJ** serves on the Data and Safety Monitoring Board for Mitsubishi Tanabe Pharma America, Inc., and Anelixis
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