24 May 2019
EMA/CHMP/290284/2019
Committee for Medicinal Products for Human Use (CHMP)

Withdrawal assessment report

Radicava

International non-proprietary name: edaravone

Procedure No. EMEA/H/C/004938/0000

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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List of abbreviations

%FVC	percent forced vital capacity
3NT	3-nitrotyrosine
ADL	Activities of Daily Living
AE	adverse event
AIS	acute ischaemic stroke
ALP	alkaline phosphatase
ALS	amyotrophic lateral sclerosis
ALSAQ40	ALS assessment questionnaire-40 items
ALSFRS-R	revised ALS functional rating scale
ANCOVA	analysis of covariance
ANOVA	analysis of variance
AUC	area under the curve
AUC_{0-24h}	area under the plasma concentration-time curve to 24 hours after the end of the infusion
$AUC_{0-\infty}$	area under the plasma concentration-time curve from time 0 to infinity
BE	bioequivalence
BID	twice a day
BMI	body mass index
C_0	initial concentration following intravenous bolus injection
C_{60min}	plasma concentration at the end of 60-minute continuous intravenous infusion
Ccr	creatinine clearance
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
C_{max}	maximum concentration
CNS	central nervous system
COMP	Committee for Orphan Medicinal Products
CSF	cerebrospinal fluid
CSR	clinical study report
DDI	Drug-drug interaction
Definite or Probable/ EESP/2y	EESP patients with Definite or Probable ALS diagnosis based on the El Escorial and revised Airlie House diagnostic criteria who are within two years of initial ALS symptom onset
DEL	Drug Establishment License
ECG	electrocardiogram
E group	edaravone group
E-E group	edaravone group in double-blind period of MCI186-19 followed by edaravone group in active extension of MCI186-19
EE group	edaravone group in Study MCI186-16 followed by edaravone group in Study MCI186-17
EP group	edaravone group in Study MCI186-16 followed by placebo group in Study MCI186-17
EESP	Efficacy Expected Subpopulation
EFNS	European Federation of Neurological Societies
EMA	European Medicines Agency
ENCALS	European Network to Cure ALS
EU	European Union
FALS	familial ALS
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
HNE	4-hydroxy-2,3-nonenal
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
IND	IND
ISE	Integrated Summary of Effectiveness
ISS	Integrated Summary of Safety
ITT	Intent-to-Treat
IV	intravenous
JaCALS	Japanese Consortium for Amyotrophic Lateral Sclerosis Research

LLT	Lowest Level Term
LLQ	lower limit of quantitation
LMN	Lower motor neuron
LOCF	last observation carried forward
LS mean	least-squares mean
MAA	Marketing Authorisation Application
MAP	Managed Access Program
MCI-186	edaravone
MedDRA	Medical Dictionary for Regulatory Activities
MHLW	Ministry of Health, Labor, and Welfare
MMRM	mixed model for repeated measures
MTPC	Mitsubishi Tanabe Pharma Corporation
NDA	New Drug Application for US
NDS	New Drug Submission for Canada
NIV	non-invasive ventilation
NOAEL	no-observed-adverse-effect-level
NRG	Name Review Group
PD	pharmacodynamic
PEG	percutaneous endoscopic gastrostomy
P group	placebo group
P-E group	placebo group in double-blind period of MCI186-19 followed by edaravone group in active extension of MCI186-19
PE group	placebo group in Study MCI186-16 followed by edaravone group in Study MCI186-17
PK	pharmacokinetic(s)
PMDA	Pharmaceuticals and Medical Devices Agency
PPK	population pharmacokinetic(s)
PT	Preferred Term
Q	quarter
QoL	quality of life
REMS	Risk Evaluation and Mitigation Strategy
RMP	Risk Management Plan
SAE	serious adverse event
SAH	subarachnoid hemorrhage
SALS	sporadic ALS
SAP	statistical analysis plan
SD	standard deviation
SE	standard error
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
sNDA	supplemental new drug application
SOC	System Organ Class
mSOD	mutant superoxide dismutase
TBD	to be determined
TEAE	treatment-emergent adverse event
UGT	uridine diphosphate glucuronosyltransferase
UMN	upper motor neuron
US	United States
V2	peripheral volume of distribution 2

1. CHMP Recommendation

Based on the review of the data and the Applicant's response to the CHMP LoQ on quality, safety, efficacy, the application for Radicava, an orphan medicinal product in the treatment of amyotrophic lateral sclerosis (ALS) is not approvable since major objections still remain, which preclude a recommendation for marketing authorisation at the present time.

Questions to be posed to additional experts

A SAG meeting is recommended in order to discuss the strength of evidence for efficacy, the clinical relevance of the results, the possibility to extrapolate the results from the Japanese population to the EU population, the most appropriate ALS population for edaravone treatment and the adequacy of the registry to provide confirmatory efficacy data, esp. on survival and survival-related endpoints such as tracheostomy and non-invasive ventilation.

List of Questions for a SAG for RADICAVA (edaravone)

1) What are the SAG's conclusions on the efficacy results from the clinical study MCI186-19? Is the difference of 2.87 in the change of ALSFRS-R (primary endpoint) compared to placebo considered sufficient to establish clinically relevant efficacy taking into account the results on the secondary endpoints and the results from other clinical studies?

2) According to the EU guideline on ALS, trials for treatments intended to be disease-modifying should address the effect of treatment on both functioning and survival. Is the totality of the survival/mortality data considered sufficient and interpretable to conclude on the effect of edaravone on survival of ALS patients? If not, do you think additional data on survival are needed before or after potential approval of the product?

3) If you consider that more data on survival are needed and could be generated post-approval, is the proposed Disease Registry considered adequate to provide comprehensive reliable comparative survival data? How might possible biases be minimised?

4) All clinical efficacy and safety data were collected in Japanese populations with ALS severity Grade 1 and 2 and distinct clinical characteristics (definite or probable/EESP/2y). Please discuss the extent to which these results can be extrapolated to a broad ALS population in Europe as defined by the proposed indication statement.

5) Considering the available data, is there a possibility to identify in practice (sub)groups of patients who would, or would not, benefit from edaravone treatment?

Inspection issues

A GMP or GCP inspection or pre-authorisation testing is not deemed necessary.

GMP inspection(s)

The European Medicines Agency Manufacturing and Quality Compliance Service has reviewed the manufacturer information in the context of this application and determined that no pre-approval inspections to verify GMP compliance are deemed necessary at this stage within the scope of this MAA evaluation procedure.

The EU and Japan reinforced their collaboration on inspections of medicine manufacturers (EMA press release 18/07/2018). The mutual recognition agreement from 2004 was updated and extends scope to sterile products, active pharmaceutical ingredients and biologicals including vaccines.

The Applicant is requested to provide a Product Quality Review of the last 3 years post approval as PAM.

No inspection or pre-authorisation testing is deemed necessary.

GCP inspection(s)

A GCP inspection is currently not required.

According to the Applicant, all studies in patients with ALS were conducted in adherence to the principles of International Council for Harmonisation, Good Clinical Practice (ICH, GCP), to relevant regulatory guidance and in accordance with the principles of the "Declaration of Helsinki" and subsequent amendments, as well as with the laws and regulations of the country in which the research was conducted.

The Pharmaceuticals and Medical Devices Agency (PMDA) in Japan has performed GCP audits on 2 clinical investigator sites in Japan and the conclusion was that the data from these sites were acceptable and that the studies were conducted adequately. In addition, the Food and Drug Administration (FDA) in the United States (US) has performed GCP audits on 6 clinical investigator sites in Japan and the conclusion was the same. Additionally, no GCP issues were identified during the review of the application.

FDA conducted a GCP inspection to monitor the CRO responsible for MCI186-16 and -MCI186-17 studies.

PMDA conducted a GCP inspection of the documentation of all clinical trial sites which participated in clinical trials for ALS (Study MCI186-12, -MCI186-17, -18, -19) kept by MTPC.

No additional audits are planned.

New active substance status

Based on the review of the data, the active substance edaravone contained in the medicinal product Radicava is considered to be qualified as a new active substance in itself.

2. Executive summary

2.1. Problem statement

Amyotrophic lateral sclerosis (ALS) is a rare progressive, fatal motor neuron disease characterised by axonal degeneration and progressive loss of the upper and lower motor neurons throughout the central nervous system. Considering the seriousness of the disease and limited options for treatment there remains an unmet medical need for efficacious and safe treatments for ALS. Riluzole is the only approved medication for modifying disease progression in ALS in the EU and apart from that treatment is mainly palliative.

2.1.1. Disease or condition

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease that affects nerve cells in the brain and the spinal cord. Rapid progression of symptoms directly results from degeneration in motor neurons causing the loss of motor function. Most patients will need assistance with activities of daily living (ADL), with subsequent progression leading to respiratory compromise and eventual respiratory failure, which is a leading cause of death in ALS. Sporadic ALS (SALS) accounts for the vast majority of cases (90-95%) whereas only a small fraction of cases are familial, with a Mendelian pattern of inheritance (FALS). Although FALS is clinically and genetically heterogeneous, the clinical presentation of FALS and SALS is very similar.

2.1.2. Epidemiology and risk factors

The reported incidence of ALS varies from 1.26 to 3.98 cases per 100,000 per year, and prevalence has been reported to range between 4.05 and 7.89 with a mean of approximately 5.40 per 100,000 individuals in the EU, which is equivalent to a total of around 40,000 people (29,971-58,244) (Chio et al 2013 and Couratier P, Revue Neurologique 2016).

The results show a variation of incidence and prevalence between geographical areas and different populations which could be explained by differences in genetics of the population and environmental and lifestyle factors. In sporadic ALS men are more commonly affected than women (1.4-2.5:1) although the number of women affected increases with increasing age. Median survival time is about 2-3 years; however, about 20% of patients may survive longer than 5 years and a small percentage even longer than 10 years. In most cases, disease onset is during late adulthood, but juvenile (prior to 25 years of age) and “young-onset” ALS cases (prior to 45 years), respectively represent approximately 1 and 10% of all cases. The mean age for typical ALS disease onset (adult-onset) is estimated at 61.8 ± 3.8 years (range 54-67 years). Incidence decreases rapidly after 80 years of age.

2.1.3. Biologic features / Aetiology and pathogenesis

The exact pathophysiology of ALS is still uncertain with emerging evidence of a complex interaction between genetic and molecular pathways. Several mechanisms have been implicated in the pathogenesis of ALS. These include excitotoxicity, oxidative stress, neuro-inflammation, mitochondrial dysfunction, disrupted nucleocytoplasmic transport and impaired proteostasis characterized by protein misfolding and aggregation. Multiple studies suggest that oxidative stress plays a role in the progression of motor neuron degeneration and astrocyte dysfunction that lead to progressive deterioration in motor function in ALS. Multiple causes of oxidative stress are likely to include agricultural chemicals, heavy metals, military service, professional sports, excessive physical exertion, chronic head trauma, and certain foods and smoking [D’Amico, 2013]. As ALS progresses, nutritional deficiency, cachexia, psychological stress, and impending respiratory failure may further increase oxidative stress.

2.1.4. Clinical presentation, diagnosis and stage / prognosis

The main presentations of ALS include limb-onset ALS with a combination of upper and lower motor neuron (UMN and LMN) signs in the limbs (70%) and bulbar onset ALS, presenting with speech and swallowing difficulties, and with limb features developing later in the course of the disease (25%). Upper motor neuron disorders present physical findings such as spasms, tendon hyperreflexia, and pathological reflexes. Lower motor neuron disorders present physical findings such as muscular weakness, muscle atrophy, and muscle fasciculation. Patients with ALS experience progressive denervation and atrophy of skeletal muscles and in the majority of cases die from respiratory failure.

Secondary symptoms observed are cognitive and behavioral impairment including pseudobulbar affect, sialorrhea, thick mucus, emotional lability, cramps, spasticity, pain and impaired communication.

Diagnosis is mainly clinical and should be based on the revised El Escorial criteria (EEC) [Brooks 2000].

The El Escorial revised Airlie House diagnostic criteria grade the certainty of the diagnosis based upon 4 clinical grades, clinically definite, probable, probable - laboratory supported and possible ALS.

Table 1 Summary of revised El Escorial research diagnostic criteria for ALS (Airlie House 1998) [Wijesekera et al. 2009 according to Brooks et al 2000]

The diagnosis of ALS requires: 1 Evidence of LMN degeneration by clinical, electrophysiological or neuropathological examination; 2 Evidence of UMN degeneration by clinical examination, and 3 Progressive spread of symptoms or signs within a region or to other regions, as determined by history or examination, Together with the absence of: [1] Electrophysiological and pathological evidence of other disease that might explain the signs of LMN and/or UMN degeneration, and [2] Neuroimaging evidence of other disease processes that might explain the observed clinical and electrophysiological signs
Categories of clinical diagnostic certainty on clinical criteria alone Definite ALS • UMN signs and LMN signs in 3 regions Probable ALS • UMN signs and LMN signs in 2 regions with at least some UMN signs rostral to LMN signs Probable ALS – Laboratory supported • UMN signs in 1 or more regions and LMN signs defined by EMG in at least 2 regions Possible ALS • UMN signs and LMN signs in 1 region (together), or • UMN signs in 2 or more regions • UMN and LMN signs in 2 regions with no UMN signs rostral to LMN signs
UMN signs: clonus, Babinski sign, absent abdominal skin reflexes, hypertonia, loss of dexterity. LMN signs: atrophy, weakness. If only fasciculation: search with EMG for active denervation. Regions reflect neuronal pools: bulbar, cervical, thoracic and lumbosacral.

In the edaravone development program, Study MCI186-19 is designed as the pivotal Phase 3 clinical trial enrolling subjects with “Definite ALS” and “Probable ALS” to ensure the diagnosis and increase likelihood of disease progression during 6-month double-blind study period.

2.1.5. Management

Riluzole (Rilutek) is the only centrally approved medication for modifying disease progression in ALS and apart from that treatment is mainly palliative including control of symptoms such as sialorrhoea, spasticity and pain, thick mucus, emotional liability, cramps, gastrostomy tube feeding to improve nutrition and quality of life and non-invasive ventilation to improve survival and quality of life (Miller 2009; EFNS guideline 2012). The indication of Rilutek is, “to extend life or the time to mechanical ventilation for patients with ALS”. However, controlled trials with riluzole have shown that while this drug has a modest survival benefit in ALS patients, it has no effect on functional aspects of the disease.

Consequently, there remains an urgent and significant unmet medical need for effective treatments for this devastating and fatal disease.

2.2. About the product

Radicava 30 mg/100 mL solution for infusion [Edaravone (MCI-186)] is a free radical-scavenger developed as a neuroprotectant by Mitsubishi Tanabe Pharma Corporation (the Sponsor). Edaravone

was first approved in 2001 in Japan, under the tradename of RADICUT, for the treatment of acute ischemic stroke (AIS) using intravenous (IV) infusion of 30 mg edaravone administered over 30 minutes for up to 14 days of treatment. Edaravone was also approved in Japan in June 2015 and in South Korea in December 2015 for the treatment of ALS based upon a series of clinical studies completed in Japan for ALS. The approved ALS dosing regimen is once a day IV infusion of 60 mg administered over 60 minutes following dosing cycles defined as follows. Cycle 1 consists of 14 consecutive treatment days followed by a 2-week drug-free period with all subsequent cycles consisting of 10 treatment days over 2 weeks followed by a 2-week drug-free period. The Applicant intends to commercialize edaravone as a solution for infusion in an IV bag (30 mg edaravone in 100 mL) in the EU.

The mechanism of action of edaravone is based upon a free radical scavenging effect. Under physiological conditions, edaravone partially exists as an anion that may donate electrons to free radical species in a non-specific manner. The resulting 4,5 dione oxidation product then either hydrolyses to the major product 2-oxo-3-(phenylhydrazono)-butanoic acid (OPB), or transiently equilibrates with a minor amount of 4-hydroxy-4-(3-methyl-1-phenyl-2-pyrazolin-5-on-4-yl)-3-methyl-1-phenyl-2-pyrazolin-5-one (= BPOH), if excess levels of edaravone are available. The generated amount of OPB was reverse proportional to the consumption of edaravone.

There are multiple publications indicating that high levels of oxidative stress were observed not only in familial ALS patients but also in sporadic ALS patients, suggesting that oxidative stress plays a major role in motor neuron degeneration and astrocyte dysfunction in broad types of ALS. However, this is rather unspecific. It is acknowledged that in the SmPC the Applicant is stating that the mechanism by which edaravone exerts its therapeutic effect in patients with ALS is unknown.

2.3. The development programme/compliance with CHMP guidance/scientific advice

The edaravone clinical development program in ALS started in 2001 after the launch of edaravone in Japan. The ALS clinical development program consisted of 1 Phase 2 and 4 Phase 3 studies. All studies were conducted and completed in Japan.

Edaravone was first approved in 2001 in Japan, under the trade name of RADICUT, for the treatment of AIS using intravenous (IV) infusion of 30 mg edaravone administered twice daily over 30 minutes for up to 14 days of treatment.

Edaravone was also approved in Japan in June 2015 and in South Korea in December 2015 for the treatment of ALS based upon a series of clinical studies completed in Japan for ALS with the following indication: “Inhibition on progression of functional disorder in patients with amyotrophic lateral sclerosis (ALS)”.

Edaravone was approved in the US in May 2017 for the broad indication “for the treatment of ALS”, under the tradename of RADICAVA.

Edaravone was designated as an orphan drug in Europe on 19 June 2015.

A paediatric investigation plan waiver was confirmed by the Paediatric Committee on 17 July 2015 as ALS currently falls under the scope of the Agency Decision CW/1/2011.

A request regarding acceptability of brandname was submitted to the Name Review Group (NRG) on 05 October 2017. Confirmation was received from the NRG on 15 December 2017 that both RADICAVA and Opradica had been accepted.

An Eligibility request and Letter of Intent were both submitted to EMA on 13 October 2017. Eligibility to the centralised procedure was confirmed by the EMA on 17 November 2017.

CHMP guidelines/Scientific Advice

An EMA Guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis (ALS) (EMA/531686/2015, Corr.1) has recently come into effect (1 June 2016).

As the development program for edaravone in ALS was carried out in Japan, Protocol Assistance was sought from the CHMP in 2015 (EMEA/H/SA/3202/1/2015/PA/III) to clarify the suitability of the data for a Marketing Authorisation Application in the EU.

Follow-up Protocol Assistance was provided by CHMP on 22 March 2018 (EMEA/H/SA/3202/1/FU/1/2018/PA/II) with respect to the ongoing registry study in Japan and the proposed registry study in the EU.

Certain issues identified during the Scientific Advice procedure were not followed by the Applicant (please see Discussion on non-clinical and Clinical Efficacy aspects).

2.4. General comments on compliance with GMP, GLP, GCP

GMP: The drug product is manufactured in accordance with Good Manufacturing Practice at the proposed commercial manufacturing site. A copy of a manufacturing license and a GMP certificate was provided.
For the manufacturer responsible for batch release in the EEA, a valid GMP certificate, based on an inspection performed was provided.
The Quality control testing site was subject to a GMP inspection. The resulting GMP compliance certificate was signed.
A recent, well founded declaration concerning GMP compliance of the active substance manufacture is provided from the *qualified person* of the manufacturer responsible for batch release in the EEA.

GLP: The pivotal toxicology studies were conducted in compliance with local Japanese GLP regulations before OECD harmonisation. With regard to safety pharmacology aspects, however, only the hERG channel *in vitro* assay followed GLP standards, whereas all other safety pharmacology investigations were performed prior to introduction of current ICH S7A and 7B guidelines (1985-1996).

GCP inspections have been performed by FDA and PMDA.
It appears that all studies were conducted in adherence to the principles of International Council for Harmonisation, Good Clinical Practice (ICH, GCP), to relevant regulatory guidance and in accordance with the principles of the "Declaration of Helsinki" and subsequent amendments, as well as with the laws and regulations of the country in which the research was conducted.

The Pharmaceuticals and Medical Devices Agency (PMDA) in Japan has performed GCP audits on 2 clinical investigator sites in Japan and the conclusion was that the data from these sites were acceptable and that the studies were conducted adequately. Moreover, the GCP Inspection Report (CIS) for Radicava shared by the FDA under the confidentiality agreement, after investigating six clinical investigator sites in Japan, the sponsor and the CRO, reported acceptable data submitted and adequate conduct of the studies.

A GCP, GMP or GLP inspection is currently not required.

2.5. Type of application and other comments on the submitted dossier

Legal basis

The legal basis for this application refers to:

Article 3(1) of Regulation (EC) No 726/2004 (mandatory scope), indent (4) orphan designated medicinal product under the provisions of Article 8.3 of Directive 2001/83/EC, as amended - complete and independent application.

The Applicant's numbering of Tables and Figures was kept in the Assessment reports for purposes of tracking and tracing in the original documents. Tables A to F have been prepared by the Assessment team.

Conditional marketing authorisation

The intent to submit a conditional marketing authorization application was earlier discussed with the SAWP on 7 March 2018 in relation to protocol assistance (EMEA/H/SA/3202/1/FU/1/2018/PA/II) and no objection to such a submission was raised.

The Applicant requested consideration of its application for a Conditional Marketing Authorisation in accordance with Article 14(7) of the above mentioned Regulation, based on the following criteria:

- The Applicant considers that the benefit-risk balance of edaravone is positive.

The ALS development program for edaravone was carried out in Japan. On the basis of this development program the product was approved as RADICUT, in Japan (June 2015) and Korea (December 2015) and as RADICAVA, in the US (May 2017). In all the countries where the product has been approved, the approval is via a 'standard' marketing authorisation. Therefore the current data package is considered to have a positive benefit risk profile in more than 2 ICH regions or associated regions and full or 'standard' approval was granted.

In Study MCI186-19, edaravone demonstrated positive results with ALSFRS-R (2.49 ± 0.76, p=0.0013) and ALSAQ40 (-8.79 ± 4.03, p=0.0309) for 24 weeks compared to placebo on top of standard of care. The effect was sustained up to 48 weeks even when both groups received active edaravone after 24 week Double Blind treatment. The %FVC and Modified Norris Score (total) also showed a positive trend favouring edaravone at 48 weeks.

The safety of edaravone has been established in approximately 1.7 million patients which have been exposed to RADICUT/RADICAVA globally (stroke and ALS). As of 1 March 2018, over 5000 patients have been treated with edaravone for ALS in Japan, South Korea and US. The most common adverse reactions in ALS that have occurred in ≥10% of RADICUT/RADICAVA treated patients were contusion, gait disturbance, and headache.

- It is likely that the Applicant will be able to provide comprehensive data

According to the Applicant, in addition to long-term data that will be generated from the Japanese and planned European registries, a South Korean post-marketing registry is ongoing. Also the following studies are ongoing or in planning with a commitment to conduct including the development of an oral formulation:

Table 1.5.5.3.3-1 Ongoing and Planned Clinical Studies of Edaravone

Study no.	Study outline	Population	Treatment	Study conduct	Study report
Registry study in Japan					
NA 'Sunrise Japan'	Postmarketing registry (up to 5-year follow-up)	Japanese ALS patients (n=800)	60 mg/day IV with dosing cycles		
Registry study in South Korea					
NA	Postmarketing	South Korean ALS	60 mg/day IV with		

Study no.	Study outline	Population	Treatment	Study conduct	Study report
	registry (up to 2-year follow-up	patients (n=190)	dosing cycles		
Registry study in EU					
NA	Postmarketing registry	European ALS patients	60 mg/day IV with dosing cycles		
Other clinical studies for IV administration					
MCI-186-J22	PK in mild/moderate renal impairment	Japanese (renal impairment vs normal)	Single dose 30 mg IV		
MCI-186-J23	PK in mild/moderate hepatic impairment	Japanese (hepatic impairment vs normal)	Single dose 30 mg IV		
MCI-186-E05	PK in severe hepatic impairment[a]	Hepatic impairment vs healthy normal subjects in Europe	Single dose 30mg IV		
MCI-186-J25	QTc study[a]	Japanese healthy Subjects	Single dose placebo, 60 mg IV and 300 mg IV		
Clinical studies for oral formulation					
MT-1186-J01	Single and multiple ascending dose including food effect	Japanese healthy subjects (with Caucasian cohort)			
MT-1186-G01	Confirmatory PK bridging	Healthy subjects			
MT-1186-G02	Phase 3 48-week safety (open-label)	ALS patients (global)			
MT-1186-G03	Phase 3b 48-week 3-dose comparison (double blind)	ALS patients (global)			

a US post-marketing requirement.
Abbreviations: BID = twice daily, CO = crossover; IV = intravenous; TBD = to be determined; Q = quarter; QD = once daily

- Unmet medical needs will be addressed

Current treatment of ALS consists primarily of supportive measures (such as treatments for pain, limb stiffness, depression, anxiety, cramps, incontinence, sleeping disorders, ventilator support, dietary considerations); no curative therapies exist. Sanofi Aventis' Rilutek (riluzole) was approved centrally for ALS in the EU in 1996. Riluzole Zentiva (riluzole) is a generic product, also marketed by Sanofi Aventis, which obtained central authorisation in the EU in 2012. Both of these products are indicated to extend life or the time to mechanical ventilation for patients with ALS (see Rilutek Summary of Product Characteristics).

Several other generic versions containing the active ingredient riluzole are also authorised nationally in different EU countries. For the purposes of discussion of 'unmet medical need', reference is made to riluzole only since edaravone is not a supportive treatment for ALS.

Riluzole remains the only treatment to have shown benefit in the treatment of ALS but there is a lack of follow-on clinical studies of riluzole in ALS/MND and the true effect remains difficult to define. According to the Applicant, the pre-clinical work with edaravone suggests that it's free-radical scavenging properties also affect glutamate pathways. This occurs most probably indirectly by elimination of lipid peroxide and hydroxyl radicals, thereby ameliorating neuronal damage. The mutation of the SOD1 gene (clearly seen in the familial form of ALS), which gives rise to a misfolding of the 153 amino-acid sequence, most probably prevents effective scavenging of free super-oxide radicals and hence provides a potential explanation for a protective effect of edaravone. The contribution of SOD1 misfolding however, is less clear in cases of sporadic ALS.

According to the Applicant, edaravone therefore has the potential to act either independently, or to complement the effect of riluzole by affecting the same part of the disease process, but at a different point within the pathophysiological mechanisms involved.

- The benefits to public health of the immediate availability outweigh the risks inherent in the fact that additional data are still required

Within the EU, due to high demands from ALS patients/carers, the Italian Drug Agency (AIFA) has granted temporary authorisation/reimbursement under Italian Law 648/96, a 'nominative Autorisations Temporaires d'Utilisation' (nATU) is in place in France, and in Germany Social Insurance is providing reimbursement for edaravone on a case-by-case basis. The decisions from the National Authorities with respect to facilitating the availability of the drug to patients before granting of a licence for the product support the statement that the benefits to public health of the immediate availability of the medicinal product outweigh the risks.

The Applicant considers that the effect of edaravone is considered to be clinically meaningful. Edaravone has already been approved in Japan, South Korea and the US and over 5000 ALS patients have been exposed with an acceptable benefit/risk balance in addition to 1.7 million exposures to stroke patients in Japan. Therefore, the immediate need for edaravone is considered to outweigh the potential risk.

New active substance status

The Applicant requested the active substance edaravone contained in the above medicinal product to be considered as a new active substance, as the Applicant claims that it is not a constituent of a medicinal product previously authorised within the European Union. This view is agreed.

Orphan designation

The COMP reached a positive opinion on orphan drug designation for edaravone on 13 May 2015 and this was ratified by the Decision of the European Commission on 19 June 2015. According to the conclusion of the COMP (European Commission Implementing Decision EU/3/15/1510 - EMA/OD/032/15, Opinion dated 19/06/2015) edaravone has received orphan designation for amyotrophic lateral sclerosis (ALS). The prevalence of the "condition" <amyotrophic lateral sclerosis (ALS)> varies in different regions of the world but has been reported to be 3.85 per 100,000 in the EU (Orphanet 2018) or 5.40 (4.06-7.89) per 100,000 individuals in the EU, which is equivalent to a total of around 40,000 people (29971-58244) based on the publication of Chio *et al*., 2013.

Similarity with orphan medicinal products

The only approved medicinal product for ALS, Riluzole, is not designated as an orphan medicinal product and a similarity report between Radicava (edaravone) and Rilutek (riluzole) is not required.

Derogation(s) from orphan market exclusivity

Not applicable

Information on paediatric requirements

There have been no paediatric studies conducted with edaravone.

The PDCO, during the plenary meeting held on 15-17 July 2015, was of the view that edaravone, for the proposed indication "treatment of amyotrophic lateral sclerosis", falls under the scope of the Agency Decision CW/1/2011 for a class waiver. The proposed indication "treatment of amyotrophic lateral sclerosis" is listed in the Agency Decision CW/1/2011 for class waivers.

3. Scientific overview and discussion

3.1. Quality aspects

3.1.1. Introduction

The finished product is presented as 100 mL infusion bag containing 30 mg Edaravone as active substance.

Other ingredients are: Sodium bisulfite, cysteine hydrochloride monohydrate, sodium chloride, sodium hydroxide, phosphoric acid and water for injections.

The product is available in 30 mg/100 mL (0.3 mg/mL) clear single-dose polypropylene bag, 2 bags per carton.

3.1.2. Active Substance

General Information

Edaravone is not described in the current Ph. Eur. and/or USP but in the current Japanese Pharmacopoeia (JP 17). Full information of the drug substance edaravone is provided in the dossier.

Manufacture, process controls and characterisation

The synthetic process has been adequately described. The proposed GMP starting materials are acceptable. The discussion on possible related substances is extensive and supported by forced degradation studies. Spectral data presented confirm the chemical structure and single polymorphic form of edaravone.

Specification, analytical procedures, reference standards, batch analysis, and container closure

The drug substance specification for edaravone is acceptable and the analytical methods used are well presented and validated.

Batch analytical results of several batches including production scale batches of edaravone are well within specifications which demonstrate consistency in manufacturing. Adequate information has been provided for reference standards used for analysing drug substance.

Double low-density polyethylene (LDPE) bags sealed with plastic ties further placed into fibre drums and fitted with steel O-rings and security pegs are used for packaging of drug substance. Satisfactory specification and statement of compliance with food safety regulation EU directive 10/2011 is provided.

Stability

Results of stability studies performed on the drug substance demonstrate that Edaravone is stable under long term and accelerated storage conditions and the proposed re-test period is acceptable.

3.1.3. Finished Medicinal Product

Description of the product and Pharmaceutical Development

Radicava solution for infusion containing 30 mg/100 ml edaravone is provided as 100 ml of sterile intravenous aqueous solution for infusion.

The drug product is contained in a printed polypropylene infusion bag which is sealed inside a polyvinyl alcohol blister. The blisters, which incorporate an oxygen absorber and an oxygen indicator, are packaged in a printed carton.

Development of MCI-186 (edaravone) solution for infusion 30 mg/100 ml is based on an approved commercial product in Japan MCI-186 (edaravone) Injection 30 mg/20 ml provided in 20 ml ampoule as RADICUT Injection 30 mg.

Formulation development has been satisfactorily drawn up, selection of excipients and concentrations are considered justified, container closure configuration was demonstrated to be suitable and compatibility is deemed acceptable.

MCI-186 (edaravone) Solution for Infusion 30 mg/100 ml and MCI-186 (edaravone) Injection 30 mg/20 ml were tested for compliance with the drug product specifications and results were found to be similar.

From the risk assessment of elemental impurities according to ICH Q3D guideline it is concluded that no additional control of elements is required for the drug substance, excipients and the drug product, including container closure system.

Development of manufacturing process was illustrated in detail. The manufacturing process (method of sterilization) was drawn up from the microbiological point of view.

The steam sterilisation process (instead of compendial method ≥121°C for 15 min) has been justified. As requested by Ph. Eur 5.1.1 the chosen combination of time and temperature was supported by appropriate validation results.

Design, quality and functionality of different components of the container closure system were explained and justified by appropriate data.

Manufacture of the product and process controls

Manufacturing process:

Batch formulae are presented for the proposed batch sizes.

Manufacture of validation batches is performed.

The process validation protocol covers the intended commercial production scale. The applied maximum batch size is considered to be acceptable. According to the validation protocol the bioburden of the compounded drug product solution before filtration is limited as per recommended from GMP. Filter integrity is confirmed on pre-filter and final filter prior and after filtration as requested. Limits for filter integrity test by bubble point were defined

Validation of moist heat sterilization:

As requested by Ph. Eur 5.1.1 the chosen combination of time and temperature was supported by validation results demonstrating that the required recommendations and a sterility assurance level are adequately fulfilled.

Results of biological indicator challenge tests confirm the adequacy of the chosen moist heat sterilization conditions.

Product specification, analytical procedures, batch analysis

Specifications have been established and many batches manufactured at varying sites did confirm suitability of tests/limits except for edaravone impurities. Limits for impurities have been tightened to during the procedure.

The analytical procedures were demonstrated to be suitable and valid for use in the identification, assay and impurity determination of edaravone in MCI-186 (edaravone) Solution for Infusion 30 mg/100 ml.

The HPLC method (2) is considered to be accurate and precise for routine quality/impurity control.

Commercial scale batches of MCI-186 (edaravone) Solution for Infusion 30 mg/100 ml manufactured at a former manufacturing site and the proposed manufacturing site gave comparable results for assay and impurities as well.

Container closure

The primary packaging components in direct contact with MCI-186 drug product solution are the polypropylene (PP) bag and the isoprene rubber plug.

Specifications for primary packaging components include all relevant tests including microbiological limits and bacterial endotoxins and are considered to be adequate.

Stability of the product

Batch and stability study results of applied product MCI-186 (edaravone) 30 mg/100 ml solution for infusion obtained from different manufacturers were presented in the present application dossier.

The manufacturing process used at the previous site is considered similar to that used at the new commercial site (documentation Table 3.2.P.2.3-20 of the application dossier). As a non-standard method of manufacture is on hand, those data are considered as supportive.

Stability study results:

A notable number of stability study results have been generated over more than ten years in Japan. Batches tested and conditions, DPMs and ASMs were provided.

Stability studies with batches manufactured at the proposed commercial site cover 12 months at present and are ongoing until 36 months are covered.

On the basis of available stability study results the Applicant claimed a shelf-life MCI-186 (edaravone) 30 mg/100 ml solution for infusion with the storage condition ”store below 25°C” which is considered acceptable.

Stability commitment:

A post approval stability protocol and stability commitment was provided (documentation Table 3.2.P.2.3-20 of the application dossier). The commitment to continue ongoing stability studies with batches manufactured at the proposed manufacturing site has been provided.

Post approval change management protocol(s)

N/A

Adventitious agents

N/A

GMO

N/A

3.1.4. Discussion and conclusions on chemical, pharmaceutical and biological aspects

Edaravone, not described in the current Ph. Eur. and/or USP but in the current Japanese Pharmacopoeia (JP 17), is manufactured via a one-step synthesis process and the proposed retest period has been accepted. Edaravone is supposed to act as a radical scavenger in biological systems.

Development of the applied drug product Radicava solution for infusion containing 30 mg/100 ml edaravone, provided as 100 ml of sterile intravenous aqueous solution for infusion is based on RADICUT Injection 30 mg for which a drug product monograph “Edaravone injection 30 mg/20 ml” exists in the Japanese Pharmacopoeia (JP 17).

Formulation development has been satisfactorily drawn up, selection of excipients and concentrations are considered justified. The proposed steam sterilisation process (instead of compendial method ≥121 C for 15 minutes) has been justified by limited heat resistance of PP infusion bags (Non-standard method of manufacture). The size of three validation batches has been defined. The applied maximum batch size is considered to be acceptable.

MCI-186 (edaravone) Solution for Infusion 30 mg/100 ml and MCI-186 (edaravone) Injection 30 mg/20 ml were tested for compliance with established drug product specifications (approved in Japan years ago) and results were found to be similar.

The drug product was shown to exhibit acceptable stability if protected from oxygen degradation. A shelf-life of drug product of 36 months is claimed if stored in in the applied, complex container closure system.

The claimed shelf-life will be confirmed for the applied recent drug product manufacturer by on-going stability studies. A respective stability commitment has been provided (Commitment 2).

3.2. Non clinical aspects

3.2.1. Pharmacology

Primary pharmacodynamics

The anion of edaravone was shown to react concentration-dependently in a non-specific manner with different stable and short-lived free radicals *in vitro* (1,1-diphenyl-2-picrylhydrazyl (=DPPH), hydroxyl and peroxyl radicals), but not with the superoxide anion radical ($\bullet O_2^-$). The resulting 4,5-dione oxidation product then either hydrolyses to the major product OPB, or transiently equilibrates with a minor amount of BPOH in the presence of excess edaravone. The generated amount of OPB was reverse proportional to the consumption of edaravone. In bovine aortic endothelial cells and rat brain homogenates *in vitro*, edaravone inhibited oxidative injury and lipid peroxidation, whereas its sulphate and glucuronide conjugate metabolites did not show any radical scavenging activity at 4 to 6.5-fold higher concentrations than the parent compound.

The primary pharmacodynamic *in vivo* activity of edaravone was originally investigated in various rat models of transient focal and global ischaemia as well as hypoxia to support licensing of the indication ischaemic stroke. In these rat stroke models, i.v. administered edaravone ≥1 mg/kg dose-dependently reduced infarction volumes and cortical oedema, which correlated with the amelioration of neurological deficits, the reduction of hydroxyl and lipid peroxide radicals and the concomitant chemical conversion of edaravone to OPB. Therefore, these studies corroborate the proposed radical scavenging mechanism of edaravone *in vivo*. Effective edaravone plasma concentrations following infusions of 1.5 or 3 mg/kg over 30 min amounted to 987.9 ± 116.4 ng/ml and 3574.4 ± 3203.3 ng/ml.

In a transgenic rat model of human FALS expressing a human SOD1 transgene with histidine to arginine substitution at position 46 (H46R), 1.5 to 3 mg/kg edaravone at different daily i.v. infusion regimen mitigated loss of body weight and food consumption and delayed impairments of certain motor functions (reductions in righting reflex and inclined plane test performance) in some of the investigations, whereas deficits in other functional parameters were not consistently attenuated (hind-foot reflex, landing foot-splay and rotarod test). In addition, respiratory function, behaviour in the open field and survival of spinal nerves was not improved. In another transgenic line of SOD1 mice with glycine to alanine replacement at position 93 (G93A), i.p. injection of 15 mg/kg edaravone slowed degenerations of motor neurons. Similarly, edaravone interfered with motor degenerations in wobbler mice, an animal model for human SALS, after daily i.p. administration of 10 mg/kg for 4 weeks, but not following a lower 1 mg/kg i.p. dose.

Secondary pharmacodynamics

Edaravone and its sulphate and glucuronide metabolites were not pharmacologically active in receptor interaction assays against a panel of 79 receptors, ion channels or transporters. The lowest edaravone test concentration of 10 µM corresponds to 1740 ng/ml, which is almost 20-fold higher than the predicted unbound plasma concentration of 88.1 ng/ml edaravone at the recommended therapeutic dose of 60 mg/60 min in humans (Pop PK report 002525).

Safety pharmacology

The majority of safety pharmacology investigations were conducted before implementation of prevailing ICH S7A and S7B guidelines (1985 – 1996). Accordingly, only the hERG channel *in vitro* assay performed in 2005 complies with GLP.

Following i.v. bolus injections of up to 100 mg/kg edaravone, transient clinical signs comprised decreased spontaneous activity and body temperature, blepharoptosis, lacrimation, pituita and salivation in mice and rats. The inhibition of pain sensation in one test was not confirmed in others.

Edaravone did not affect hERG currents up to 100 µM, ECG parameters or respiratory rate in dogs at an i.v. dose of 300 mg/kg in a 30 days repeated-dose toxicity study, which corresponds to an unbound plasma concentration of ~240-280 µg/ml. Considering the unbound edaravone C_{max} in humans (0.088 µg/ml), safety margins of ~200- and >2700-fold are derived, respectively. However, transient increases of heart rate, arterial blood flow, cardiac output, glomerular filtration rate and urinary output were determined at i.v. doses of ≥30 mg/kg, which was attributed to decreased blood pressure.

Furthermore, i.v. edaravone doses of ≥30 mg/kg inhibited gastrointestinal motility and transport. The absence of an effect on acetylcholine-, histamine- or $BaCl_2$-induced contraction of isolated ileum preparations indicates that edaravone might indirectly affect gastrointestinal function.

Pharmacodynamic drug interactions

Possible pharmacodynamic interactions of edaravone have been principally investigated with drugs that are commonly used for the treatment of ischaemic stroke. Only Aspirin slightly increased the radical scavenging activity of edaravone, whereas all other compounds had not effect. Another pharmacodynamic interaction, which could be expected from the anti-oedema action of edaravone in rat stroke models, was the increased effective oedema reduction in combination with glycerol.

3.2.2. Pharmacokinetics

Absorption

Edaravone was rapidly absorbed following single i.v. bolus injection with t_{max} of 0.25 h in mice and rats and its exposure (C_{max}, AUC_{0-t}) increased dose-proportionally in rats, dogs and monkeys. Steady state was reached within 2 h and plasma levels remained constant during continuous i.v. infusion over 24 h in rats, dogs and monkeys. Upon termination of i.v. bolus injection or infusion, edaravone was quickly eliminated from plasma of all species. The elimination half-life in mice was 0.33 h after i.v. administration. In line with the biphasic elimination characteristics, $t_{1/2\beta}$ of 1.26, 5.09, 0.70, and 1.24 h were determined in male and female rats, male dogs, and male monkeys, respectively.

As expected from the short half-life of edaravone, no accumulation or exposure differences between genders were evident after repeated i.v. bolus injections, 2 h or continuous i.v. infusions of edaravone for up to 28 days in rats, dogs and monkeys.

Distribution

After repeated i.v. bolus injection of ^{14}C-labelled edaravone in rats, drug-related radioactivity quickly distributed throughout tissues. Compared to plasma, higher levels were determined in kidneys and aorta, whereas lower concentrations were detectable in liver, brain, spinal cord, fat pad, bone, testes, seminal vesicles, uterus and ovaries. Subsequently, tissue radioactivity rapidly declined along with plasma, except in the aorta. Interestingly, OPB was identified within the aorta of rats and dogs. Among different species, the tissue distribution of edaravone was generally higher in monkeys (0.76 l/kg) compared to dogs (0.46 l/kg) and rats (0.36-0.38 l/kg). Accordingly, its clearance was lower in monkeys (1.57 l/kg/h) than in dogs (3.34 l/kg/h) and rats (2.44-2.53 l/kg/h).

Edaravone showed extensive binding to serum proteins *in vitro* of 89 to 90 % in mice, 81 to 86 % in rats, 37 to 52% in dogs, 85 % to 89 % in monkeys and 91 to 92 % in humans with preference for albumin. The sulphate metabolite showed more extensive protein binding of 93 % in mice, 98 % in rats and dogs as well as 99 % in humans, whereas lower protein binding of 11 to 15 % in mice, 24 to 28 % in rats, around 20 % in dogs and 36 to 39 % in humans was determined for the glucuronide.

Edaravone crossed the blood-brain-barrier at equivalent levels to unbound compound in plasma. Maximum edaravone concentrations in plasma and cerebrospinal fluid (CSF) were detectable

immediately upon cessation of dosing and were similarly eliminated with $t_{1/2}$ of 0.25 and 0.31 h, respectively. The CSF/plasma ratio was 0.50 to 0.65 from 15 min to 3 h after the start of infusion.

Passage of edaravone across the placental barrier was also noted. Edaravone concentrations in foetal tissues increased between gestation day (GD) 14 and GD19 up to approximately 1/10 of the maternal plasma concentration. Highest foetal concentrations were determined in gastrointestinal tract, kidney, liver and brain. About 3.4 % and 1.7 % of the maternal plasma concentration accounted for the sulphate and glucuronide metabolites in the foetuses. Thus, no gross differences in the tissue distribution were observed between pregnant and non-pregnant rats.

Metabolism

Edaravone is rapidly metabolised to sulphate and glucuronide conjugates. The amount of the predominant sulphate metabolite time-dependently increased to substantially higher plasma levels than unchanged edaravone in rats and dogs, whereas the glucuronide metabolite was only elevated in dogs and reached similar levels like the parent substance in rats. Likewise, the sulphate metabolite was the only drug-related compound in plasma at 6 h post dose in monkeys. Exposure of the sulphate and glucuronide metabolites appeared to plateau in plasma and tissues about one week post initial dosing. Elimination plasma half-lives of both metabolites were generally comparable between genders. The $t_{1/2\beta}$ of the sulphate metabolite in plasma was 1.48 to 1.68 h in rats and 4.53 ± 0.67 h in dogs, while $t_{1/2\beta}$ of the glucuronide metabolite was 0.63 to 2.39 h in rats and 3.19 ± 1.75 h in dogs, respectively. The plasma $AUC_{0-\infty}$ of the sulphate and glucuronide metabolites accounted for 31 to 33 % and ~6.2 % of the administered dose in rats compared to 61 % and 16 % in dogs.

Both sulphate and glucuronide conjugates are primarily generated in the liver compared to the kidney of all species and hepatic sulfotransferase activity was clearly higher than hepatic uridine 5'-diphosphate glucuronosyltransferase (UGT) activity. Deconjugation reactions were also detected in the liver of all species. The enzymatic activities of β-glucuronidase in rats and of sulfatase in humans were comparable to the respective conjugation reactions. In the kidneys, sulfotransferase activity was substantially higher in rats and dogs compared to humans, whereas UGT and pronounced sulfatase activity were only identified in monkeys and humans. It is therefore assumed that the sulphate metabolite undergoes deconjugation in human kidneys followed by glucuronidation and urinary excretion of the glucuronide metabolite.

Edaravone and its metabolites crossed the blood-brain-barrier in low amounts in rats and monkeys as evident by dose-dependent increases in CSF. Unchanged edaravone constituted the majority of the drug-related material in brain and liver, whereas particularly the sulphate metabolite, but also the glucuronide conjugate were detected at higher levels than the parent compound in the kidneys.

Excretion

In all animal species, about 75 to 85 % of the administered ^{14}C-labelled edaravone was excreted by the renal route within 24 h and up to 92 % were recovered at 192 h post dose. Substantially lower amounts up to 13 % of the radioactive dose were determined in faeces of rats and dogs as opposed to just 3.8 % in the faeces of monkeys.

The recovered radioactivity in urine comprised predominantly the sulphate metabolite in rats, monkeys and dogs (~51 to 65 %), whereas clearly lower amounts of the glucuronide metabolite were detected in rats and dogs (6.9 to 9.6 %) than in monkeys (~40 %). In all three animal species, low levels of unchanged parent compound (1.4 to 1.8 % in rats, ~2.8 % in dogs, ~7.4 % in monkeys) were excreted via urine, while only a minor fraction was found in faeces (0.3 to 1.1 % in rats, 0.6 to 1 % in dogs). The formation and excretion rate of these metabolites remained constant after repeated administrations in rats (urinary and faecal excretion of 88.4 % and 10.4 % of the radioactive dose).

In bile duct-cannulated rats, just 4.6 % of the i.v. administered ^{14}C-labelled edaravone was recovered in bile by 72 h, representing mainly the glucuronide conjugate. In contrast, 92 % of the edaravone dose was still eliminated via urine. When bile samples of these animals were injected into the duodenum of untreated bile duct-cannulated rats, the majority of the radioactivity was again excreted via urine (52.8 %), whereas about 14.6 % of the radioactivity was recovered in bile. Therefore, the small amount of edaravone and its metabolites, which is excreted into bile, enters enterohepatic circulation and is mostly reabsorbed.

In lactating rats, about 18.5 % of the administered edaravone dose was transferred into milk showing a prolonged elimination half-life of 11.3 h compared to plasma $t_{1/2\alpha}$ of 0.4 h and $t_{1/2\beta}$ of 6.9 h. Based on $AUC_{0-\infty}$, the milk exposure was 1.3-fold higher than in plasma. The amounts of the sulphate and glucuronide metabolites increased in milk each from 36.1 to 76.7 % and 17 to 19.5 % within 2 h post dosing, while the parent substance declined to 1.6 %.

Pharmacokinetic interactions

Repeated i.v. injections of edaravone for 21 days in rats did not reveal any change in the liver content of Cytochrome P450 or Cytochrome b5 and in the hepatic enzymatic activities of NADPH cytochrome c reductase, aniline p-hydroxylase, aminopyrine N -demethylase, 7-ethoxycoumarin O-deethylase, UGT or sulfotransferase.

Edaravone was 2-times more efficiently transported by human organic anion transporter 1 (hOAT1) and 3 (hOAT3) than control substrates, while its sulphate metabolite showed even 22- and 20-times higher transport rates, respectively. The K_m for uptake of the sulphate conjugate by hOAT1 and hOAT3 was 10.8 and 15.1 µM, respectively. In contrast, the glucuronide metabolite was not transported by hOAT1 and revealed low uptake by hOAT3. Hence, edaravone and particularly its sulphate metabolite are substrates for the uptake transporters hOAT1 and hOAT3 that are expressed on basolateral membranes of renal tubular epithelial cells.

In addition, the sulphate metabolite served also as substrate for human breast cancer resistance protein (hBCRP) with 18.4-times more efficient efflux transport than a control substrate (K_m value of 16.5 µM), but was not transported by human multi-drug-resistance-associated protein 4 (hMRP4). Slight efflux transport by hMRP4 was also noted for the glucuronide conjugate.

In monkeys, the plasma exposure and urinary excretion of edaravone or its sulphate and glucuronide metabolites was not significantly altered by concomitant administration of the cephalosporin antibiotics cefotiam and cefalotin, respectively. However, edaravone increased the renal AUC_{1-4h} of cefalotin approximately 3.7-fold, which was further enhanced by water-deprivation. Thus, edaravone potentially influences the exposure of drugs that distribute to the kidneys, particularly under water-deprived conditions.

3.2.3. Toxicology

The toxicology program was primarily designed to support the earlier marketing authorisation of edaravone as treatment of acute ischaemic stroke in Japan. Pivotal studies were performed in accordance with local Japanese GLP regulations, which were effective before OECD harmonisation. In line with clinical administration route in the proposed clinical indication ALS, edaravone was administered in repeat-dose toxicity studies by either once daily i.v. bolus injection for up to 26 weeks in rats and dogs, as once daily i.v. infusion for 2 h or 28 days in dogs or as continuous i.v. infusion for 28 days in rats, dogs and monkeys. As edaravone is rapidly absorbed and eliminated, the cycling dose regimen envisaged for clinical ALS therapy was not replicated in animals. In addition, toxicokinetic exposure data were only obtained in repeated-dose toxicity investigations testing continuous i.v. infusion of edaravone for up to 28 days in rats, dogs and monkeys.

Single dose toxicity

In single dose toxicity studies, congestion and haemorrhages in lung, vacuolar hepatocyte degeneration, as well as dyspnoea/bradypnea, lacrimation, salivation, hematuria and CNS-depressive effects including sedation, staggering gait/ataxia and nictation were consistently observed across mice, rats and dogs. The mortality of mice and rats was noted within 2 to 3 h after i.v. injection, which was related to respiratory paralysis and/or acute circulatory failure and was delayed for up to 1 or 2 days following oral gavage or s.c. administrations. The LD_{50} after i.v. injection was 588 to 602 mg/kg in mice and 631 to 800 mg/kg in rats, respectively. In dogs, only the minimum lethal i.v. dose of 600 mg/kg was determined, because one of the two animals of the group died from persistent hypotension, haemolytic anaemia and renal anaemic infarct.

Repeated-dose toxicity

CNS suppression

In repeated-dose toxicity studies, i.v. bolus injections of edaravone elicited signs of CNS suppression like nictation, lacrimation, incomplete eyelid closure, salivation, sneezing, staggering gait, hindlimb weakness, languid appearance or crouching position. These effects were transiently observed immediately after edaravone doses of 30 mg/kg/day or above in rats and 100 mg/kg/day or higher in dogs, but were not evident following continuous i.v. infusion of edaravone in rats, dogs and monkeys.

Haemolytic anaemia

Edaravone produced prominent haemolytic anaemia after i.v. bolus injections or continuous i.v. infusions ≥200 mg/kg/day in rats and ≥100 mg/kg/day in dogs, while milder effects were noted after continuous i.v. infusion of 1000 mg/kg for 28 days in monkeys. The anaemia manifested as dose-dependent reduction in red blood cell parameters, increased red blood cell turnover and augmented haematopoiesis (bone marrow hypertrophy, extramedullary haematopoiesis and erythrophagocytosis in spleen, hemosiderin deposits in hepatic Kupffer cells, spleen and in proximal kidney tubules). It has been clarified that the orange-brown discolouration of the urine (hematuria) seen after i.v. administration of ≥30 mg/kg/day edaravone in rats or at dosages ≥100 mg/kg/day in dogs most likely reflects renal excretion of edaravone and its metabolites rather than urinary elimination of increased bilirubin. The anaemia was reversible upon termination of edaravone, but required more than 2 weeks for complete recovery in rats.

Mechanistic investigations did not unveil a direct haemolytic potential up to 4 mg/ml edaravone in cultures of rabbit or human red blood cells *in vitro*. An impact of the osmolality of the edaravone solution was also excluded, because signs of anaemia were only detectable in rats after i.v. injection of 300 and 500 mg/kg edaravone for 14 days, but not in controls receiving a saline solution of high osmolality. In a direct anti-globulin assay (*"Coombs test"*), edaravone concentrations up to 25 mg/ml

did not cause aggregation of red blood cells and, hence, does not adhere to the surface of red blood cells.

Neurotoxicity

Irrespective of the CNS suppression, dose-dependently impaired motor function developed in dogs from 13 days (300 mg/kg/day) or 18 days of treatment (≥60 mg/kg/day) in the course of the 14 and 28 days repeated-dose toxicity studies with continuous i.v. infusion of edaravone. The motor deficits initially started with limited limb usage, tremor, loss of motor coordination and muscle tone in the hindlimbs and then proceeded to the forelimbs one or two days later with increasing severity. The dogs progressively dehydrated, lost body weight and had to be prematurely euthanized between days 22 and 25, if they were unable to stand up. This loss of motor function in dogs was associated with axonal degeneration of peripheral nerves fibres (intercostal, tibial, radial, phrenic and sciatic nerves) and in the CNS (dorsal funiculus of the spinal cord, vestibulocochlear nerve fibres) and accounted for the majority of prematurely sacrificed dogs.

No comparable motor impairments or nerve degenerations were noted following continuous i.v. infusion of up to 1000 mg/kg/day edaravone for 28 days in rats. In monkeys, motor deficits became eminent in the third and fourth week of the 28 days repeated-dose toxicity study with continuous i.v. infusion of 1000 mg/kg/day edaravone. Similar to dogs, these clinical signs correlated histologically with minimal to severe nerve fibre degenerations with axonal swelling, cellular debris and macrophages/mononuclear cell infiltrates in the central (Medulla oblongata of the brain, vestibulocochlear nerve, dorsal and ventral funiculus of the spinal cord) and peripheral nervous system (dorsal root ganglion, ventral root, adductor muscle as well as intercostal, phrenic, radial, sciatic, sural and tibial nerves). In addition, minimal gliosis was detectable in the dorsal funiculus and grey matter of the spinal cord and in the midbrain (microglia, eosinophils).

Further mechanistic investigations in dogs revealed that the onset of the axonal nerve fibre degenerations was dependent on the continuously infused i.v. dose (day 11 after 300 mg/kg/day and day 15 after 120 mg/kg/day). Of note, nerve fibre degenerations even developed following cessation of edaravone administration in the recovery period, initiated in peripheral nerves and subsequently spread into the spinal cord tissue. At the end of a 13 week recovery period, however, nerve fibre degenerations were confined to the dorsal funiculus of the lumbar spinal cord and not detectable in peripheral nerves, which contained phagocytic cells indicating ongoing repair mechanisms. Accordingly, the patellar reflex recovered between weeks 6 and 12 of the recovery period.

In accordance with the known association of vitamin B6 deficiency with epilepsy, neuromuscular and neurodegenerative disorders, continuous i.v. infusions of 1000 mg/kg edaravone for 5 or 10 days or 300 mg/kg for 14 days were found to reduce the levels of pyridoxal 5'-phosphate (PLP), the active form of vitamin B6, in dogs. Concomitantly, the urinary excretion of xanthurenic acid, a marker for vitamin B6 deficiency, was increased. The PLP levels only partially recovered within a subsequent 2 weeks recovery period. When edaravone administration was combined with vitamin B6 in dogs, the decline of pyridoxal was attenuated. In addition, nerve fibre degenerations emerged delayed and less severe in the peripheral nervous system.

Other toxicities

In accordance with the absence of prominent kidney and liver findings in repeated-dose toxicity studies, edaravone and its sulphate conjugate metabolite only decreased viability of human renal proximal tubule epithelial cells, human renal cortex epithelial cells and human hepatocytes at high concentrations of 1000 µM *in vitro* (~30 %). The glucuronide conjugate was not cytotoxic. Likewise, single edaravone doses did not impact on proximal renal tubular epithelium or renal blood flow *in vivo.*

However, edaravone aggravated the damage of proximal renal tubular epithelia in rats when combined with the known nephrotoxic cephalosporin antibiotic cefalotin and glycerol. Degenerations and necrosis of renal proximal tubule epithelia was further deteriorated, if edaravone was administered shortly after cefalotin and glycerol, by additional water deprivation or concomitant administration of the diuretic furosemide. Gene expression profiling showed transient induction of drug-metabolising enzymes by edaravone alone, whereas the combination with cefalotin and glycerol altered the expression of numerous stress and cell injury-responsive genes. Despite post marketing reports of serious renal impairment including acute renal failure in Japan, edaravone itself does not exert a substantial nephrotoxic potential, but may possibly deteriorate the impact on renal function by other agents at high dosages, especially under water-deprived conditions.

Intravenously administered edaravone did not demonstrate a clinically relevant antigenic potential in rabbits, guinea pigs and mice. In line with the ICH S8 guideline (CHMP/167235/2004), dedicated immunotoxicity investigations have not been performed.

Genotoxicity/Carcinogenicity

Edaravone and its degradation products were not genotoxic *in vitro* and *in vivo*.

The Applicant did not conduct carcinogenicity studies with edaravone, but two investigations are referenced, which were performed in 1978 with dietary administration of edaravone for 2 years by the US National Cancer Institute in B6C3F1 mice and Fischer 344 rats without evidence for carcinogenicity. However, both investigations are afflicted by methodological deficiencies, which limit the reliability of their outcome (only two dose levels tested; selected maximum dose in rats too low).

Reproductive and developmental toxicity

In the fertility and early embryonic development study, edaravone prolonged the oestrus cycle in different rats strains (Slc:Wistar, Wistar Imamichi) and promoted body weight loss. Fertility, mating or pregnancy parameters in male and female rats were not affected under the conditions of the study.

In embryo-foetal development studies, embryo-foetal toxicity in association with maternal toxicity was noted in rats (delayed foetal development, differentiation) and rabbits (increased embryo-foetal lethality). However, edaravone was not teratogenic in both species. Toxicokinetic determinations in pregnant rats and rabbits were not performed. Hence, safety factors with regard to human exposure at the recommended clinical dose could not be determined, which should be addressed in sections 4.6 and 5.3 of the SmPC.

In peri-/postnatal development studies, edaravone increased mortality of the F1 generation of the Slc:Wistar rat strain on postnatal day 4 and their activity was increased in the neurobehavioral open field test. In Wistar Imamichi rats, increased stillbirths, a reduction in the viability index (postnatal day 4) and a delayed physical development (vaginal opening in pups) was eminent. Reproductive function of the F1 generation was not affected in both investigations.

The wording of 4.6 and 5.3 of the SmPC should be amended as indicated in the corresponding file.

Juvenile toxicity

The treatment of paediatric ALS patients is currently not considered and a Class Waiver had been granted by EMA (PIP Decision Number EMA/454118/2015). Nonetheless, the Applicant provided juvenile toxicity studies in rats and dogs, which had been conducted to support the therapy of paediatric patients with acute ischemic stroke in Japan. The age of the animals in these studies covers a paediatric age range from 2 years to more than 12 years. Target organs did not differ between juvenile and adult animals (CNS suppression and haemolytic/regenerative anaemia) and even toxicokinetic values were in the same range.

Local tolerance

The local tolerance of edaravone was investigated as part of the repeated-dose toxicity studies in rats, dogs and monkeys. In addition, local reactions in rabbits after single i.v. or s.c. or repeated i.v. injections for up to 5 days were mainly related to the administration procedure and not attributable to edaravone, which is supported by the clinical treatment in acute ischaemic stroke and ALS.

Dependence

Edaravone did not unveil any dependence potential in a withdrawal study in rats and demonstrated place aversion in mice, which contrasts the place preference induced by cocaine. Considering the estimated unbound concentration of edaravone in human plasma (88 ng/ml), rats and mice had been sufficiently exposed.

In monkeys, edaravone doses up to 4 mg/kg sporadically increased the number of self-administrations, while at the 8 mg/kg high dose, the initial increase within the first 2 weeks subsequently either declined or remained relatively constant. Although the study was afflicted by several shortcomings (i.e. small number of animals, different drug availability schedule, doses and drugs tested in consecutive order), the reinforcing potential of edaravone was rather mild and clearly different from that of the comparator pentobarbital.

Metabolites

In single i.v. dose toxicity studies in mice, the glucuronide conjugate metabolite did not evoke toxicities up to the 2000 mg/kg high dose level, whereas nominal doses of 439 and 877 mg/kg of the sulphate metabolite induced comparable clinical signs as previously reported for the parent substance (transiently decreased locomotor activity, abnormal gait, prone position, irregular respiration, tonic convulsions and lacrimation). Thus, the acute toxicity of the sulphate metabolite was clearly lower than that of edaravone (i.v. LD_{50} of 588 to 602 mg/kg).

Impurities

The systemic toxicity of the degradation product contained in the edaravone drug product was investigated after single and repeated i.v. bolus injections for 2 weeks in mice and rats, respectively. The degradation product was qualified in the same i.v. repeated dose toxicity study. Similarly, no toxicities were evident both for degradation products, after repeated i.v. administration of the 1 mg/kg/day high dose. Considering the proposed limit of NMT for both degradation products, this high dose is above the maximum amount that would be administered at the recommended clinical dose of edaravone (0.003 mg/kg/day for a 60 kg individual). In addition, neither of the degradation products showed mutagenic nor clastogenic potential in bacteria and mammalian cells *in vitro* as well as in a Micronucleus test *in vivo*. Thus, they were regarded sufficiently qualified.

However, one impurity has a well-established mutagenic and carcinogenic potential (class 1 impurity according to the ICH M7 guideline; EMA/CHMP/ICH/458894/2015). Considering the deficiencies of available carcinogenicity data (see also above) and available long-term stability data (see Quality assessment), the CHMP previously advised during protocol assistance (EMEA/H/SA/3202/1/2015/PA/III) to tighten the proposed limit for one of the impurities in the drug product, which is endorsed from a toxicological point of view and should be pursued by adequate Quality measures.

3.2.4. Ecotoxicity / environmental risk assessment

Edaravone is not expected to pose a risk to the environment when used for the proposed indication ALS, because its $PEC_{SURFACEWATER}$ value is <0.01 µg/l and the log Kow is <4.5.

3.2.5. Discussion on non-clinical aspects

Edaravone partially exists as an anion under physiological conditions and is, hence, able to donate electrons to free radical species resulting in its oxidation to OPB. This mechanism of action has been demonstrated *in vitro*. In addition, different rat models of transient focal and global ischaemia as well as hypoxia that were performed to support the original marketing authorisation of edaravone for clinical treatment of ischaemic stroke corroborate this radical scavenging mechanism *in vivo*, because the reductions of hydroxyl and lipid peroxide radicals and the chemical conversion of edaravone to OPB correlated with amelioration of sequelae from cerebral infarction.

In order to support the currently proposed clinical treatment of ALS, the Applicant conducted various studies in transgenic SOD1 models of human FALS. However, daily i.v. infusions of 1.5 to 3 mg/kg did not consistently ameliorate the deficits in motor functional parameters across different studies in SOD1 transgenic rats. In addition, respiratory function, behaviour in the open field and survival of spinal nerves was not improved. It was not clarified, which adverse effects precluded testing of higher dose levels. With regard to the variable treatment regimen, the absence of a clear dose-response or PK/PD relationship, the inconsistent results barely support clinical treatment of ALS with edaravone. Similarly, the degeneration of motor neurons were only delayed in transgenic SOD1 mice and signs of neuroprotection were limited to a high i.p. dose in wobbler mice, an animal model of human SALS. It should be also noted that SOD1 transgenic animals primarily constitute models for FALS (Philips and Rothstein, 2015; Pichet-Martel *et al*., 2016). Thus, efficacy of edaravone in the predominant SALS patient population cannot necessarily be assumed based on non-clinical pharmacodynamic results in SOD1 transgenic rodents or in wobbler mice.

Edaravone did not show relevant interaction with a panel of 79 receptors, ion channels or transporters at a 20-fold higher concentration than the predicted unbound human plasma concentration at the recommended clinical dose of 60 mg/60 min, indicating a low risk for *"off-target effects"*.

Except a GLP compliant hERG *in vitro* assay, all other safety pharmacological investigations were performed between 1985 and 1996 and do not follow current ICH S7A and S7B guidelines or GLP standards. Nonetheless, the studies revealed primarily clinical signs of CNS suppression that were also frequently observed within toxicology studies (see below). Edaravone also inhibited gastrointestinal passage at doses ≥30 mg/kg. Apart from transiently decreased blood pressure related effects, edaravone did not significantly impact on cardiovascular function. Given the long-term clinical experience since first authorisation of edaravone in 2001, further safety pharmacological studies are not deemed necessary.

The pharmacokinetic characteristics of edaravone have been thoroughly analysed in mice, rats, dogs and monkeys using single or repeated i.v. bolus injections or infusions over 0.5, 2 or 24 h of unlabelled and ^{14}C-labelled compound. Additional investigations are not warranted.

The portfolio of toxicological studies was also principally conducted for the earlier marketing authorisation of edaravone in ischaemic stroke. These investigation followed local GLP requirements before OECD harmonisation, lack toxicokinetic data when edaravone was administered by i.v. bolus injections and do not replicate the envisaged cycling dose regimen for clinical ALS therapy. However, edaravone was shown to achieve maximum plasma levels after completion of i.v. dosing for 30 min to 2 h in animals regardless of its administration as bolus injection or by continuous infusion and did not accumulate upon repeated infusions. Moreover, exposure of the edaravone metabolites tended to

plateau one week after repeated dosing. Therefore, the lack of toxicokinetic data in studies with i.v. bolus injection and the deviating treatment regimen in repeated-dose toxicity studies is regarded acceptable to support the proposed clinical treatment cycles in ALS. It seems noteworthy that the consistent induction of anaemia across various single and multiple dose toxicity studies further corroborates appropriate exposure of the animals.

Despite the use of rather young healthy animals in toxicology studies compared to the envisaged ALS patient population of mainly advanced age with potentially compromised blood-brain-barrier, specific toxicological evaluation of the radical scavenging product OPB is not deemed necessary given the short half-life, lack of accumulation and limited passage of edaravone across the blood-brain-barrier. Furthermore, edaravone has been safely used since 2001 in ischaemic stroke patients, who may also suffer from blood-brain-barrier disruption (reviewed by Kassner and Merali, 2015).

In single and repeated i.v. bolus toxicity studies, edaravone doses of 30 mg/kg/day or above produced transient CNS suppression in rats and 100 mg/kg/day or higher in dogs. In contrast, CNS suppression was not observed following continuous i.v. infusion of edaravone in rats, dogs and monkeys and is, hence, most likely associated with elevated C_{max}-levels of edaravone. The glucuronide metabolite did not induce toxicities up to the single i.v. 2000 mg/kg high dose, whereas the acute toxicity of the sulphate was clearly lower than that of the parent substance.

Regardless of the administration by either i.v. bolus injection or continuous infusions, edaravone dose-dependently induced haemolytic anaemia in rats (≥200 mg/kg/day), dogs (≥100 mg/kg/day) and monkeys (1000 mg/kg/day). A direct haemolytic effect of edaravone was excluded in red blood cultures *in vitro*. In addition, the osmolality of the edaravone solution had no effect on the development of anaemia and the adsorption of edaravone onto the surface of red blood cells seems unlikely based on a direct anti-globulin assay. The haemolytic anaemia associated with edaravone has been attributed to its oxidative potential at high concentrations. A major contribution of the sulphate and glucuronide metabolites of edaravone seems unlikely given the hydrophilicity of both conjugates. Based on the AUC of free edaravone (not bound to plasma proteins) at the NOAELs in animals with regard to the anticipated human therapeutic exposure, safety margins of around 4-fold, ~80-fold and ~30-fold are derived for rats, dogs and monkeys, respectively. Accordingly, no relevant anaemia findings have been reported during clinical edaravone therapy so far.

Following prolonged continuous i.v. infusions for more than 11 days, edaravone caused dose-dependent and progressive deterioration of motor function in repeated-dose toxicity studies in dogs, which was caused by axonal degeneration of nerves in the PNS and CNS from 11 days (300 mg/kg/day), 15 days (120 mg/kg/day) or 18 days of treatment (≥60 mg/kg/day). These nerve degenerations necessitated the majority of premature sacrifices of affected animals. Comparable axonal degenerations involving additionally the Medulla oblongata and the vestibulocochlear nerve in the brain developed from the third week of continuous i.v. infusions in the 28 days repeated-dose toxicity study in monkeys, albeit at a higher dose of 1000 mg/kg/day. No similar motor impairments or neurotoxicity was noted up to 1000 mg/kg/day edaravone for 28 days in rats.

The nerve fibre degenerations even developed after termination of edaravone infusions in the recovery period. However, degenerated axons apparently recovered in the PNS until the end of a 13 weeks treatment-free period in dogs, although they remained detectable in the lumbar spinal cord. Thus, the nerve degenerations reversed in the periphery, but did not recover in the spinal cord.

Interestingly, continuous i.v. infusions of 1000 mg/kg/day edaravone reduced the levels of PLP, the active form of vitamin B6, while the combinatorial treatment of edaravone and vitamin B6 in dogs attenuated development and severity of nerve fibre lesions in the PNS. With respect to the short half-live and lack of accumulation of edaravone, the delayed onset of peripheral and central nerve fibre degenerations even after cessation of dosing and the incomplete reversibility within a 13 weeks

treatment-free recovery period, the clinical risk assessment can apparently not solely rely on presumptive safety margins based on AUC_{24h} of edaravone. In addition, deterioration of neurodegenerative symptoms during clinical therapy of ALS will most likely escape immediate attention as it will rather be attributed to disease progression than to neurotoxicity of edaravone. It seems noteworthy, that similar axonal degenerations associated with decreases of vitamin B6 have been observed during tuberculosis therapy with the antibiotic isoniazid. Accordingly, supplementation with vitamin B6 is generally recommended during clinical isoniazid therapy and even fixed dose combinations of isoniazid and vitamin B6 have been licensed in the EU. Moreover, various vitamin B6 supplements have been approved and vitamin B6 is on the list of essential medicines of the World Health Organization. For this reason, appropriate recommendations for monitoring and supplementation of vitamin B6 in edaravone-treated patients should be provided by the Applicant, particularly when the difficulties of adequate nutrition of patients with advanced ALS are considered. In order to allow for early detection of neurotoxicity during treatment with edaravone, routine supervision of patients for sensory and motor nerve function should be also implemented. As the scientific rationale for reduction of vitamin B6 with edaravone treatment is regarded established, no further non-clinical investigations are deemed necessary. This issue will therefore be pursued clinically.Edaravone and its degradation products did not show any genotoxic potential *in vitro* or *in vivo*. Differences in treatment durations, number of evaluated metaphases and erythrocytes in the *in vitro* and *in vivo* chromosomal aberration tests were related to earlier guideline versions that were effective at the time of the study conducts. Nevertheless, all tests were negative and although parts of the testing would be slightly different under contemporary regulations, the results can be considered as valid and reveal no evidence for a genotoxic potential of edaravone. Toxicokinetic determinations of the exposure in the *in vivo* chromosomal aberration study were not performed, so a proof of systemic exposure is lacking and safety margins with respect to human exposure could not be derived. However, the systemic exposure determined after single i.p. administration of a 10-fold lower dose in mice suggests adequate exposure of the animals at multiples of the anticipated clinical exposure.

No carcinogenicity studies with edaravone were performed by the Applicant. However, two early bioassays with dietary administration of edaravone over 2 years by the US National Cancer Institute in B6C3F1 mice and Fischer 344 rats did not suspect any carcinogenic potential. As part of a post marketing obligation in the USA, the Applicant committed to conduct carcinogenicity studies in transgenic mice and rats. With respect to the average short life expectancy and limited effective treatment alternatives in ALS, it is therefore agreed that carcinogenicity studies are not required prior to marketing authorisation of edaravone, but it is expected that adequate exposure to edaravone, its main metabolites and impurity will be ensured in the planned carcinogenicity investigations and the envisaged schedule for submission of the final study reports (October 2020 for transgenic mice and February 2022 for rats) should be fixed as PAM.

In reproductive and developmental toxicity studies, edaravone prolonged female oestrus cycles in different rat strains. Edaravone was not teratogenic, but elicited embryo-foetal toxicity in association with maternal toxicity. In peri-/postnatal studies, edaravone increased the number of stillbirths, increased postnatal mortality and delayed physical development of F1 pups. It should be noted that toxicokinetic data are not available from reproductive and developmental toxicity studies. For this reason, the human risk assessment should be based on human equivalent doses. Section 5.3 should be revised accordingly.

Except local reactions that were attributable to the i.v. administration procedure, edaravone provoked no local intolerabilities.

Withdrawal, place preference and self-administration studies in rats, mice and monkeys did not indicate signs for dependence. This is corroborated by the lack of withdrawal symptoms after chronic i.v. bolus injections of edaravone for up to 26 weeks in rats and dogs or following continuous i.v.

infusion for up to 28 days in dogs and monkeys. As edaravone also did not reveal any interaction with targets involved in drug dependence *in vitro*, the human risk is considered low and acceptable for the proposed treatment of ALS.

The degradation products have been adequately qualified with respect to their potential for genotoxicity and systemic toxicity. However, the limit for the well-established mutagenic and carcinogenic impurity (class 1 impurity according to the ICH M7 guideline; EMA/CHMP/ICH/458894/2015) needs to be lowered in the drug product as previously advised during protocol assistance by the CHMP (EMEA/H/SA/3202/1/2015/PA/III;(see Quality assessment).

3.2.6. Conclusion on non-clinical aspects

All non-clinical *"Other concerns"* are considered resolved. However, the previous concern regarding the neurotoxic potential of edaravone will require further risk mitigation measures for monitoring and supervision of edaravone-treated ALS patients that will be clinically pursued.

3.3. Clinical aspects

• *Tabular overview of clinical studies*

The studies which have been considered relevant for the ALS indication are summarized in the following Table. The Applicant has also summarized additional studies that have been performed in Acute Ischaemic Stroke (AIS) and Sub Arachnoid Hemorrhage (SAH) indications (a Table listing all clinical studies is included in Module 5.2).

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects* (edaravone [ED])	Healthy Subjects or Diagnosis of Patients	Treatment Duration	Study Status; Type of Report
Healthy PK Phase I	MCI186-01	**5.3.3.1**	Assess the safety and PK of ED administered as single and multiple intravenous infusions to healthy volunteers.	PC, SB	Placebo, IV, 40 min or 3 hr/day 0.2 mg/kg, IV, 40 min/day 0.5 mg/kg, IV, 40 min/day 1.0 mg/kg, IV, 40 min/day 1.5 mg/kg, IV, 40 min/day 2.0 mg/kg, IV, 3 hr/day	35 (25)	Japanese healthy male subjects	1 day	Completed; Publication in literature Citation (Shibata H. et al. Jpn J Clin Pharmacol Ther 1998)
					Placebo, IV, 40 min/day 1.0 mg/kg, IV, 40 min/day	7 (5)		7 days	
Healthy PK Phase 3	MCI186-14 (02A0029)	**5.3.3.1**	Evaluate PK profile of ED administered by continuous intravenous drip infusion for 48 hours in healthy adult male volunteers (time-course of plasma concentrations of unchanged ED, assay of unchanged ED in urine, and metabolites in plasma and urine [sulfate conjugate and glucuronide conjugate]).	OL	120 mg, IV, 24 hr/day	8 (8)	Japanese healthy male subjects	2 days	Completed; full CSR and report
Healthy PK Phase I	MCI186-E01	**5.3.3.1**	Assess the safety and tolerability of ED administered as single intravenous infusion in ascending doses to healthy male and female Caucasians. Determine the PK profile of these treatments in healthy Caucasians. Explore the influence of gender on the PK of ED.	DB, RPC	Placebo, IV, 6 hr/day 0.6 mg/kg, IV, 6 hr/day 1.8 mg/kg, IV, 6 hr/day	24 (20)	Healthy male/ female subjects (Caucasian)	1 day	Completed; full CSR

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects* (edaravone [ED])	Healthy Subjects or Diagnosis of Patients	Treatment Duration	Study Status; Type of Report
Healthy PK Phase I	MCI186-E02	**5.3.3.1**	Assess the safety, tolerability, and local tolerance of ascending single doses of ED in male and female Caucasian subjects. Determine the PK profiles of ascending single doses of ED in male and female Caucasian subjects.	DB, RPC	Placebo, IV, 24 hr/day 0.05 mg/kg bolus + 0.125 mg/kg/hr, IV, 23 hr 57 min/day 0.1 mg/kg bolus + 0.25 mg/kg/hr, IV, 23 hr 57min/day 0.2 mg/kg bolus + 0.50 mg/kg/hr, IV, 23 hr 57min/day	46 (33)	Healthy male/ female subjects (Caucasian)	1 day	Completed; full CSR
Intrinsic factor PK study Phase 3	MCI186-10	**5.3.3.3**	PK of ED in blood and urine is examined after MCI-186 (ED) injection is repeatedly administered in healthy elderly subjects aged over 65 y and healthy adult men twice daily, 30 minutes each for 2 days (4 times in total).	SB, PC	Placebo, IV, 30 min, BID 0.5 mg/kg, IV, 30 min, BID	14 (10)	Japanese healthy male adult and elderly subjects	2 days	Completed; full CSR
ALS Phase 3	MCI186-19	**5.3.5.1**	Investigate the efficacy of ED 60 mg versus placebo administered daily in patients with ALS by comparing the changes in ALSFRS-R scores at 24 weeks of treatment. Investigate the safety of ED in patients with ALS.	DB, RPC, PG	Placebo, IV, 60 min/day 60 mg, IV, 60 min/day	137 (69)	Japanese ALS patients	Cycle 1: 14 days Cycle 2 to 6: 10 days	Completed; full CSR
				OL	60 mg, IV, 60 min/day	123 (123)		Cycle 7 to 12: 10 days	

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects* (edaravone [ED])	Healthy Subjects or Diagnosis of Patients	Treatment Duration	Study Status; Type of Report
ALS Phase 3	MCI186-16	**5.3.5.1**	Confirm the efficacy of ED at a once daily dose of 60 mg or placebo administered to patients with ALS based on comparison of changes in the degree of ALS-related dysfunction (Revised ALS Functional Rating Scale; ALSFRS-R) 24 weeks after treatment initiation. Examine the safety of ED in ALS patients.	DB, RPC, PG	Placebo, IV, 60 min/day 60 mg, IV, 60 min/day	206 (102)	Japanese ALS patients	Cycle 1: 14 days Cycle 2 to 6: 10 days	Completed; full CSR
ALS Phase 3	MCI186-17	**5.3.5.1**	Investigate the sustainability of effects of ED as well as its long-term efficacy and safety by administering ED 60 mg or matching placebo once daily in patients who have completed MCI186-16. Collect information when ED administration is resumed following placebo administration.	DB, RPC, PG	Cycle 7 to 12: Placebo, IV, 60 min/day 60 mg, IV, 60 min/day Cycle 13 to 15 60 mg, IV, 60 min/day	181 (136)	Japanese ALS patients	Cycle 7 to 15: 10 days	Completed; full CSR

Type of Study	Study Identifier	Location of Study Report	Objective(s) of the study	Study Design and Type of Control	Test Product(s); Dosage Regimen; Route of Administration	Number of Subjects* (edaravone [ED])	Healthy Subjects or Diagnosis of Patients	Treatment Duration	Study Status; Type of Report
ALS Phase 3	MCI186-18	**5.3.5.1**	Explore the efficacy of ED at a once daily dose of 60 mg or placebo administered to patients with severity grade 3 ALS based on the Japan ALS severity classification based on comparison of changes in, e.g., the degree of ALS-related dysfunction (ALSFRS-R) 24 weeks after treatment initiation. Examine the safety of ED in patients with severity grade 3 ALS.	DB, RPC, PG	Placebo, IV, 60 min/day 60 mg, IV, 60 min/day	25 (13)	Japanese ALS patients	Cycle 1: 14 days Cycle 2 to 6: 10 days	Completed; full CSR
ALS Phase 2	MCI186-12	**5.3.5.2**	Examine efficacy and safety of the free radical scavenger, ED in ALS patients.	OL	30 mg, IV, 30 min/day 60 mg, IV, 60 min/day	20 (20)	Japanese ALS patients	Cycle 1: 14 days Cycle 2 to 6: 10 days	Completed; full CSR

3.3.1. Pharmacokinetics

Introduction

The pharmacokinetics of edaravone were investigated in five clinical trials in healthy volunteers. Three of the trials (MCI186-01, MCI186-14 and MCI186-10) were conducted with male Japanese subjects; the remaining trials (MCI186-E01, MCI186-E02) were conducted in Caucasian males and females. These five studies form the basis for the development of the population PK model.

The first-in-human trial MCI186-01 was conducted before the implementation of ICH-GCP. All off the trials used different dosing regimens with different doses and infusion durations, ranging from single dose infusions given over 40 minutes to continuous infusions for 48 hours. The differences in dosing regimens and study populations between the different trials make the interpretation of the results difficult.

Table 2. Dosing Regimens and Pharmacokinetic Sampling Plans

Study Number	Design	Treatment	Dosage	Planned Number of Postdose PK Samples Per Subject
MCI-186-J01	SB, PC, HV	Single dose	40-minute iv infusion at 0.2, 0.5, 1.0, 1.5 mg/kg and 3-hour iv infusion at 2.0 mg/kg	15
		Multiple dose 7 days/ doses	40-minute iv infusion at 1.0 mg/kg daily for 7 days	39
MCI-186-J10	SB, PC, HV	Multiple dose 2 days/ 4 doses	30-minute iv infusion at 0 and 0.5 mg/kg twice daily for 2 days	14
MCI-186-J14	OL, HV	Single dose	48-hour iv infusion at 120 mg/day	22
MCI-186-E01	DB, PC, HV	Single dose	6-hour iv infusion at 0.6 and 1.8 mg/kg	19
MCI-186-E02	DB, PC, HV	Bolus + continuous infusion	0.05 mg/kg (3 minutes) + 0.125 mg/kg/h for 23.95 hours 0.1 mg/kg (3 minutes) + 0.25 mg/kg/h for 23.95 hours 0.2 mg/kg (3 minutes) + 0.5 mg/kg/h for 23.95 hours	20

Abbreviations: DB, double blind; HV, healthy volunteer; iv, intravenous; OL, open label; PC, placebo controlled; PK, pharmacokinetic; SB, single blind.

Only minimal PK data exist for the proposed dose of 60 mg/60 min edaravone for ALS patients. The QT/QTc study MCI-186-J25 in Japanese healthy volunteers is the only study with the 60 mg/60 min dose that collected PK samples. The pharmacokinetic parameters presented by the Applicant are therefore mostly based on simulation results from the population PK analysis. This analysis however has not made use of data from study MCI-186-J25. A refined model including all additional PK data could be very helpful in improving the overall model fit and in drawing conclusions from the population analyses.

Table 2.7.2.3.3-1 Simulation Results from Population Pharmacokinetic Analyses for 60 mg/60 min, Once Daily for 14 Days (Simulation for Virtual 1000 Patients per Subpopulation)

Simulated Exposure Measure		Japanese		Non-Japanese (US/EU)	
		Day 1	Day 14	Day 1	Day 14
C_{max} (ng/mL)	Mean (SD)	1048.1 (114.2)	1049.3 (114.8)	1046.6 (117.0)	1048.6 (117.6)
	Median	1040	1040	1040	1040
	Min, Max	760, 1430	754, 1430	603, 1510	602, 1520
$AUC_{(0\text{-}24h)}$ (ng*hr/mL)	Mean (SD)	1367.0 (191.2)	1373.5 (193.2)	1362.3 (194.6)	1374.3 (198.6)
	Median	1360	1360	1340	1360
	Min, Max	904, 2050	905, 2070	697, 2160	699, 2190

Source: PPK report 002525 (Module 5.3.3.5).

Methods

A gas chromatography-mass spectrometry (GC-MS) method was initially developed to measure edaravone and its metabolites in plasma and urine. A liquid chromatography-tandem mass spectrometry (LC-MS/MS) method was subsequently developed in order to simplify pre-treatment of samples and improve operational efficiency. The LC-MS/MS method also improved specificity in determining the concentration of edaravone. The GC-MS method was used for Studies MCI186-01, MCI186-10, and MCI186-E01. The LC-MS/MS method was used in Studies MCI186-14 and MCI186-E02.

Although analytical methods used within the clinical pharmacology development have been adequately validated, several points required additional data for clarification. All issues have been adequately addressed by the Applicant and no outstanding issues remain.

In order to investigate ethnic factors on PK, population-PK analyses were performed using PK data from all 5 healthy volunteer studies in Japanese and Caucasian subjects. A 3-compartment model with Michaelis-Menten plus linear elimination was selected as the best fit model to present edaravone PK. The PPK model is further discussed below.

Absorption

Edaravone is administered intravenously and therefore the bioavailability is 100%. With short infusion times the maximum plasma concentrations were reached at the end of infusion (C_{max}=C_{end}). In study MCI186-01 C_{max} increased dose proportionally in the single dose cohorts. In the highest single dose group the maximum plasma concentration reached was 3061 ng/mL. In the multiple dose cohort the plasma concentrations at end of infusion showed no tendency to increase during the 7 day study period.

In study MCI186-14 edaravone was given as a continuous infusion over 48 hours. C_{max} of 100.1 ± 9.1 ng/mL was reached at 4 hours and edaravone plasma concentrations remained at steady state within a range between 80.6 and 106.6 ng/mL for the remainder of the infusion.

The maximum plasma concentration for the proposed dosing schedule for ALS has not been determined in patients. Based on the population PK simulation the mean C_{max} for Caucasian patients is expected to be 1046.6 to 1048.6 ng/mL (min/max: 602/1520 ng/mL).

Distribution

No human mass balance study was conducted. Tissue distribution of total radioactivity was studied by measurement of excised tissue radioactivity and whole-body autoradiography after a single IV bolus injection of [^{14}C]edaravone at 2 mg/kg/day to male and female Wistar rats and after 21-day repeated bolus injection to male Wistar rats. After a single bolus injection, the radioactivity was rapidly distributed systemically, especially in the kidney and aortas, but was poorly distributed into brain, spinal cord, fat pad, bone, testes, seminal vesicles, uterus, and ovaries after 5 minutes. In both male and female rats, elimination of radioactivity was rapid except from the aorta. After repeated doses for 21 days, the accumulation of radioactivity (i.e., edaravone and/or metabolites and reactant after scavenging free radicals) was found mainly in the aorta.

In a non-clinical study in dogs edaravone concentrations were measured in plasma and cerebrospinal fluid (CSF) after a single 3-hour IV infusion. The ratios of concentrations in CSF to plasma were 0.50 to 0.65 from 15 minutes to 3 hours after the start of infusion. Edaravone is considered to transfer into CSF through the blood brain barrier.

There are no clinical data available about the ability of edaravone to penetrate the human blood-brain-barrier. Concentration of edaravone in CSF has neither been measured in healthy volunteers nor in ALS patients.

The binding rate of edaravone to human serum protein is 91% to 92%. Protein binding rates for the sulfate and glucuronide were 99% and 36% to 39%, respectively. Plasma protein binding rate of edaravone and its metabolites (sulfate and glucuronide) was determined using [^{14}C]edaravone and human serum, purified human serum albumin, and human α1-acid glycoprotein in vitro.

While a human mass balance study might be unfeasible there is also a lack of supportive data about edaravones ability to penetrate the blood-brain-barrier. For a disease affecting the CNS this information should be available. The Applicant is therefore asked to further investigate edaravones PK, and specifically its ability to penetrate into the CNS, during the further development program for the oral form. The draft protocol for the oral dose comparison study should be provided. Metabolism

The metabolism of edaravone has been investigated in an in-vitro drug metabolism study. Concentrations of edaravone and its metabolites have been measured in plasma and urine in most of the pharmacology studies. No pharmacologically active metabolites have been identified.

Cytochromes are not involved in edaravones metabolism. It is metabolized directly by UDP-glucuronosyltransferases (UGT) and sulfotransferases (SULT) without a previous Phase-1-reaction. UGTs that are involved in the glucuronide conjugation of edaravone with relatively high activity were identified to be UGT1A6, UGT1A8, UGT1A9, and UGT2B17. Due to enzyme expression levels in liver and kidney the highest contributor in the glucuronide reaction of edaravone is likely to be UGT1A9. While more detailed data about the contribution of different UGTs to edaravone's metabolism/clearance are not available the likelihood of pharmacokinetic drug-drug interactions is low for drugs that are metabolized by multiple UGT. While ethnic difference between Asians and Caucasian in the UGT1A9 gene variants were reported these differences are expected to not be clinically relevant for the same reason. This assumption is somewhat supported by the similarity of metabolic profiles in urine in Japanese and Caucasian subjects.

In the human liver sulfotransferase activity is higher than UGT activity. Therefore the predominant metabolite in plasma is the sulfate. In the human kidney however the activity of sulfatase is high and the activity of SULT is not detected. It is therefore assumed that the sulfate of edaravone is hydrolysed in the kidney and then reconjugated with glucuronic acid in the human kidney before excretion in the urine. This metabolic pathway is consistent with the distribution of metabolites and parent compound found in plasma and urine.

Excretion

The major excretion route for edaravone is urinary elimination. In the first-in-human study MCI186-01 the urinary excretion rates of glucuronic acid conjugate, sulfuric acid conjugate and the unchanged drug were found to be 68% to 84%, 5% to 14%, and 0.5% to 1% of the dose respectively. Approximately 50%, 80% and 90% of dose were excreted out of the body in 2, 8 and 24 hours after administration. This pattern of metabolites in urine was found to be consistent throughout the clinical pharmacology studies and unaffected by dose and dosing regimen, age, race and gender. The Applicant has further investigated the effects of renal insufficiency in Study MCI-186-J22. Based on the available data and the remaining issues with the population PK model restrictions to the label are warranted and edaravone should be used with caution in patients with moderate renal impairment.

Elimination

After the end of IV infusion edaravone is metabolized and eliminated rapidly. Study MCI186-01 found a biphasic elimination with half-lives of 0.15-0.17 hours ($t_{1/2}\alpha$) and 1.45 hours ($t_{1/2}\beta$) in the 0.2 mg/kg and 0.5 mg/kg dosing groups, and a triphasic elimination with half-lives of 0.17 hours ($t_{1/2}\alpha$), 0.81-0.85 hours ($t_{1/2}\beta$), and 4.50-5.16 ($t_{1/2}\gamma$) hours in the 1.0 mg/kg and 1.5 mg/kg dosing groups. In the study report it is speculated that at doses of 1.0 mg/kg and above edaravone is formed in plasma by an enzymatic cleavage of edaravone glucuronide into edaravone and glucuronic acid. This causes a delay in elimination of edaravone from plasma. While the exact reasons for the triphasic elimination are not known it is likely that the deconjugate reaction in the kidney is probably involved.

Dose proportionality and time dependency

Dose proportionality was shown in the single ascending dose part of the FIH study MCI186-01. Four doses adjusted to body weight (0.2, 0.5, 1.0 and 1.5 mg/kg) were given intravenously for 40 minutes and one dose (2.0 mg/kg) for 3 hours. For a 60 kg person this would cover a dose range from 12 to 120 mg. AUC and C_{max} increased in a dose proportional manner.

Some data conflicting with dose proportionality were found in study MCI186-E01 where a tripling of the dose led to a 5.2-fold increase of AUC and C_{max}. The study however was terminated early due to non-clinical neurotoxicity findings and only two dose levels were investigated, severely limiting the interpretability of the data.

Study MCI186-E02 generated PK data in three different dose levels. The daily amount of edaravone administered was 244, 487, and 974 mg respectively. Maximum plasma concentration after administration and C_{end} showed linear dose proportionality, and departures from linearity for C_{ave} and $AUC_{0-\infty}$ were considered to be small.

Based on the simulation from PPK analysis, the PK of edaravone is almost linear over a dose range of 30 mg/60 min to 120 mg/60 min as indicated by a 2.2 to 2.3 times greater AUC when dose is doubled. The calculated half-lives of each elimination phases (α, β, and γ) in Japanese were 0.15, 0.86, and 4.41 hours, and those in non-Japanese (US/EU) were 0.15, 0.88, and 6.34 hours, respectively.

In the multiple dosing part of study MCI186-01 in healthy subjects AUC after the last administration (day 7) was similar to that after the first administration without accumulation. The half-lives of edaravone after the end of the last infusion were similar to those observed after the end of the first infusion. These data suggest time-independent PK and are consistent with the short half-life.

Intra- and inter-individual variability and population PK model

The population PK model is considered to have several limitations. The mechanistic rationale of including a non-linear clearance with a circadian rhythm is still not adequately justified. If, as the applicant points out, the fluctuation is caused by circadian expression of metabolic enzymes, this

should also be reflected by the metabolite profiles. This has not been demonstrated by the applicant so far. Potential effects of race, weight and age on the PK of edaravone could not be finally excluded during population pharmacokinetic analysis. While the Applicant provided additional data and discussion, the now available PK data from Study MCI-186-J25 show an obvious discrepancy to predicted values in the elimination phase. An adjustment of the model including all additional available PK data is required and additional PK samples should be taken during development of the oral formulation.

Pharmacokinetics in target population

Pharmacokinetic data in patients with ALS have not been obtained. Furthermore, only limited PK data are available for the selected dosing regimen in healthy Japanese volunteers. The clinically relevant dose has therefore primarily been simulated with the population PK model, which has been developed based on healthy volunteer PK data. Similarity between the PK profiles of healthy volunteers and ALS patients is further supported by similarity in metabolic profiles of Japanese and Caucasians.

It may be possible that PK between Japanese healthy subjects and Caucasian healthy subjects, or between healthy subjects and ALS patients are slightly different when edaravone is administered orally. Factors related to absorption such as different food, culture, potentially different gastrointestinal morbidity (including gastric tube) may than need to be taken into account. The Applicant intends to collect PK data in ALS patients globally in an open-label safety study using an oral suspension formulation of edaravone (MT-1186-A01) to perform PPK analyses.

Special populations

The Applicant has conducted Study MCI-186-J22 to investigate the pharmacokinetics (PK) of edaravone after a single intravenous (IV) infusion of 30 mg/60 min in Japanese subjects with mild or moderate renal impairment compared to Japanese healthy subjects with normal renal function. As expected a clear trend of increasing exposure (Cmax, AUC) with decreases in renal capacity was found.

AUC and C_{max} in subjects with moderate renal impairment increased by approximately 25% to 30%. In addition, while the sample size in the renal impairment study was small, there was a high degree of variability. Drug exposure in subjects with moderate renal impairment cannot be considered equivalent to healthy subjects. Furthermore, the renal impairment study used the 30 mg/60 min infusion dosing regimen and not the clinically relevant one with 60 mg/60 min. Elimination is not accurately predicted by the population PK model, increase of exposure might therefore be even higher in the clinical setting. This requires further clarification and also changes to the SmPC.

The Applicant has conducted study MCI-186-J23 to assess the pharmacokinetics (PK) of edaravone after a single intravenous (IV) infusion of 30 mg/60 min in Japanese subjects with mild or moderate hepatic impairment compared to Japanese healthy subjects with normal hepatic function. The results were comparable to Study MCI-186-J22, the increases in exposure were however less prominent. None the less, exposure in moderate hepatic impairment increases significantly further clarification as well as changes to the SmPC are also warranted.

Drug-drug-interactions

The drug-drug-interaction potential for edaravone has been investigated in a number of in-vitro studies. Prior to the initial Japanese New Drug Application (NDA) for AIS, before the International Conference on Harmonisation (ICH) guideline was in place, 9 in vitro studies were completed using human biological samples. Additionally, 5 in vitro studies were recently performed according to the current Food and Drug Administration (FDA) guidance for DDI and therefore also meeting EU requirements.

Edaravone itself is not a substrate of cytochromes. No CYP-inhibition was found and although a concentration dependent induction of CYP1A2 was observed this effect can be considered to be clinically not relevant.

Inhibitory effects of edaravone and its metabolites on UGTs and common drug transporters were also investigated. At clinically relevant concentrations no inhibitory effect are expected. Furthermore there are no signs for interaction through protein binding.

Overall, based on the negative results of the in-vitro studies no clinical DDI studies were conducted.

3.3.2. Pharmacodynamics

Pharmacodynamic effects of edaravone have been investigated as exploratory endpoints only in two studies. MCI186-10 was a study in healthy and elderly healthy Japanese volunteers. Lipid peroxide and free fatty acid concentrations in blood before and after administration of edaravone were measured as surrogate parameters for reduction of oxidative stress. MCI186-12 was an exploratory study in ALS patients. Concentrations of 3-nitrotyrosine (3NT) and lipid peroxides in CSF, and lipid peroxides in blood were measured as surrogate parameters for reduction of oxidative stress.

The aetiology of amyotrophic lateral sclerosis (ALS) is unknown. Several studies suggest that oxidative stress plays a role in the progression of motor neuron degeneration. This is supported by consistent increases in oxidative stress biomarkers in blood, urine, lumbar cord, or CSF in ALS patients. However no pharmacodynamic biomarker has so far been established as a validated surrogate parameter for efficacy in treatment of ALS.

Mechanism of action

The mechanism of action of edaravone is based upon a free radical scavenging effect; thus the effect is a simple redox chemical reaction in body tissues. There is no specific target for edaravone in the CNS, all tissues should be somehow affected depending on the drug distribution.

Free radicals are traditionally regarded as harmful by-products of aerobic cellular metabolism. This view has changed and it is now evident that production of reactive oxygen species (ROS) and reactive nitrogen species (RNS) are strongly regulated processes that play central roles in most cell signalling. Low concentration of these molecules influences cell growth, differentiation or proliferation. They take part in physiological processes such as signal transduction, regulation of protein kinases or transcription factors. ROS and RNS regulate redox balance, regulate immune responses, activate macrophages and neutrophils. Under their control is cell adhesion and relaxation of smooth muscles. These molecules are very important for correct function and life of the cell.

Consideration should therefore be given to how physiological function of radicals might be affected by treatment with edaravone.

Primary pharmacology

Study MCI186-10 was a Phase I, single-blind, placebo-controlled study to evaluate the safety and PK profile in healthy male subjects and healthy elderly subjects receiving 0.5 mg/kg/30 min BID for 2 days. Additional PD endpoints of lipid peroxide and free fatty acid concentrations in blood before and after administration of edaravone were also measured to investigate the effect of edaravone as a free radical scavenger. Measurements were taken 30 minutes before the first administration and on the day after completion of administration, 12 hours after the last administration of study drug.

No statistically significant change was observed for either biomarker taken 30 minutes before the first administration versus on the day after the last administration of study drug. No statistical significant differences were observed between the edaravone group and placebo group in either healthy elderly

subjects or healthy adult men. Edaravone might not affect lipid peroxide or the free fatty acid concentration in blood in healthy volunteers or healthy elderly subjects or the study was insensitive to detect the change due to the timing of blood sampling and/or the limited number of subjects.

Study MCI186-12 was an open-label exploratory Phase 2 study with the objectives of determining the efficacy and safety of edaravone in patients with ALS. Two doses (30 mg and 60 mg once daily) were investigated over six 4-week cycles. The primary efficacy endpoint was the change from baseline in the revised ALS functional rating scale (ALSFRS-R) score at 24 weeks. As secondary efficacy endpoints, concentrations of 3-nitrotyrosine (3NT) and lipid peroxides in CSF, and lipid peroxides in blood at 24 weeks from initiation of administration of edaravone were measured.

For the 60-mg group, the decrease in 3NT levels at the end of Cycle 6 ($p = 0.007$), compared to baseline, was statistically significant. In most subjects in both the 30-mg and 60-mg groups, the 3NT levels in CSF decreased from Baseline in Cycle 1 to less than or close to the detection limit at the end of administration in Cycle 6. In the 60-mg group, there was a statistically significant decrease in mean lipid peroxide levels in blood following 1 cycle of 60 mg edaravone compared to baseline, however the mean lipid peroxide concentrations in the blood were not sensitive to 6 cycles of edaravone administration.

Give the unspecific nature of the mode of action some changes in biomarkers for oxidative stress can be expected. The exploratory data from studies MCI186-10 and MCI186-12 are rather limited and inconclusive. No clear and consistent effects were found. The primary pharmacology of edaravone is not well characterized and the data appears unsuitable to support claims of efficacy in ALS.

Secondary pharmacology

Specific secondary pharmacology studies have not been conducted with edaravone. The mechanism of action of edaravone is a radical scavenging effect leading to protection of endothelial cells and neuronal cells. In an in-vitro study, edaravone and its metabolites did not show significant affinity to any of the tested CNS receptors/channels/transporters at 10 µM. Unspecific interaction with radicals in tissues outside of the CNS is however to be expected.

Pharmacodynamic interactions

Due to the unspecific nature of the mechanism of action edaravone can be expected to act as a radical scavenger in all tissues. While there is a hypothetical potential for pharmacodynamic interaction with other compounds that might affect radicals in tissues based on the scientific literature these kind of interactions have to be considered highly unlikely.

Genetic differences in PD response

The mechanism of action of edaravone is based upon a free radical scavenging effect; thus the effect is a simple redox chemical reaction in body tissues. It cannot be excluded that the role of oxidative stress may be influenced by genetic or ethnic differences. This might have an influence on efficacy of edaravone.

Dose-response relationship

Edaravone has been originally developed as a drug for the treatment of acute ischemic stroke (AIS). The twice daily administration by infusion was feasible because the patients were expected to be hospitalized. When developing edaravone for treatment of ALS the dosing schedule was only adapted slightly to a once daily application by infusion. A 14 days off-treatment period within 4-week schedules was chosen to reduce patient burden but is not scientifically justified with PK/PD data.

The dose-response relationship of edaravone in patients with ALS has not been investigated, no dose finding study has been conducted. Neither dose nor infusion duration are adequately justified. Efficacy

data from non-clinical studies in rats are inconclusive and exposure data from these studies is unsuitable to support the dose in ALS patients. While the need to reduce patient burden is recognized, based on the mechanism of action and the short half-life of edaravone the two weeks without treatment are implausible since a treatment pause should overall decrease the efficacy of the drug.

Biomarkers for oxidative stress were investigated in studies MCI186-10 and MCI186-12. However, no biomarker has been established yet as a surrogate parameter for efficacy in ALS. Furthermore, the results were inconclusive. The pharmacodynamic data cannot support claims of efficacy of edaravone in ALS. This is concerning since the MAA is based on a single pivotal trial and Phase 2 data should provide strong supportive evidence.

The lack of a clinical dose finding study is clearly noticeable. The dosing regimen is not well justified. It remains unclear, if a higher or even a lower dose could be more beneficial to patients. This can hopefully be remedied with further investigation of the pharmacology of the oral formulation of edaravone currently in development. The Applicant should provide more data about the planned studies, including the current versions of the draft protocols.

Furthermore, the dose-response relationship when using the oral formulation will be further investigated using ALS biomarkers. The Applicant should provide additional information about this aspect of the development program.

3.3.3. Discussion on clinical pharmacology

The pharmacokinetics of edaravone have been investigated in five healthy volunteer studies in Japanese and Caucasians. Since the original clinical development was for acute ischemic stroke, different dosing regimens than for ALS have been explored in the pharmacology studies. Only limited PK data for the dosing scheme 60 mg/60 min are available from the QT/QTc study in healthy Japanese subjects. The distribution of the drug is not well described and questions remain regarding CNS penetration in humans.

Of additional concern is the population PK model which the Applicant uses to justify the transferability of efficacy data from Japanese ALS patients to Caucasians. While several of the original concerns have been addressed comparison between predicted and measured values shows obvious discrepancies, especially in the elimination phase. The model therefore requires further refining and inclusion of the newly available PK data.

Edaravone has no specific target in the CNS and acts through a simple redox reaction. Possible (long term) side-effects, both in and outside the CNS, must be considered. A comprehensive discussion is required, taking into account the increasing understanding of the many important functions of reactive oxygen species (ROS) and reactive nitrogen species (RNS) in most cell signalling.

The dosing schedule for ALS patients is not supported by a dose finding study and lacks adequate scientific justification. Overall, important information about the pharmacodynamics of edaravone is missing. The Applicant should provide more details about the planned studies with the oral formulation and how the clinical pharmacology of edaravone will be further investigated.

3.3.4. Conclusions on clinical pharmacology

Missing PK bridging data between Japanese and Caucasian subjects and the general lack of PK data in ALS patients lead to concerns about the population PK models ability to justify the transfer of data

from Japanese to Caucasian patients. Discrepancies between predicted and measured values have become obvious. Without an established dose-response relationship the dosing regimen remains scientifically not justified. Overall there is insufficient data from clinical pharmacology studies to support claims of efficacy of edaravone in ALS. The further development of the oral formulation offers a chance for further study of the PK and PD of edaravone and should be pursued.

3.3.5. Clinical efficacy

Tables with a letter e.g. A, B, C, etc. have been prepared by the assessment teams. The Applicant's numbering of Tables and Figures was kept in the Assessment reports for purposes of tracking and tracing in the original documents.

The Applicant is applying for the broad therapeutic indication for the treatment of amyotrophic lateral sclerosis (ALS) (which includes disease modifying effects). The clinical program consisted of one phase 2 study (study MCI186-12) and four phase 3 completed studies (MCI186-16, MCI186-17, MCI186-18, MCI-186-19). All studies were performed in Japan with Japanese patients. The main clinical studies submitted in support for this application for edaravone in ALS are summarized in the following Table.

Table 2.7.3 -2 Phase 2 and Phase 3 Studies in Japanese Patients with Amyotrophic Lateral Sclerosis

Phase / Study number	Description	Study type	Number of subjects in FAS (active)	Treatment regimen	Primary / main endpoint	Results
Phase 2						
MCI186-12	Exploratory study	OL	19 (19)	30 and 60 mg[b]	ALSFRS-R suppression rate (Baseline to Cycle 6)	Table 2.7.3-6 Module 2.7.3
Phase 3						
MCI186-16	Confirmatory study in ALS grade 1 and 2	DB PC	205 (101)	Placebo or 60 mg[b]	ALSFRS-R score (Baseline to Cycle 6) (For MCI186-17, Cycle 7 to Cycle 12)	Table 2.5.4-1
MCI186-17	Extension study of MCI186-16	DB PC	180 (136)			Table 2.5.4-2
MCI186-18	Exploratory study in ALS grade 3	DB PC	25 (13)			Table 2.5.4-4
MCI186-19	Pivotal replication of confirmatory study in ALS grade 1 and 2[a] [and extension study]	DB PC [OL]	137 (69) [(123)]			Table 2.5.4-5

[a] Inclusion criteria in Study MCI186-19 were further refined using ALSFRS-R, %FVC, etc. as described in the relevant section.

[b] Cycle 1: IV administration of the study drug once each day for 14 consecutive days, followed by a 2-week drug-free period. Cycle 2 and thereafter: IV administration of the study drug once a day for any 10 days within 2-week period, followed by a 2-week drug-free period.

Source: MCI-186-12, -16, -17, -18 and -19 CSRs.

All four (4) phase 3 studies were randomised, double-blind, parallel group, placebo controlled trials. Study MCI186-16 had duration of 6 months and study MCI186-17 was its double-blind extension for another 6 months. In study MCI186-18, a 12-week pre-observation period before the start of Cycle 1 was designed and this was followed by a 24 weeks double-blind period. MCI186-19 had a 12 week pre-observation period, 24 weeks double period and 24 weeks active treatment period (in total 12 months for double blind and active treatment periods). 547 patients with ALS participated in the four phase 3 studies. From these patients 363 received at least one administration of edaravone and 184 received placebo.

Dose-response studies and main clinical studies

Dose response

In Acute Ischaemic Stroke (AIS), a Japanese Phase 2b study investigated 10 mg/30 min, 30 mg/30 min, and 45 mg/30 min of edaravone IV infusion twice a day and, based upon these findings, 30 mg/30 min twice a day (60 mg as daily dose) was selected for the Phase 3 study of AIS. There was no difference in efficacy between 30 mg/30 min and 45 mg/30 min (Study MCI186-05 CSR). The 30 mg/30 min of edaravone IV infusion twice a day up to 14 days was approved after the positive results from the placebo-controlled Phase 3 study (Study MCI186-07 CSR).

A PK/PD analysis was not conducted in the ALS development program. The PPK analysis indicated almost dose-proportional relationship between dose level and AUC in a range of 30 mg/60 min to 120 mg/60 min (2.2 to 2.3 times increase in AUC when doubling the dose level to the upper range).

As a result of a Japanese Phase 2b study for AIS (Study MCI186-05) which investigated 10 mg/30 min, 30 mg/30 min, and 45 mg/30 min twice a day (BID), the 30 mg/30 min BID (60 mg as daily dose) was selected for the Phase 3 study of stroke because the efficacies of 30 mg/30 min and 45 mg/30 min did not differ. The 30 mg/30 min BID was approved after the positive results from the Phase 3 study.

It should be noted that in a QT/QTc study (MCI-186-J25), PK data of 60 mg/60 min IV administration in Japanese healthy subjects were obtained. This was the only study that investigated the actual clinical dosing regimen was the QT/QTc study MCI-186-J25 in Japanese healthy subjects. These data, however, were not included in the PPK analysis. The following Figure below is presenting the data from this study and the simulations form PPK analysis.

The Applicant is obtaining PK data of 30 mg/60 min IV administration in Japanese healthy subjects as well as in renal/hepatic impairment patients (Study MCI-186-J22, MCI-186-J23, MCI-186-J24) and plans to collect PK data in ALS patients globally in an open-label safety study using an oral suspension formulation of edaravone (MT-1186-A01) to perform PPK analyses.

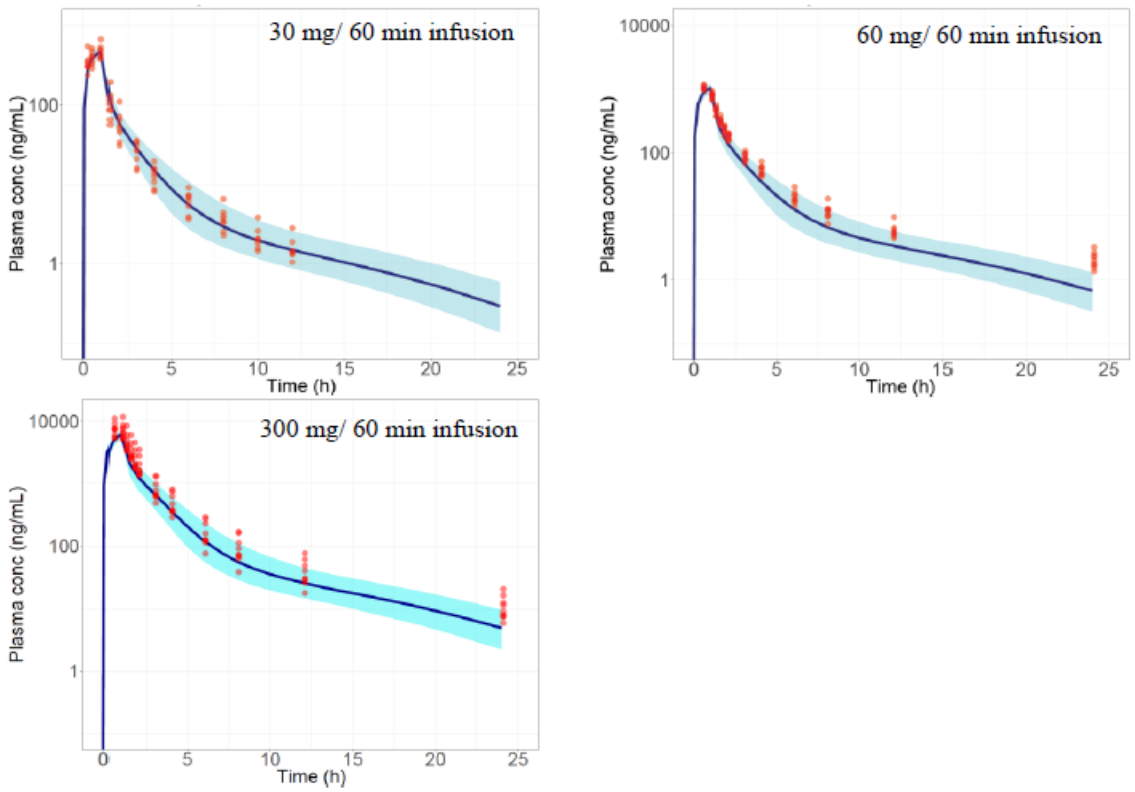


Figure 73-1: Observed and simulated plasma concentration-time profile of edaravone after 30mg/60min (healthy subjects in MCI-186-J22 study), 60mg/60min (MCI-186-J25 study) and 300mg/60min (MCI-186-J25 study) infusion. Red circle represents observed data form each study. Solid line represents median and band represents 90 percentiles based on PPK simulation (n=1000).

While there is no conclusive evidence for a PK/PD dose-response based on ALSFRS-R as primary endpoint, 3NT data from Study MCI186-12 indicated that 30 mg could reduce oxidative stress and 60 mg would be sufficient to inhibit oxidative stress. Therefore, PK/PD relationship may be flat rather than steep over 60 mg/day of edaravone.

Since the safety profile was based upon AIS dosing that confirmed the safety of up to 60 mg/day for 14 days, all dosing in ALS is based upon 14-day administration followed by 2-week drug-free period. A dosing cycle with 2-week on/off was set also in consideration of patients' burden on everyday IV infusion. Finally, a 60 mg/60 min dosing regimen with treatment cycles demonstrated the efficacy and safety of edaravone through Phase 3 programs.

The dosage regimen utilised in all ALS phase 3 studies in Japan with treatment cycles was as follows:

- Cycle 1: 30 mg/30 min (Study MCI186-12 only) or 60 mg/60 min (all Phase 3 studies) IV administration of edaravone once each day for 14 consecutive days, followed by a 2-week drug-free period
- Cycle 2 and thereafter: 30 mg/30 min (Study MCI186-12 only) or 60 mg/60 min (all Phase 3 studies) IV administration of edaravone once a day for any 10 days within 2-week period, followed by a 2-week drug-free period.

There is no dedicated dose response clinical study. The Applicant has utilised information from the AIS studies and a population PK analysis to justify the dosage regimen. Apart from that, studies were conducted only in Japanese patients (see section 2.1.8).

The population PK model is considered complex and has some limitations, making both the transferability of data from Japanese to Caucasian patients and the extrapolation of the dosage related data from AIS and SAH studies to ALS unreliable/questionable. The Applicant should include all additionally available data and reconduct a covariate analysis with the enlarged dataset in order to evaluate whether a dose-adjustment is needed with respect to the patient's body weight .

RADICAVA solution for infusion is intended to be supplied as a 30 mg/100 mL (0.3 mg/mL) single-dose bag with 2 bags per carton and the recommended dosage is an intravenous infusion of 60 mg administered over a 60-minute period. It is noted that the Applicant has submitted the regulatory application of 60mg/100mL BAG to US FDA. In case of approval, a written commitment needs to be submitted.

Main studies

Studies MCI186-12, MCI186-16, MCI186-17, MCI186-18 and MCI186-19

Methods

Study MCI186-12 (Phase 2 study)

Study MCI186-12 was an open label phase 2 study in a total of 20 patients in any grade of ALS severity. This study served as proof of concept and assessed a 30mg and a 60mg edaravone dose, using difference in ALSFRS-R score between baseline and end of observation period (24 weeks).

Study MCI186-16 - Initial Phase 3 Confirmatory Study

Study MCI186-16 was a double-blind, parallel-group, placebo-controlled Phase 3 trial to evaluate the efficacy and safety of 60 mg/day edaravone with a duration of 24 weeks (6 cycles).

Study MCI186-17 - Extension of Study MCI186-16

Study MCI186-17 was a double-blind, parallel-group, placebo-controlled, Phase 3 study to investigate the sustainability of effects of edaravone as well as its long-term efficacy and safety in ALS subjects who completed Study MCI186-16 (n=181).

The diagnostic criteria for ALS in studies MCI186-16 and MCI186-17 were the revised El Escorial research diagnostic criteria for ALS (Airlie House 98), as mentioned in the European ALS Guideline (EMA/531686/2015, Corr.1) or as the Applicant mentions them, "El Escorial revised Airlie House diagnostic criteria". Patients fulfilled the EL Escorial revised Airlie House criteria for definite, probable or probable-laboratory supported ALS, were grade 1 or 2 based on the Japan ALS severity classification and had normal respiratory function %FVC ≥70%.

Study MCI186-18 - Exploratory Study (ALS Severity Grade 3)

Study MCI186-18 was a randomised, placebo-controlled, exploratory study of 25 subjects with more advanced ALS (Japan ALS severity grade 3) administered study drug for 6 cycles (24 weeks) performed as part of a request by Pharmaceutical and Medical Devices Agency (PMDA). MTPC and PMDA agreed to evaluate efficacy of edaravone using ALSFRS-R primarily in subjects with Japan ALS severity grade 1 or 2 and, thus, this study in patients with ALS severity grade 3 was not powered to detect a statistical difference between placebo and edaravone.

Study MCI186-19 - Pivotal Phase 3 Study

Study MCI186-19 was a placebo-controlled, double-blind, parallel-group study to investigate the efficacy and safety of edaravone 60 mg/day versus placebo in patients that had shown efficacy in a retrospectively defined subgroup of study MCI-186-16 as no statistical significance was shown in the broad population (Full Analysis Set, FAS).

Study MCI186-19 is considered the main pivotal study in this application.

Study Participants

Study MCI186-12 enrolled ALS patients regardless of ALS severity; however, all Phase 3 studies screened patients for enrolment based upon the severity classification of the "Specified Disease Treatment Research Program for ALS of the Ministry of Health, Labor and Welfare (MHLW) of Japan" Severity Scale. ALS function is rated on a scale from 1 to 5 as follows:

The Japan ALS severity classification

Severity Classification: 1	Able to work or perform housework
2	Independent living but unable to work
3	Requiring assistance for eating, excretion or ambulation
4	Presence of respiratory insufficiency, difficulty in coughing out sputum or dysphagia
5	Using a tracheostomy tube, tube feeding or tracheostomy positive pressure ventilation.

Studies MCI186-16 and -17 enrolled grade 1 and 2 ALS patients, while Study MCI186-18 enrolled only grade 3 to explore efficacy and safety of edaravone in more advanced ALS. Exploratory analyses in Study MCI186-16, found a beneficial effect of edaravone in subjects who had functionality retained in most ADL domains with normal respiratory function. This population is referred to as Efficacy Expected Subpopulation (EESP). Within the EESP, the population likely to have significant disease progression during 6-cycle study period is referred to "Definite or Probable/EESP/2y". Based upon the findings in Study MCI186-16, Study MCI186-19 was prospectively designed to enroll the Definite or Probable/EESP/2y ALS population.

The population and the efficacy endpoints evaluated in the clinical development program of edaravone for ALS are presented concisely in the following Table:

Table 2.7.3-3: Comparison of the Populations Evaluated for Efficacy (Inclusion Criteria)

	MCI186-12 (FAS)	MCI186-16 (FAS)	MCI186-16 (EESP)[a]	MCI186-16 (Definite or Probable/EESP/2y)[b]	MCI186-17	MCI186-18 (FAS)	MCI186-19 (FAS)
El Escorial and revised Airlie House diagnostic criteria	Not prespecified	Definite Probable Probable-laboratory-supported	Definite Probable Probable-laboratory-supported	Definite Probable	Patients who completed Study MCI186-16 (FAS, EESP, Definite or Probable /EESP/2y)	Definite Probable Probable-laboratory-supported	Definite Probable
ALS severity classification	Not prespecified	Grade 1 Grade 2				Grade 3	Grade 1 Grade 2
ALSFRS-R score at Baseline	Not prespecified	Not prespecified	≥2 points on each individual items			Not prespecified	≥2 points on each individual items
Change in ALSFRS-R score during 12-week pre-observation period	Not prespecified	Changed by -1 to -4 points				Changed by -1 to -4 points	Changed by -1 to -4 points
Respiratory function (%FVC)	Not prespecified	%FVC ≥70%	%FVC ≥80%			%FVC ≥60%	%FVC ≥80%
Respiratory function (other criteria)	Without impaired respiratory function (complaining respiratory discomfort)[c]	4 points on items of Dyspnea, Orthopnea, and Respiratory insufficiency in ALSFRS-R score				4 points on items of Dyspnea, Orthopnea, and Respiratory insufficiency in ALSFRS-R score	4 points on items of Dyspnea, Orthopnea, and Respiratory insufficiency in ALSFRS-R score
Onset of ALS	Not prespecified	Within 3 years		Within 2 years		Within 3 years	Within 2 years

a EESP: patients with "2 points or better, on each of the individual items of the ALSFRS-R" and "%FVC greater than or equal to 80%" in the FAS. EESP was set in an additional exploratory analysis of Study MCI186-16, and was specified before the code break of Study MCI186-17.
b Definite or Probable/EESP/2y: patients with "definite or probable diagnostic criteria for ALS" and "within 2 years after the onset of ALS" in the EESP.
c Patients who underwent a tracheotomy or were using a ventilator were excluded.
Source: MCI186-12, -16, -17, -18, and -19 CSRs.

Study MCI186-12 (Phase 2 study)

A total of 20 subjects were enrolled, and the efficacy analyses were performed in the FAS, for a total of 19 subjects which included 5 treated subjects in the 30-mg/day group and 14 treated subjects in the 60-mg/day group. One subject in the 60-mg/day group was excluded from the FAS because administration of edaravone was discontinued during the study because the subject was revealed not to have ALS.

Study MCI186-16 - Initial Phase 3 Confirmatory Study

The main analyses were performed in the FAS, which consisted of 101 subjects in the edaravone (E) group and 104 subjects in the placebo (P) group, for a total of 205 subjects. Nine subjects in E group and 14 subjects in P group were discontinued before the end of Cycle 6.

The following subpopulations were defined:

Efficacy Expected Subpopulation (EESP) Definition: Subjects who met the following criteria:

- Each individual item of the ALSFRS-R of 2 or better at Baseline (i.e., Functionality retained in most ADL domains)
- A percent forced vital capacity (%FVC) of 80% or greater at Baseline (i.e., Normal respiratory function).

In addition, stable subjects unlikely to have significant disease progression during the study period (24 weeks) were excluded in order to evaluate the efficacy of edaravone. In addition to the EESP criteria, subjects meeting the additional following 2 criteria were defined as “Definite or Probable/EESP/2y”.

Definite or Probable/EESP/2y Definition: In addition to meeting EESP criteria,

- Definite or Probable ALS diagnosis based on the El Escorial and revised Airlie House diagnostic criteria at preregistration (to ensure diagnosis of ALS)
- Within 2 years of initial ALS symptom onset at preregistration (to exclude subjects who were stable for long-term with ALS).

Study MCI186-17 - Extension of Study MCI186-16

Study MCI186-17 was a combined extension and randomised placebo-controlled study for 6 cycles with subjects continuing from Study MCI186-16. A total of 181 subjects were enrolled in the study. Patients who completed Cycle 6 (24 weeks) of Study MCI186-16 continued to receive treatment on the same schedule during Cycles 7 to 15 in a 1:1:2 ratio to 3 treatment groups. The main analyses were performed in the FAS, consisting of a total of 180 subjects: a) Study MCI186-16 edaravone – Study MCI186-17 placebo (EP group), (n=44), b) study MCI186-16 edaravone – Study MCI186-17 edaravone (EE group) (n=48) and c) Study MCI186-16 placebo – Study MCI186-17 edaravone (PE group) (n=88). Of these, 7 subjects in EP group, 14 subjects in EE group and 16 subjects in PE group were discontinued before the end of Cycle 12.

Study MCI186-18 - Exploratory Study (ALS Severity Grade 3)

Study MCI186-18 was designed as an exploratory study. It was a randomised, double-blind, placebo-controlled, exploratory study for 6 cycles. MTPC and PMDA agreed to evaluate efficacy of edaravone using ALSFRS-R primarily in subjects with Japan ALS severity grade 1 or 2 and, thus, this study MCI186-18 in patients with ALS severity grade 3 was not powered to detect a statistical difference between placebo and edaravone.

A total of 25 subjects were enrolled and included in the FAS including 12 subjects in P group and 13 subjects in E group. Among them, none in P group and 4 in E group discontinued before the end of Cycle 6.

Study MCI186-19 - Pivotal Phase 3 Study

A total of 68 subjects were randomised to receive placebo (P) and 69 subjects were randomised to receive edaravone (E), in a total of 137 subjects, participating in this study. Of those, 8 subjects in the P group were discontinued and 2 subjects in E group were discontinued before the end of Cycle 6 (see below in the Summary of studies).

Treatments

The dosage regimen evaluated in the all Phase 2 and Phase 3 studies in Japan defined the following treatment cycles:

- Cycle 1: IV administration of the study drug once each day for 14 consecutive days, followed by a 2-week drug-free period
- Cycle 2 and thereafter: IV administration of the study drug once a day for any 10 days within a 2-week period, followed by a 2-week drug-free period.

Table 2.7.3-4: Study Period and Cycles of Administration (by Study)

Study number	Group		Cycles of administration[a]			
			Pre-observation period (12 weeks)	6 cycles (24 weeks)	6 cycles (24 weeks)	3 cycles (12 weeks)
MCI186-12 (Phase II)	30 mg		Not set	30 mg		
	60 mg			60 mg		
MCI186-16 (Initial Phase III) / MCI186-17 (Extension)	*MCI186-16*	*MCI186-17*	*MCI186-16*		*MCI186-17*	
	E group	EE group	No study drug	60 mg	60 mg	60 mg
		EP group			Placebo	
	P group	PE group		Placebo	60 mg	
MCI186-18 (Exploratory in ALS severity grade 3)	E group		No study drug	60 mg		
	P group			Placebo		
MCI186-19 (Phase III replication as pivotal)	*Double-blind period*	*Active extension*	No study drug	*Double-blind period*	*Active extension*	
	E group	E-E group		60 mg	60 mg	
	P group	P-E group		Placebo		

a Cycle 1: administration of the study drug once each day for 14 consecutive days, followed by a drug-free period of 2 weeks. Cycle 2 and after: administration of the study drug once a day for any 10 days within 2 weeks, followed by a drug-free period of 2 weeks.
Source: Study MCI186-12, -16, -17, -18, and -19 CSRs.

It is noted that in study MCI186-17 extension of study MCI186-16, patients were re-randomised in 3 groups edaravone-placebo (EP), placebo-edaravone (PE) and edaravone-edaravone (EE).

Objectives

The objectives in the Phase 2 and 3 clinical trials were the following:

Study	Objective
Exploratory phase 2 study MCI186-12	To examine efficacy and safety of the free radical scavenger MCI-186 (edaravone) in ALS patients
confirmatory trials	to confirm the efficacy of edaravone at a once daily dose of 60 mg or placebo administered to patients with amyotrophic lateral sclerosis (ALS).

MCI186-16 and MCI186-19	Change in ALSFRS-R was selected as the primary endpoint in all ALS studies except for Study MCI186-18, in which the endpoint was exploratory.
extension study MCI186-17	to investigate the sustainability of effects of edaravone as well as its long-term efficacy and safety by administering edaravone 60 mg or matching placebo once daily.
MCI186-18	to explore the efficacy of edaravone at a once daily dose of 60 mg or placebo administered to patients with severity grade 3 ALS based on the Japan ALS severity classification.

Outcomes/endpoints

The efficacy endpoints of each study are shown in Table 2.7.3-5. Rationales are provided below for the primary and secondary endpoints that are summarised in module 2.7.3 Summary of Clinical Efficacy and below (ALSFRS-R score, time to death or certain signs of disease progression, %FVC, ALSAQ40 score, Modified Norris Scale, Grip/pinch grip strength, and 3NT in CSF).

Revised Amyotrophic Lateral Sclerosis Functional Rating Score (ALSFRS-R)

The differences between treatment group and placebo in the changes of ALSFRS-R score from Baseline to end of treatment cycles (either cycle 6 with duration 24 weeks or cycle 12 with duration of 48 weeks) will be mentioned as change in ALSFRS-R score to avoid repetition.

Change in ALSFRS-R was selected as the primary endpoint in all ALS studies except for Study MCI186-18, in which the endpoint was exploratory. The ALSFRS-R was created and validated in the US to measure the degree of daily functional loss in patients with ALS. It is well accepted in the ALS expert community and has been used frequently in clinical trials and also clinical practice. The ALSFRS-R strongly correlates with both objective measures of disease status and level of disability. The Japanese version of the ALSFRS-R has also been validated and is feasible for clinical evaluation in ALS studies. In addition to the translation, which retained the overall structure, the Japanese version was revised to better reflect the Japanese lifestyle. For example, in the “no gastrostomy” section of the “Cutting Food and Handling Utensils” entry, the Japanese version evaluated the use of utensils such as chopsticks and fork.

Each category in the ALSFRS-R is clinically important, and because each domain includes only 5 levels that span from 0 (cannot do) to 4 (normal), prevention of even 1 unit of worsening in a single domain seems meaningful and desirable for individuals with ALS and indicates a relevance of ALSFRS-R benefit to patient QoL and survival.

Time to Death or Certain Signs of Disease Progression

Time to death or time to certain aspects of terminal disease progress (e.g., ventilator dependence or tracheostomy) can be important and were relevant to the published clinical studies of riluzole in ALS. Death, disability of independent ambulation, loss of upper limb function, tracheotomy, use of respirator (except bilevel positive airway pressure), use of tube feeding, and loss of useful speech (which was applied in Study MCI186-19 only) were analysed as discrete events. These events were assessed according to the protocols from Baseline to the End of Cycle 6 or 12 (or 2 weeks after the last dose when subjects discontinued the study). Except in the cases of death and tracheotomy, subjects with these events continued the study.

Percent Forced Vital Capacity

Respiratory function is one of the most important individual items of measurement in ALS. The evaluation methods for respiratory function in ALS noted in the ALS treatment guidelines (2002), suggest decline of %FVC to 50% or less as a criterion to introduce respiratory support. Respiratory function was also reported as a predictive parameter in ALS of a very rapid decline in functionality and survival.

Amyotrophic Lateral Sclerosis Assessment Questionnaire-40 Items Score

The ALSAQ40 score is a measure of QoL for patients with ALS and was an efficacy endpoint in the four Phase 3 clinical studies of edaravone. The ALSAQ40 evaluates domains that include physical mobility, ADL and independence, eating and drinking, communication, and emotional reactions. The validity of the Japanese version of the ALSAQ40 has been confirmed.

Modified Norris Scale

The Modified Norris Scale is a measure of movement disorder for patients with ALS. The Modified Norris Scale has been set as an efficacy endpoint in the four Phase 3 clinical studies to evaluate movement disorder associated with ALS. The validity of the Japanese version of the Modified Norris Scale has been confirmed.

Grip Strength and Pinch Grip Strength

Grip strength and pinch grip strength were set as an objective measurement to assess muscle weakness as muscle strength decreases in ALS patients as a result of motor neuron dysfunction.

Nitrotyrosine in CSF

To investigate the mechanism of action of edaravone as a radical scavenger, 3NT in CSF as a biomarker for protein oxidisation was used as a secondary endpoint in Study MCI186-12.

Table 2.7.3-5: Efficacy Endpoints

Efficacy endpoint	MCI186-12	MCI186-16	MCI186-17	MCI186-18[a]	MCI186-19
ALSFRS-R score	++	++	++	+	++
Time to death or certain signs of disease progression[b]	–	+	+	+	+
%FVC	+	+	+	+	+
ALSAQ40 score	–	+	+	+	+
Modified Norris Scale	–	+	+	+	+
CSF, 3-NT	+	–	–	–	–
ALSFRS-R score for each domain	–	+	+	+	+
Grip strength	–	+	+	+	+
Pinch grip strength	–	+	+	+	+
ALS severity classification	–	+	+	+	+
Blood gas	+	–	–	+	–
Manual muscle test	+	–	–	–	–
CSF, protein	+	–	–	–	–
CSF, changes in lipid peroxide	+	–	–	–	–

++: primary endpoint set in the protocol, +: endpoint or assessment for efficacy other than primary endpoint, -: Not applicable.
[a] No primary endpoint was defined in this study.

[b] Death, disability of independent ambulation, loss of upper limb function, tracheotomy, use of respirator, use of tube feeding, and loss of useful speech (the loss of useful speech was applied in Study MCI186-19 only). Source: MCI186-12, -16, -17, -18, and -19 CSRs.

The primary efficacy endpoint in the phase 3 studies was the change from baseline in the ASLFRS-R scale which is a validated measure of function in ALS and recommended in the EU ALS Guideline. Secondary endpoints included Time to Death or Certain Signs of Disease Progression (which were analysed as discrete events), %FVC, ALSAQ40 score, Modified Norris Scale, Grip strength, Pinch grip strength, ASLFRS-R score for each domain, Japan ALS severity classification. In the phase 2 studies certain biomarkers were also included (see table 2.7.3-5).

Study MCI186-12 (Phase 2 study)

This was a Phase 2, open-label, exploratory study for 6 cycles in patients in any grade of ALS severity.

The primary efficacy endpoint was the change from Baseline to 24 weeks in ALSFRS-R. Secondary efficacy endpoints were changes in %FVC, other respiratory function testing, manual muscle testing, arterial blood gas, CSF proteins (total protein, albumin, and immunoglobulin G), 3NT, lipid peroxides in CSF, and blood at 24 weeks from the initiation of administration of edaravone. The results of the primary endpoint and changes in CSF 3NT are presented here and the remaining endpoints are summarised in the Study MCI186-12 Clinical Study Report (CSR) in Module 5.3.5.2.

Study MCI186-16 - Initial Phase 3 Confirmatory Study

Study MCI186-16 initiated the Phase 3 program and was designed as a confirmatory placebo-controlled Phase 3 study for 6 cycles using change in ALSFRS-R as primary endpoint.

Secondary endpoints were time to death or certain disease progression, domain-specific ALSFRS-R score, %FVC, Modified Norris Scale score, ALSAQ40 score, grip strength, and pinch grip strength.

Study MCI186-17 - Extension of Study MCI186-16

In study MCI186-17 the endpoints of study MCI186-16 were used, since MCI186-17 was a combined extension and randomised placebo-controlled study for 6 cycles with subjects continuing from Study MCI186-16.

Study MCI186-18 - Exploratory Study (ALS Severity Grade 3)

No primary efficacy endpoint was defined because various exploratory analyses were planned in the small sample size. The efficacy endpoints were ALSFRS-R score, time to death or certain disease progression (death, disability of independent ambulation, loss of upper arm function, tracheotomy, use of respirator, and use of tube feeding), domain-specific ALSFRS-R scores, %FVC, Modified Norris Scale score, ALSAQ40 score, grip strength, pinch grip strength, Japan ALS severity classification, and blood gas.

Study MCI186-19 - Pivotal Phase 3 Replication Study

Study MCI186-19 was a Phase 3, randomised, placebo-controlled study, prospectively designed as a pivotal trial of the Definite or Probable/EESP/2y population defined in the exploratory analysis of Study MCI186-16 and the same endpoints were used.

Randomisation and blinding (masking)

All phase 3 studies were randomised and double-blind trials.

Statistical methods

Study MCI186-16

- Full Analysis Set (FAS): All patients randomised excluding patients
    - with diseases other than the target disease
    - with significant GCP violations
    - who are not treated with the investigational product
    - with no efficacy data available
- Per Protocol Set (PPS) patients from the FAS excluding patients
    - who deviate from any of the inclusion criteria
    - who correspond to any of the exclusion criteria
    - who use any prohibited concomitant drug or start riluzole newly
    - who received 70% or lower of the protocol-specified total dose of the investigational product
- Safety analysis set All study patients excluding patients
    - with significant GCP violations
    - who are not treated with the investigational product
    - with no efficacy data available

Study MCI186-19

- Full Analysis Set (FAS): The FAS comprised all patients except patients
    - without ALS
    - not administered an investigational product
    - with no efficacy data after administration of the investigational product
- Per Protocol Set (PPS): All FAS patients except patients
    - who deviated from the inclusion criteria
    - who met an exclusion criterion
    - with violations of the provision on prohibited concomitant drugs
    - for whom the frequency of investigational product treatment was ≤70% of that specified in the protocol
- Safety analysis set: All patients except patients
    - not administered the investigational product
    - with no safety data after administration of the investigational product

Primary analysis

For efficacy analyses, the FAS was used for primary analysis.

In all studies the primary analysis was based on ANCOVA or ANOVA models. The change from "baseline in Cycle 1" to "the end of Cycle 6 (or discontinuation)" was compared between the groups using factors used in dynamic allocation as covariates.

For MCI186-16 FAS, the ANOVA model included treatment group, change in ALSFRS-R score during the pre-study observation period, concomitant riluzole and initial symptom as fixed effects. For MCI186-18 FAS, the ANOVA model included treatment group, change in ALSFRS-R score during the pre-study observation period as fixed effects. For MCI186-19 FAS, the ANCOVA model included treatment group, change in ALSFRS-R score during the pre-study observation period, El Escorial revised Airlie House diagnostic criteria and Age as fixed effects.

Missing data

In the analysis, for patients with missing values at "the end of Cycle 6," data imputation was conducted using the last observation carried forward (LOCF) method. In double-blind periods of Studies MCI186-16, -18, and -19, for subjects whose data at “the end of Cycle 6” were missing, missing data were imputed by the last observation carried forward (LOCF), however, data in subjects discontinued before Cycle 3 were excluded from the statistical analyses according to the prespecified statistical analysis plan (SAP). In Study MCI186-17, for subjects whose data at “the end of Cycle 12” were missing, missing data were imputed by LOCF, however, data in subjects discontinued before Cycle 9 were excluded from the statistical analyses according to the pre-specified SAP. Therefore, 2 types of sensitivity analyses with LOCF including all randomised subject (ALL LOCF), and mixed model for repeated measures analysis (MMRM) including all available data were conducted for the FAS population to examine robustness for the prespecified method for missing data, using a model with treatment group, time, and treatment group-by-time interaction, factors used for the dynamic allocation as fixed effects, and baseline value as the covariates. An unstructured covariance matrix was used to model the covariance of within-patient scores. The Kenward-Roger approximation was used to estimate the denominator degrees of freedom.

Dynamic allocation

In Studies MCI186-16, -18, and -19, in order to achieve balanced allocation, a minimisation method with dynamic allocation was applied using important prognostic factors. The factors used for the dynamic allocation were used in the primary analysis of analysis of variance (ANOVA) for ALSFRS-R as well as secondary endpoints including %FVC, ALSAQ40, Modified Norris Scale, grip strength, and pinch grip strength (SAPs for Studies MCI186-16, MCI186-18, and MCI186-19). In Study MCI186-17, the factors used for the dynamic allocation in Study MCI186-16 were used in the primary analysis of ANOVA for ALSFRS-R and secondary endpoints (SAP for Study MCI186-17).

In Study MCI186-19, the pivotal study, a permutation test was performed to check an effect of statistical inference of the primary analysis for changes in ALSFRS-R score by using dynamic allocation.

Other analyses

Secondary endpoints %FVC, modified Norris Scale scores, ALSAQ40, grip strength and pinch grip strength were analysed with the same approach as used for ALSFRS-R score.

In survival analyses for time to event (death or certain disease progression), if multiple events occurred in one subject, the date of the first events was counted as the date of event. Log-rank test and generalised Wilcoxon tests were prespecified and performed for the 6-cycle double-blind period. In the active extension phase in Study MCI186-19 that included a full 12 cycles of treatment, these events were collected according to the prespecified protocol and an additional statistical analysis for the time to event was also performed for 12 cycles (12 months).

The primary efficacy endpoint in Study MCI186-17 was the ALSFRS-R score. For subjects whose data at “the end of Cycle 12” were missing, data were imputed by the LOCF, however, data in subjects discontinued before Cycle 9 were excluded from the statistical analyses.

For a slope analysis ALSFRS-R score in each time point, a mixed effect model implemented as random coefficient model, using the intercept and slope of each treatment group as fixed effects and the intercept and slope of each patient as random effects was performed. The intercepts and slopes were assumed to be normally distributed with an unstructured covariance matrix. The within-patient error was assumed to be independent and normally distributed with mean zero and a common variance.

Subgroups analysis was not pre-specified in the Statistical Analysis Plan and was performed post-hoc for the primary endpoint ALSFRS-R score to confirm the consistency of the results with regard to selected demographic and baseline factors:

- Sex
- Age
- Disease duration
- Initial symptom
- El Escorial revised Airlie House diagnostic criteria
- Japan ALS severity classification
- Concomitant riluzole use
- Complications
- Change in ALSFRS-R score during the pre-observation period

For the Integrated Summary of Efficacy and the EMA MAA additional analyses were performed. These include additional subgroups analyses and a time-to-event analysis for Study MCI186-19 (FAS), for which an ALSFRS-R score decrease by 6 points or more and by 12 points or more from baseline to end of cycle 6 were defined as events.

Results

Participant flow

Study MCI186-16 - Initial Phase 3 Confirmatory Study

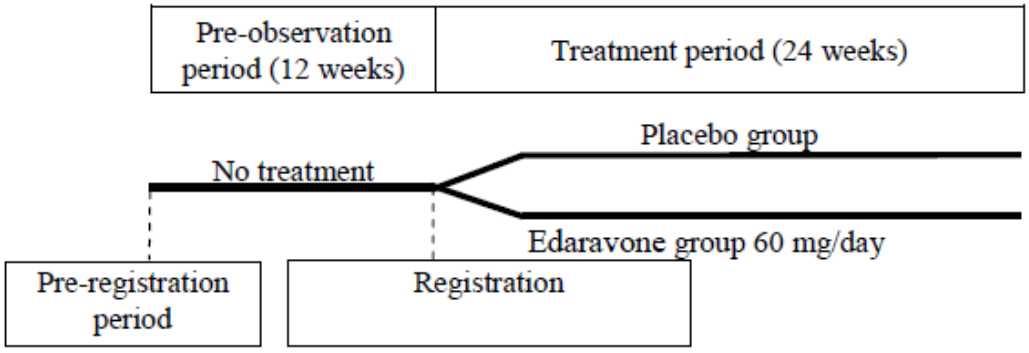


Figure 9.1.6-1 (MCI186-16 CSR) Outline of study design

Study MCI186-17 Extension of Study MCI186-16

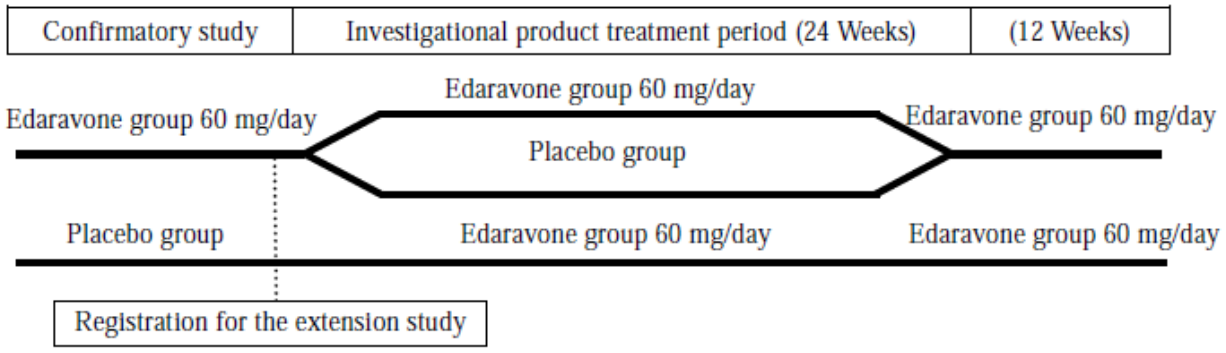


Figure 9.1.6-1 (MCI186-17 CSR) Summary of study design

Study MCI186-19 - Pivotal Phase 3 Replication Study

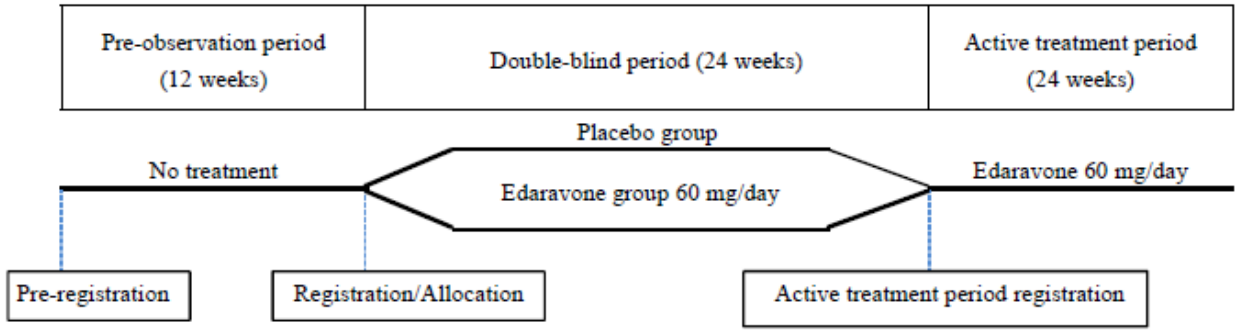


Figure 9.1.6-1 (MCI186-19 CSR) Study design

Baseline data

Study MCI186-16 - Initial Phase 3 Confirmatory Study

At baseline, some numerical imbalances were observed in age, disease duration, ALSFRS-R score and EL Escorial Revised Airlie House Diagnostic Criteria. Only a small percentage of patients did not use riluzole.

Table 11.2-1 (MCI186-16 CSR) Demographic and other baseline characteristics (FAS) (1/2)

Group		Placebo		Edaravone		Test
No. of patients		104		101		
Factor		n	(%)	n	(%)	
Sex	Male	69	(66.3)	63	(62.4)	$P = 0.5633$ (Fisher)
	Female	35	(33.7)	38	(37.6)	
Age (years)	n	104		101		$P = 0.8973$ (2-sample t-test)
	Mean	57.7		57.9		
	S.D.	10.2		9.8		
	Min.	28		29		
	Median	58.5		58.0		
	Max.	75		73		
	< 20 years	0	(0.0)	0	(0.0)	$P = 0.9971$ (2-sample Wilcoxon test)
	≥ 20 years, < 30 years	1	(1.0)	1	(1.0)	
	≥ 30 years, < 40 years	6	(5.8)	5	(5.0)	
	≥ 40 years, < 50 years	17	(16.3)	10	(9.9)	
	≥ 50 years, < 60 years	31	(29.8)	39	(38.6)	
	≥ 60 years, < 70 years	33	(31.7)	36	(35.6)	
	≥ 70 years	16	(15.4)	10	(9.9)	
	< 65 years	71	(68.3)	73	(72.3)	$P = 0.5451$ (Fisher)
	≥ 65 years	33	(31.7)	28	(27.7)	
Height (cm)	n	104		101		$P = 0.6687$ (2-sample t-test)
	Mean	163.4		162.9		
	S.D.	8.2		8.3		
	Min.	146		145		
	Median	163.0		163.0		
	Max.	182		180		
Body weight (kg)	n	104		101		$P = 0.6175$ (2-sample t-test)
	Mean	59.0		58.3		
	S.D.	12.1		8.8		
	Min.	37		35		
	Median	57.0		57.0		
	Max.	109		77		
Duration of disease (years)	n	104		101		$P = 0.1041$ (2-sample t-test)
	Mean	1.30		1.44		
	S.D.	0.63		0.63		
	Min.	0.3		0.4		
	Median	1.20		1.30		
	Max.	3.0		2.9		
	< 1 year	37	(35.6)	29	(28.7)	$P = 0.0876$ (2-sample Wilcoxon test)
	≥ 1 year, < 2 years	54	(51.9)	49	(48.5)	
	≥ 2 years	13	(12.5)	23	(22.8)	
Initial symptom*	Bulbar symptoms	20	(19.2)	18	(17.8)	$P = 0.8583$ (Fisher)
	Limb symptoms	84	(80.8)	83	(82.2)	
ALS diagnosis	Sporadic	100	(96.2)	100	(99.0)	$P = 0.3691$ (Fisher)
	Familial	4	(3.8)	1	(1.0)	

* Factors for dynamic allocation

Table 11.2-1 (MCI186-16 CSR) Demographic and other baseline characteristics (FAS) (2/2)

Group			Placebo		Edaravone		Test
No. of patients			104		101		
Factor			n	(%)	n	(%)	
El Escorial revised Airlie House diagnostic criteria		Definite ALS	21	(20.2)	29	(28.7)	$P = 0.3070$ (χ^2 Test)
		Probable ALS	54	(51.9)	52	(51.5)	
		Probable ALS Laboratory supported	28	(26.9)	20	(19.8)	
		Possible ALS	1	(1.0)	0	(0.0)	
		Suspected ALS	0	(0.0)	0	(0.0)	
ALS severity classification		Grade I	40	(38.5)	36	(35.6)	$P = 0.7725$ (Fisher)
		Grade II	64	(61.5)	65	(64.4)	
		Grade III					
Rationale for ALS diagnosis	Upper motor neuron dysfunction	No	0	(0.0)	0	(0.0)	–
		Yes	104	(100.0)	101	(100.0)	
	Lower motor neuron dysfunction	No	0	(0.0)	0	(0.0)	–
		Yes	104	(100.0)	101	(100.0)	
	Acute denervation findings in needle electrode exam.	No	4	(3.9)	3	(3.0)	$P = 1.0000$ (Fisher)
		Yes	99	(96.1)	98	(97.0)	
		Not tested	1		0		(excluding patients not tested)
Concomitant use of riluzole*		No	12	(11.5)	11	(10.9)	$P = 1.0000$ (Fisher)
		Yes	92	(88.5)	90	(89.1)	
Complications		No	13	(12.5)	13	(12.9)	$P = 1.0000$ (Fisher)
		Yes	91	(87.5)	88	(87.1)	
ALSFRS-R score during the pre-observation period	Before pre-registration	n	104		101		$P = 0.0650$ (2-sample *t*-test)
		Mean	43.3		42.5		
		S.D.	2.6		3.4		
		Min.	35		31		
		Median	44.0		43.0		
		Max.	48		48		
	At baseline in Treatment cycle 1	n	104		101		$P = 0.1464$ (2-sample *t*-test)
		Mean	41.2		40.6		
		S.D.	2.9		3.5		
		Min.	32		29		
		Median	42.0		41.0		
		Max.	47		47		
	Changes from before pre-registration to at baseline in Treatment cycle 1*	–4	11	(10.6)	8	(7.9)	$P = 0.3328$ (2-sample Wilcoxon test)
		–3	21	(20.2)	21	(20.8)	
		–2	39	(37.5)	32	(31.7)	
		–1	33	(31.7)	40	(39.6)	
		–4, –3	32	(30.8)	29	(28.7)	$P = 0.7623$ (Fisher)
		–2, –1	72	(69.2)	72	(71.3)	
Concomitant therapy		No	22	(21.2)	31	(30.7)	$P = 0.1509$ (Fisher)
		Yes	82	(78.8)	70	(69.3)	
Concomitant drug (excluding riluzole)		No	1	(1.0)	1	(1.0)	$P = 1.0000$ (Fisher)
		Yes	103	(99.0)	100	(99.0)	

*: Factors for dynamic allocation

Summary Table. Comparisons of demographics and baseline characteristics between analysis population sets (Study MCI186-16)

	FAS		**EESP**		**Definite / or probable / EESP / 2y**	
	Placebo	Edaravone	Placebo	Edaravone	Placebo	Edaravone
Age, mean (SD)	57.7 (10.2)	57.9 (9.8)	59.1 (10.0)	55.7 (10.4)	57.2 (10.4)	55.4 (9.6)
Age ≥65 yrs (%)	33 (31.7)	28 (27.7)	18 (36.0)	11 (20.4)	8 (25.0)	6 (15.0)
Disease duration Median (min-max)	1.20 (0.63)	1.30 (0.4-2.9)	1.05 (0.3-2.9)	1.25 (0.5-2.8)	0.95 (0.3-1.8)	1.20 (0.5-2.0)
Diagnostic criteria (%)						
- Definite	21 (20.2)	29 (28.7)	10 (20.0)	19 (35.2)	9 (28.1)	18 (45.0)
- Probable	54 (51.9)	52 (51.5)	25 (50.0)	27 (50.0)	23 (71.9)	22 (55.0)
ALS severity (%)						
- Grade I	40 (38.5)	36 (35.6)	24 (48.0)	28 (51.9)	16 (50.0)	21 (52.5)
- Grade II	64 (61.5)	65 (64.4)	26 (52.0)	26 (48.1)	16 (50.0)	19 (47.5)
Concomitant riluzole (%)	92 (88.5)	90 (89.1)	41 (82.0)	49 (90.7)	25 (78.1)	37 (92.5)

Study MCI186-17 – Extension of Study MCI186-16

There were no factors showing imbalance in any of the analysis sets during examination of the homogeneity between the groups in “baseline in Cycle 7”.

Table 11.2-1 (MCI186-17 CSR) Demographic and other baseline characteristics (FAS) (2/2)

Treatment group			Edaravone-placebo		Edaravone-edaravone		Placebo-edaravone		Statistical test (edaravone-placebo vs. edaravone-edaravone)
No. of patients			44		48		88		
Variable			No. of patients	(%)	No. of patients	(%)	No. of patients	(%)	
El Escorial revised Airlie House diagnostic criteria		Definite ALS	11	(25.0)	14	(29.2)	18	(20.5)	P=0.9013 χ^2-test
		Probable ALS	23	(52.3)	24	(50.0)	46	(52.3)	
		Clinically probable laboratory supported ALS	10	(22.7)	10	(20.8)	23	(26.1)	
		Possible ALS	0	(0.0)	0	(0.0)	1	(1.1)	
		Suspected ALS	0	(0.0)	0	(0.0)	0	(0.0)	
Japan ALS severity classification		Stage I	16	(36.4)	17	(35.4)	36	(40.9)	P=1.0000 (Fisher)
		Stage II	28	(63.6)	31	(64.6)	52	(59.1)	
		Stage III							
Basis for ALS diagnosis	Upper motor neuron involvement	Absent	0	(0.0)	0	(0.0)	0	(0.0)	-
		Present	44	(100.0)	48	(100.0)	88	(100.0)	
	Lower motor neuron involvement	Absent	0	(0.0)	0	(0.0)	0	(0.0)	-
		Present	44	(100.0)	48	(100.0)	88	(100.0)	
	Acute denervation findings in needle electromyography	Absent	2	(4.5)	0	(0.0)	4	(4.6)	P=0.2260 (Fisher) (Excluding those not examined)
		Present	42	(95.5)	48	(100.0)	83	(95.4)	
		Not examined	0		0		1		
Concomitant use of riluzole*		Absent	5	(11.4)	6	(12.5)	8	(9.1)	P=1.0000 (Fisher)
		Present	39	(88.6)	42	(87.5)	80	(90.9)	
Complications		Absent	5	(11.4)	8	(16.7)	10	(11.4)	P=0.5566 (Fisher)
		Present	39	(88.6)	40	(83.3)	78	(88.6)	
ALSFRS-R score during the pre-observation period	Before pre-registration	No. of patients	44		48		88		P=0.4100 (Two-sample t-test)
		Mean	42.9		42.3		43.3		
		SD	2.9		3.9		2.6		
		Minimum	37		31		35		
		Median	43.0		43.0		44.0		
		Maximum	48		48		48		
	At baseline in Cycle 1	No. of patients	44		48		88		P=0.5604 (Two-sample t-test)
		Mean	40.9		40.5		41.3		
		SD	3.1		3.8		2.8		
		Minimum	34		29		32		
		Median	41.0		42.0		42.0		
		Maximum	47		47		47		
	Change from pre-registration to baseline in Cycle 1*	-4	5	(11.4)	1	(2.1)	8	(9.1)	P=0.4678 (Two-sample Wilcoxon test)
		-3	6	(13.6)	12	(25.0)	18	(20.5)	
		-2	17	(38.6)	13	(27.1)	32	(36.4)	
		-1	16	(36.4)	22	(45.8)	30	(34.1)	
		-4, -3	11	(25.0)	13	(27.1)	26	(29.5)	P=1.0000 (Fisher)
		-2, -1	33	(75.0)	35	(72.9)	62	(70.5)	

* Factor used in dynamic assignment

Study MCI186-18 - Exploratory Study (ALS Severity Grade 3)

Table 11.2-1 (MCI186-18 CSR) Demographic and other baseline characteristics (FAS) (2/2)

Group			Placebo		Edaravone		Test
n			12		13		
Factor			n	(%)	n	(%)	
El Escorial revised Airlie House diagnostic criteria		Definite ALS	2	(16.7)	7	(53.8)	$P = 0.1302$ (χ^2 test)
		Probable ALS	8	(66.7)	4	(30.8)	
		Probable ALS Laboratory supported	2	(16.7)	2	(15.4)	
		Possible ALS	0	(0.0)	0	(0.0)	
		Suspected ALS	0	(0.0)	0	(0.0)	
Japan ALS severity classification		Grade 1					
		Grade 2					
		Grade 3	12	(100.0)	13	(100.0)	
Rationale for ALS diagnosis	Upper motor neuron involvement	No	0	(0.0)	0	(0.0)	–
		Yes	12	(100.0)	13	(100.0)	
	Lower motor neuron involvement	No	0	(0.0)	0	(0.0)	–
		Yes	12	(100.0)	13	(100.0)	
	Acute denervation findings in needle electrode exam.	No	0	(0.0)	1	(8.3)	$P = 1.0000$ (Fisher) (excluding patients not tested)
		Yes	12	(100.0)	11	(91.7)	
		Not tested	0		1		
Concomitant use of riluzole		No	1	(8.3)	3	(23.1)	$P = 0.5930$ (Fisher)
		Yes	11	(91.7)	10	(76.9)	
Complications		No	0	(0.0)	1	(7.7)	$P = 1.0000$ (Fisher)
		Yes	12	(100.0)	12	(92.3)	
ALSFRS-R score during the pre-observation period	Before pre-registration	n	12		13		$P = 0.2452$ (2-sample t-test)
		Mean	36.8		34.5		
		S.D.	3.6		5.4		
		Min.	29		25		
		Median	37.0		36.0		
		Max.	43		42		
	At baseline in Cycle 1	n	12		13		$P = 0.2599$ (2-sample t-test)
		Mean	34.6		32.5		
		S.D.	3.3		5.5		
		Min.	28		23		
		Median	35.0		32.0		
		Max.	41		40		
	Changes from before pre-registration to at baseline in Cycle 1*	–4	2	(16.7)	2	(15.4)	$P = 0.8421$ (2-sample Wilcoxon test)
		–3	2	(16.7)	2	(15.4)	
		–2	4	(33.3)	4	(30.8)	
		–1	4	(33.3)	5	(38.5)	
		–4, –3	4	(33.3)	4	(30.8)	$P = 1.0000$ (Fisher)
		–2, –1	8	(66.7)	9	(69.2)	
Concomitant therapy		No	3	(25.0)	0	(0.0)	$P = 0.0957$ (Fisher)
		Yes	9	(75.0)	13	(100.0)	
Concomitant drug (excluding riluzole)		No	0	(0.0)	0	(0.0)	–
		Yes	12	(100.0)	13	(100.0)	

*: Factors used for dynamic allocation

Table 11.2.1-1 (MCI186-19 CSR) Demographic and other baseline characteristics (FAS) (1/2)

Treatment group		Placebo		Edaravone		Statistical test
No. of patients		68		69		
Variable		No. of patients	(%)	No. of patients	(%)	
Sex	Male	41	(60.3)	38	(55.1)	*P*=0.6051 (Fisher)
	Female	27	(39.7)	31	(44.9)	
Age* (yrs)	No. of patients	68		69		*P*=0.8111 (Two-sample *t*-test)
	Mean	60.1		60.5		
	SD	9.6		10.1		
	Minimum	38		30		
	Median	61.5		62.0		
	Maximum	75		75		
	<20	0	(0.0)	0	(0.0)	*P*=0.9837 (Two-sample Wilcoxon test)
	≥20, <30	0	(0.0)	0	(0.0)	
	≥30, <40	2	(2.9)	5	(7.2)	
	≥40, <50	7	(10.3)	5	(7.2)	
	≥50, <60	18	(26.5)	16	(23.2)	
	≥60, <70	29	(42.6)	31	(44.9)	
	≤70	12	(17.6)	12	(17.4)	
	<65	46	(67.6)	46	(66.7)	*P*=1.0000 (Fisher)
	≥65	22	(32.4)	23	(33.3)	
Body weight (kg)	No. of patients	68		69		*P*=0.9749 (Two-sample *t*-test)
	Mean	57.8		57.9		
	SD	9.3		12.9		
	Minimum	41		38		
	Median	56.5		55.0		
	Maximum	84		105		
Height (cm)	No. of patients	68		69		*P*=0.6478 (Two-sample *t*-test)
	Mean	162.5		161.8		
	SD	8.4		9.5		
	Minimum	146		141		
	Median	164.5		162.0		
	Maximum	176		186		
Disease duration (yrs)	No. of patients	68		69		*P*=0.3980 (Two-sample *t*-test)
	Mean	1.06		1.13		
	SD	0.47		0.46		
	Minimum	0.2		0.3		
	Median	1.00		1.00		
	Maximum	1.9		2.0		
	<1	33	(48.5)	27	(39.1)	*P*=0.3037 (Fisher)
	≥1	35	(51.5)	42	(60.9)	
Initial symptom	Bulbar symptom	14	(20.6)	16	(23.2)	*P*=0.8368 (Fisher)
	Limb symptom	54	(79.4)	53	(76.8)	
ALS diagnosis	Sporadic	66	(97.1)	68	(98.6)	*P*=0.6195 (Fisher)
	Familial	2	(2.9)	1	(1.4)	

Table 11.2.1-1 (MCI186-19 CSR) Demographic and other baseline characteristics (FAS) (2/2)

Treatment group			Placebo		Edaravone		Statistical test
No. of patients			68		69		
Variable			No. of patients	(%)	No. of patients	(%)	
El Escorial revised Airlie House diagnostic criteria*		Definite ALS	27	(39.7)	28	(40.6)	*P*=1.0000 (Fisher)
		Probable ALS	41	(60.3)	41	(59.4)	
Japan ALS severity classification		Grade1	16	(23.5)	22	(31.9)	*P*=0.3408 (Fisher)
		Grade 2	52	(76.5)	47	(68.1)	
Complications		Absent	6	(8.8)	4	(5.8)	*P*=0.5316 (Fisher)
		Present	62	(91.2)	65	(94.2)	
Pre-observation period ALSFRS-R score	Before pre-registration	No. of patients	68		69		*P*=0.8331 (Two-sample *t*-test)
		Mean	43.5		43.6		
		SD	2.2		2.2		
		Minimum	39		38		
		Median	44.0		44.0		
		Maximum	48		48		
	At baseline in Cycle 1	No. of patients	68		69		*P*=0.8225 (Two-sample *t*-test)
		Mean	41.8		41.9		
		SD	2.2		2.4		
		Minimum	37		36		
		Median	42.0		42.0		
		Maximum	47		47		
	Change from before pre-registration to Cycle 1 baseline*	-4	3	(4.4)	5	(7.2)	*P*=0.7226 (two-sample Wilcoxon test)
		-3	8	(11.8)	7	(10.1)	
		-2	25	(36.8)	21	(30.4)	
		-1	32	(47.1)	36	(52.2)	
		-4, -3	11	(16.2)	12	(17.4)	*P*=1.0000 (Fisher)
		-2, -1	57	(83.8)	57	(82.6)	
Concomitant therapy		Absent	7	(10.3)	11	(15.9)	*P*=0.4491 (Fisher)
		Present	61	(89.7)	58	(84.1)	
Concomitant riluzole		Absent	6	(8.8)	6	(8.7)	*P*=1.0000 (Fisher)
		Present	62	(91.2)	63	(91.3)	
Concomitant drugs other than riluzole		Absent	1	(1.5)	1	(1.4)	*P*=1.0000 (Fisher)
		Present	67	(98.5)	68	(98.6)	

*Factor used in dynamic allocation

Population analyzed: FAS in the double-blind period

Numbers analysed

Study MCI186-16 - Initial Phase 3 Confirmatory Study

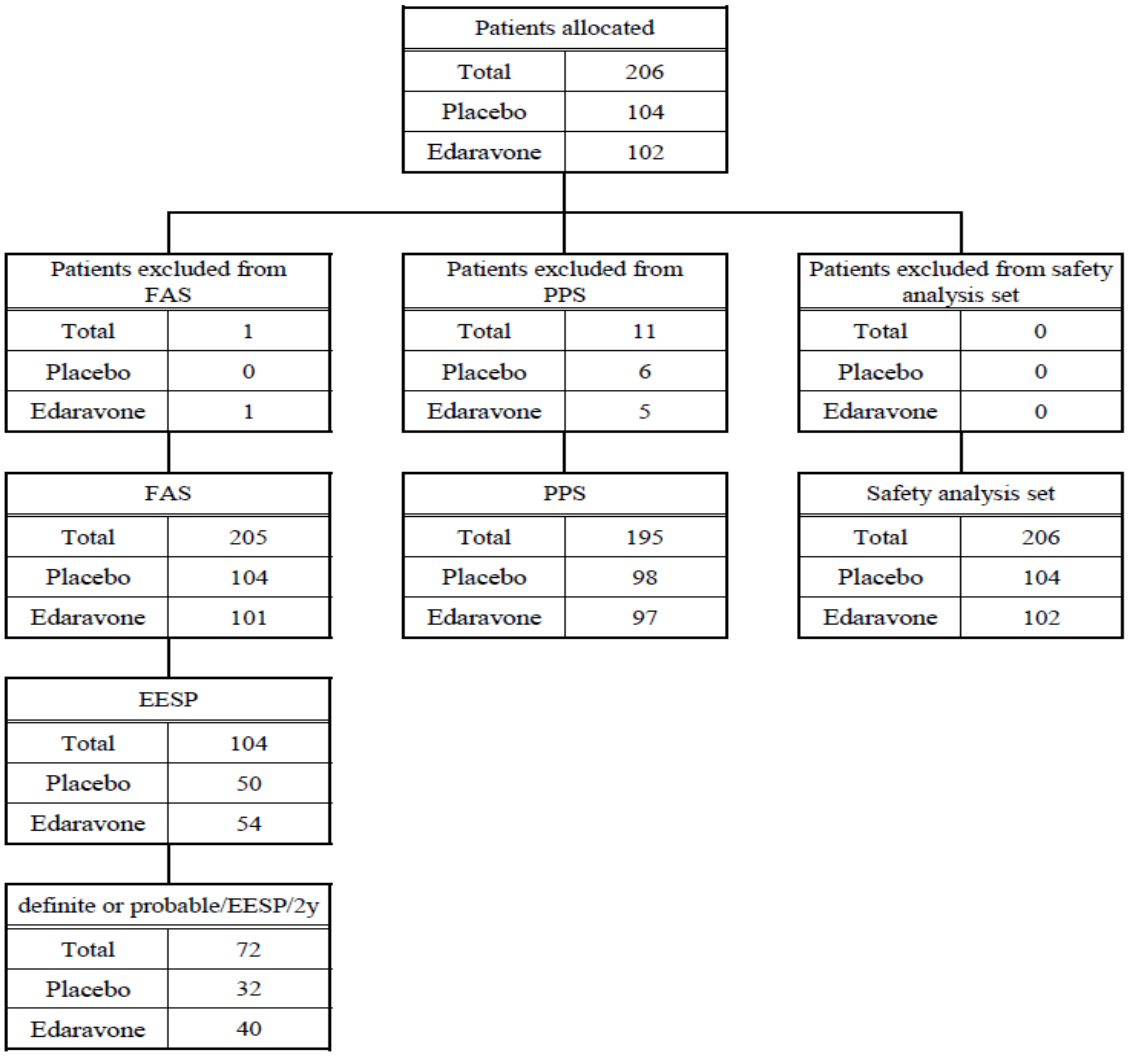


Figure 11.1-1 (MCI186-16 CSR) Disposition of patients

Study MCI186-17- Extension of Study MCI186-16

Patients assigned	
Total	181
Edaravone-placebo	45
Edaravone-edaravone	48
Placebo-edaravone	88

Patients excluded from FAS	
Total	1
Edaravone-placebo	1
Edaravone-edaravone	0
Placebo-edaravone	0

Patients excluded from PPS	
Total	9
Edaravone-placebo	3
Edaravone-edaravone	2
Placebo-edaravone	4

Patients excluded from safety analysis set	
Total	0
Edaravone-placebo	0
Edaravone-edaravone	0
Placebo-edaravone	0

FAS	
Total	180
Edaravone-placebo	44
Edaravone-edaravone	48
Placebo-edaravone	88

PPS	
Total	172
Edaravone-placebo	42
Edaravone-edaravone	46
Placebo-edaravone	84

Safety analysis set	
Total	181
Edaravone-placebo	45
Edaravone-edaravone	48
Placebo-edaravone	88

EESP	
Total	96
Edaravone-placebo	25
Edaravone-edaravone	27
Placebo-edaravone	44

non-EESP	
Total	84
Edaravone-placebo	19
Edaravone-edaravone	21
Placebo-edaravone	44

Figure 11.1-1 (MCI186-17 CSR) Disposition of patients

Study MCI186-18 - Exploratory Study (ALS Severity Grade 3)

Patients enrolled	
Total	25
Placebo	12
Edaravone	13

Patients excluded from FAS	
Total	0
Placebo	0
Edaravone	0

Patients excluded from PPS	
Total	1
Placebo	0
Edaravone	1

Patients excluded from safety analysis set	
Total	0
Placebo	0
Edaravone	0

FAS	
Total	25
Placebo	12
Edaravone	13

PPS	
Total	24
Placebo	12
Edaravone	12

Safety analysis set	
Total	25
Placebo	12
Edaravone	13

Figure 11.1-1 (MCI186-18 CSR) Disposition of patients

Study MCI186-19 - Pivotal Phase 3 “Replication” Study

Number of patients providing informed consent	
Total	213

Number of patients pre-registered	
Total	192

Number of patients excluded from the study	
Total	21

Number of patients registered	
Total	137
Placebo	68
Edaravone	69

Number of patients who discontinued from the study during the pre-observation period	
Total	55

Number of patients receiving the investigational product	
Total	137
Placebo	68
Edaravone	69

Number of patients who completed the study	
Total	127
Placebo	60
Edaravone	67

Number of patients who discontinued from the study	
Total	10
Placebo	8
Edaravone	2

Figure 10.1.1-1 (MCI186-19 CSR) Disposition of patients

The total number of patients included in the studies was 547, from whom 363 have received at least one administration of edaravone and 184 received placebo. 109 patients in the edaravone group and 100 patients in the placebo group (in total 209) were evaluated for demonstration of efficacy in the two pivotal confirmatory Phase 3 studies. The first confirmatory study MCI186-16 did not show statistically significant results in the FAS and a subpopulation with less advanced disease was selected for analysis. This subpopulation included patients who fulfilled the El Escorial revised Airlie House diagnostic criteria for definite or probable ALS, were of Grade 1 or 2 in the Japan ALS severity classification, having normal respiratory function measured by forced vital capacity (%FVC) not less than 80% (studies MCI186-16 and MCI186-19), had an onset of ALS within 2 years and had a change of -1 up to -4 points in the ALSFRS-R score during 12-week pre-observation period.

Outcomes and estimation

Study MCI186-12 (Phase 2 study)

The difference between the change in ALSFRS-R during 6 months before the start of treatment and the change during 6 months after the start of treatment was also calculated as the degree of suppression of ALSFRS-R decline in 6 months after the start of treatment and used as an indicator of the degree of disease progression. For subjects who completed the study, the mean ± standard deviation (SD) degree of suppression in the ALSFRS-R score at 6 months after the start of treatment was 2.3 ± 3.9 (p = 0.337) in the 30-mg group and a 2.4 ± 3.5 (p = 0.035) in the 60-mg group (Table 2.7.3-6).

Table 2.7.3-6: Degree of Suppression of ALSFRS-R 6 Months after the Start of Treatment

Open-label Edaravone group (N excluding withdrawals)	Total ALSFRS-R			Summary statistics			
	6 months before start of treatment (mean)	Start of treatment (Baseline) (mean)	6 months after start of treatment (mean)	Change from 6 months before start of treatment to Baseline[a] (mean)	Change from Baseline to end of Cycle 6[b] (mean)	Degree of suppression 6 months. after start of treatment[c] (mean ± SD)	Paired t-test
30 mg (N=4)	39.3	32.0	27.0	−7.3	−5.0	2.3 ± 3.9	P=0.337
60 mg (N=12)	42.7	38.0	35.8	−4.7	−2.3	2.4 ± 3.5	**P=0.035**

a Baseline minus 6 months before the start of treatment.
b End of Cycle 6 minus Baseline.
c (End of Cycle 6 minus Baseline) minus (Baseline minus 6 months before the start of treatment).
Source: ISE Study MCI186-12 Post-hoc analysis in Module 5.3.5.3.

The CSF was collected in this study. The average differences in 3NT levels between Baseline in Cycle 1 and at the end of administration in Cycle 6 were -0.63 ng/mL in the 30-mg group (4 subjects) and -1.12 ng/mL in the 60-mg group (12 subjects).

Study MCI186-16 - Initial Phase 3 Confirmatory Study

The results of the analysis of the primary efficacy endpoint of change from Baseline to the End of Cycle 6 in ALSFRS-R are shown in Table 2.7.3-8. While a beneficial trend favouring edaravone was observed in the FAS, the prespecified primary analyses did not statistically significantly demonstrate the efficacy of edaravone in comparison to placebo.

In additional exploratory analyses, the beneficial trend favouring edaravone was mainly driven by data from subjects who had functionality retained in most ADL domains with normal respiratory function. This population was described as the “EESP”.

Changes in ALSFRS-R scores were analysed in these study subgroups. The EESP and Definite or Probable/EESP/2y showed favourable trends with p-values less than 0.05 as shown in Table 2.7.3-8.

Table 2.7.3-8: Difference in ALSFRS-R between Baseline in Cycle 1 and the End of Cycle 6 (LOCF) for Study MCI186-16 (FAS, EESP, Definite or Probable/EESP/2y)

Study number (Population)	Group	Number of subjects in LOCF analyses	Adjusted mean	Between-group differences in the adjusted mean	p-value
			LS mean±SE	LS mean±SE (95% CI)	
MCI186-16 (FAS)	P group	99	-6.35±0.84	0.65±0.78 (-0.90 ,2.19)	p=0.4108
	E group	100	-5.70±0.85		
MCI186-16 (EESP)[a]	P group	46	-7.06±1.13	2.20±1.03 (0.15 , 4.26)	**p=0.0360**
	E group	53	-4.85±1.24		
MCI186-16 (definite or probable/EESP/2y) [a]	P group	29	-7.59±1.34	3.01±1.33 (0.35 , 5.67)	**p=0.0270**
	E group	39	-4.58±1.55		
MCI186-16 (non-EESP) [a]	P group	53	-5.24±1.25	-1.42±1.16 (-3.73 , 0.89)	p=0.2251
	E group	47	-6.65±1.17		
MCI186-16 (non-"definite or probable/EESP/2y") [a]	P group	70	-5.54±1.08	-0.57±1.00 (-2.55 , 1.41)	p=0.5711
	E group	61	-6.11±1.03		

Note: LOCF was applied to subjects who completed Cycle 3 (subjects who reached 81 days after treatment initiation). Subjects who dropped out before Day 81 were excluded.
a EESP, Definite or Probable/EESP/2y, non-EESP, and non-"Definite or Probable EESP/2y" analyses were post-hoc.
Source: ISE Table 3.1.1, Table 3.1.2, Table 3.1.3, Table 3.1.4, and Table 3.1.5 in Module 5.3.5.3.

Study MCI186-17 – Extension of Study MCI186-16

A trend for a beneficial effect favouring edaravone was observed in the FAS, which was however not statistically significant. Results for the change from Cycle 7 Baseline to the End of Cycle 12 in ALSFRS-R for the EESP and Definite or Probable/EESP/2y populations (i.e., population met criteria of EESP or Definite or Probable/EESP/2y at the start of Study MCI186-16) showed favourable trends with larger differences from placebo compared to that observed in the FAS (Table 2.7.3-10).

Table 2.7.3-10: Differences in ALSFRS-R between Baseline in Cycle 7 and the End of Cycle 12 (LOCF) for Study MCI186-17 (FAS, EESP, Definite or Probable/EESP/2y)

Study number (Population)	Group	Number of subjects	Adjusted mean	Between-group differences in the adjusted mean	p-value
			LS mean±SE	LS mean±SE (95% CI)	
MCI186-17 (FAS)[a]	EP group	41	-5.58±0.74	1.16±0.93 (-0.70, 3.01)	p=0.2176
	EE group	44	-4.42±0.69		
MCI186-17 (EESP)[a]	EP group	25	-5.86±0.98	1.85 ± 1.14 (-0.45, 4.15)	p=0.1127
	EE group	27	-4.01±0.86		
MCI186-17 (definite or probable/EESP/2y)[b]	EP group	16	-7.02±1.39	2.79 ± 1.51 (-0.26, 5.85)	p=0.0719
	EE group	22	-4.22±1.04		
MCI186-17 (non-"EESP")[b]	EP group	16	-5.66±1.17	0.46 ± 1.61 (-2.83, 3.74)	p=0.7790
	EE group	17	-5.20±1.17		
MCI186-17 (non- "definite or probable/EESP/2y")[b]	EP group	25	-4.96±0.88	0.13 ± 1.24 (-2.36, 2.62)	p=0.9164
	EE group	22	-4.83±0.95		

Note: LOCF was applied to the subjects who completed Cycle 9 (subjects who reached 249 days after the start of treatment). Subjects who dropped out before Day 249 were excluded.
a FAS and EESP analyses were prespecified before code break.
b Definite or Probable/EESP/2y, non-EESP, and non-"Definite or Probable EESP/2y" analyses were post-hoc.
Source: ISE Table 3.2.1, Table 3.2.2, Table 3.2.3, Table 3.2.4, and Table 3.2.5 in Module 5.3.5.3.

Both ALL LOCF (which included and data from patients who discontinued before Cycle 3) and MMRM approaches showed similar results with prespecified LOCF analyses; however, some variability among analyses were observed due to the limited number of subjects.

According to the Applicant, there was no difference in %FVC or other endpoints between the EP group and EE group due to the limited number of subjects in each group as a result of further division from edaravone group in Study MCI186-16.

The combined results of MCI186-16 and MCI186-17 as changes in ALSFRS-R scores in Study MCI186-16 followed by Study MCI186-17 in the Definite or Probable/EESP/2y subpopulation from Baseline in Cycle 1 to the End of Cycle 12 are presented below (graphical representation of scores without an imputation analysis).

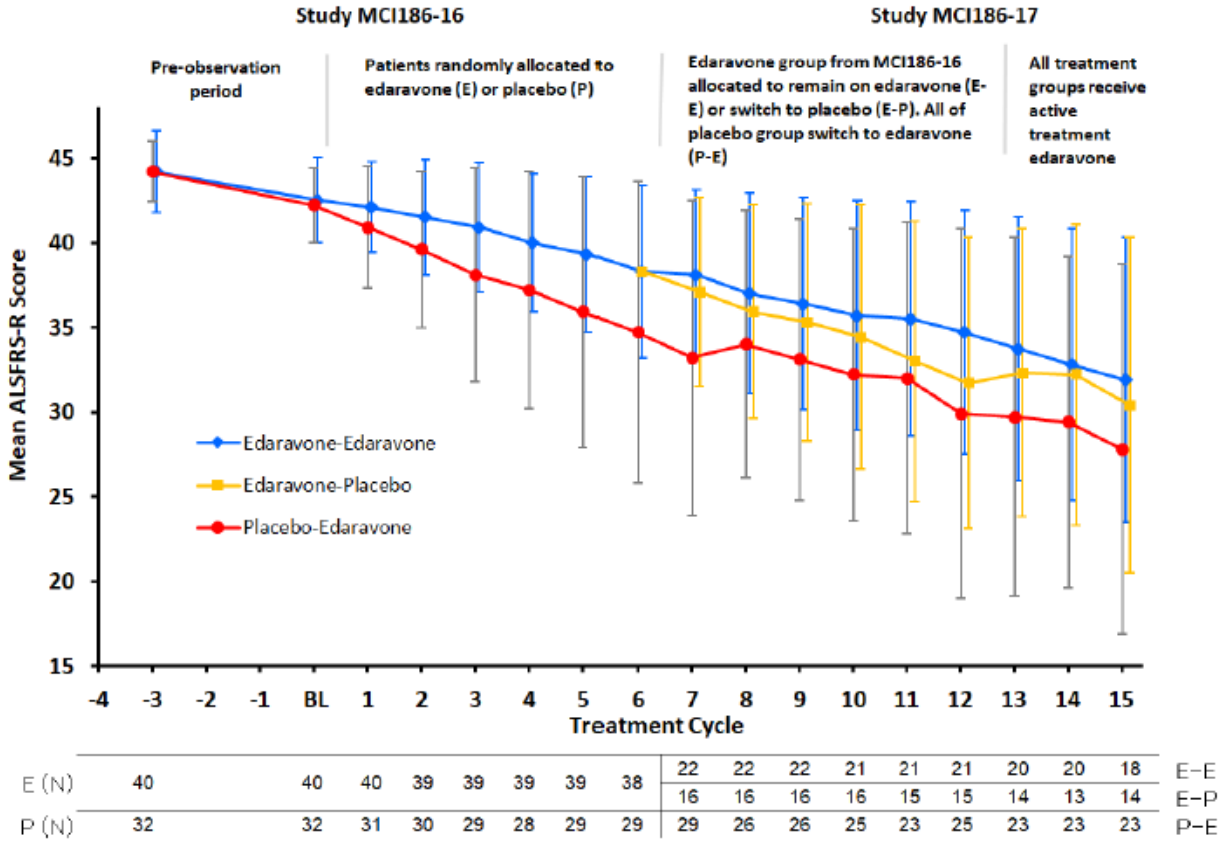


Figure 2.7.3-3: ALSFRS-R Score over Time (Mean ± SD) in Study MCI186-16 Followed by Study MCI186-17 (Definite or Probable/EESP/2y Subpopulation, Observed Cases)
Source: ISE Figure 9.1 in Module 5.3.5.3 (modified).Takahashi F et al. 2017.60

Study MCI186-18 - Exploratory Study (ALS Severity Grade 3)

In addition to the primary endpoint and the secondary endpoints used in studies MCI186-16 and MCCI186-17, efficacy evaluation also included blood gas. Only 1 patient in the edaravone group was excluded from the PPS, showing no substantial difference in analysis results between the FAS and PPS.

Table 2.7.3-13: Change in ALSFRS-R Scores from Baseline in Cycle 1 to the End of Cycle 6 (LOCF) for Study MCI186-18 (FAS)

Group	Number of subjects in the LOCF analysis	Adjusted mean change from Baseline	Between-group differences in the adjusted mean	p-value
		LS mean±SE	LS mean±SE (95% CI)	
P group	12	-6.00±1.83	-0.52±2.46 (-5.62, 4.58)	p=0.8347
E group	13	-6.52±1.78		

Note: LOCF was applied to subjects who completed Cycle 3 (subjects who reached 81 days after treatment initiation). Subjects who dropped out before Day 81 were excluded.
Source: MCI186-18 CSR.

There was no meaningful difference between treatment groups in the change in the ALSFRS-R score.

Study MCI186-19 - Pivotal Phase 3 Replication Study

The least-squares (LS) mean ± standard error (SE) of the between-group difference in the change of ALSFRS-R from Baseline to end of Cycle 6 (24 weeks) and its 95% confidence interval (CI) were 2.49 ± 0.76 (0.99, 3.98), showing a statistically significant difference between the groups (p = 0.0013).

Table 2.7.3-16: Primary Analysis of the Change in ALSFRS-R Scores from Baseline in Cycle 1 to the End of Cycle 6 (LOCF) (Study MCI186-19 Double-blind, FAS)

Group	Number of subjects in LOCF analysis	Adjusted mean change from Baseline	Between-group differences in the adjusted mean	
		LS mean±SE	LS mean±SE (95% CI)	p-value
P group	66	-7.50±0.66	2.49±0.76 (0.99, 3.98)	p=0.0013
E group	68	-5.01±0.64		

LOCF was applied to the subjects who completed Cycle 3 (subjects who reached 81 days after treatment initiation). Subjects who dropped out before Day 81 were excluded.
Source: MCI186-19 CSR Table 11.4.1.1-2.

Secondary endpoints

The results of the secondary endpoints in study MCI186-19 are summarised in the following Tables:

Table 2.7.3-19: List of Number of Events for Death or Certain Signs of Disease Progression (Study MCI186-19 Double-blind, FAS)

Name of event[a]	P group (n=68)	E group (n=69)
Death	**0**	**0**
Disability of independent ambulation	2	0
Loss of upper limbs function	0	0
Tracheotomy	**0**	**1**
Use of respirator	**0**	**0**

Use of tube feeding	1	0
Loss of useful speech	3	1
Number of subjects with event[b]	6	2
Between-group comparison	p=0.1284 (log-rank test)	

Table 2.7.3-20: Analysis of the Change in %FVC from Baseline in Cycle 1 to the End of Cycle 6 (LOCF) (Study MCI186-19 Double-blind, FAS)

Group	Number of subjects in LOCF analysis	Adjusted mean change from Baseline	Between-group differences in the adjusted mean		
		LS mean±SE	LS mean±SE (95% CI)	t-value	p-value
P group	66	-20.40±2.48	4.78±2.84 (-0.83, 10.40)	t=1.69	p=0.0942
E group	67	-15.61±2.41			

Note: LOCF was applied to the subjects who completed Cycle 3 (subjects who reached 81 days after treatment initiation). Subjects who dropped out before Day 81 were excluded.
Source: MCI186-19 CSR Table 11.4.1.1-24.

Table 2.7.3-22: Analysis of Other Secondary Endpoints of Change from Baseline in Cycle 1 to the End of Cycle 6 (LOCF) (Study MCI186-19 Double-blind, FAS).

Endpoints	Group	Number of subjects	Adjusted mean change from Baseline	Adjusted mean change from Baseline	
			LS mean ± SE	LS mean ± SE (95% CI)	p-value
ALSAQ40 score	P group	64	26.04 ± 3.53	-8.79 ± 4.03 (-16.76, -0.82)	p=0.0309
	E group	68	17.25 ± 3.39		
Modified Norris Scale score (Total)	P group	63	-20.80±2.06	4.89±2.35 (0.24, 9.54)	p=0.0393
	E group	68	-15.91±1.97		
Grip strength	P group	66	-4.19±0.56	0.11±0.64 (-1.15, 1.38)	p=0.8583
	E group	68	-4.08±0.54		
Pinch grip strength	P group	66	-0.88±0.14	0.10±0.16 (-0.23, 0.42)	p=0.5478
	E group	68	-0.78±0.14		

LOCF was applied to the subjects who completed Cycle 3 (subjects who reached 81 days after treatment initiation). Subjects who dropped out before Day 81 were excluded.
Source: MCI186-19 CSR Table 11.4.1.1-31, 33, 35, 37, and 38.

Ancillary analyses

Study MCI186-16 - Initial Phase 3 Confirmatory Study

Sensitivity analyses were also conducted in the FAS population in which LOCF was applied to all subjects (ALL LOCF, including data from patients who discontinued before Cycle 3) and MMRM analysis was applied to all available subject data, and showed similar results with prespecified LOCF analyses (Table 2.7.3-9).

Table 2.7.3-9: Sensitivity Analyses of the Difference in ALSFRS-R Scores between Baseline in Cycle 1 and the End of Cycle 6 (ALL LOCF and MMRM) (Study MCI186-16 Double-blind, Definite or Probable/EESP/2y, Post-hoc)

Analytical method	Group	Number of subjects	Adjusted mean	Between-group differences in the adjusted mean	
			LS mean±SE	LS mean±SE (95% CI)	p-value
ALL LOCF	P group	32	-6.82 ± 1.23	**3.11±1.27** (0.57, 5.65)	**p=0.0170**
	E group	40	-3.70 ± 1.44		
MMRM	P group	31 (29)[a]	-6.97 ± 1.00	**3.44±1.29** (0.86 , 6.02)	**p=0.0097**
	E group	40 (38)[a]	-3.54 ± 0.90		

LOCF was applied to all randomised subjects.

For MMRM analysis, data from a subject who did not have the baseline ALSFRS-R value were excluded because MMRM required the Baseline value as a covariate for the analysis.

a Number of subjects included in MMRM analyses; at Baseline (at end of Cycle 6)).

Source: ISE Table 3.1.3 in Module 5.3.5.3.

Post-hoc MMRM analysis for the primary endpoint ALSFRS-R in study MCI186-16 confirmed the statistically significant results in favour of edaravone for the subpopulation of Definite or Probable/EESP/2y.

Study MCI186-19 - Pivotal Phase 3 Replication Study

A series of sensitivity analyses prespecified in their SAP were performed to verify the primary analysis and showed robust statistical results (Section 11.4.1.1.1.2 in Study MCI186-19 CSR). In addition, LOCF was applied to all subjects or MMRM was applied to all available subject data showed similar results with prespecified LOCF analyses (Table 2.7.3-17).

Table 2.7.3-17: Sensitivity Analyses of the Difference in ALSFRS-R Scores between Baseline in Cycle 1 and the End of Cycle 6 (ALL LOCF) and MMRM (Study MCI186-19 Double-blind, FAS, Post-hoc)

Analytical method	Group	Number of subjects	Adjusted mean	Between-group differences in the adjusted mean	
			LS mean±SE	LS mean±SE (95% CI)	p-value
ALL LOCF	P group	68	-7.41±0.65	2.37±0.75 (0.89, 3.84)	p=0.0019
	E group	69	-5.04±0.64		
MMRM	P group	67 (61)[a]	-7.37±0.57	2.81±0.78 (1.27, 4.35)	p=0.0004
	E group	69 (68)[a]	-4.56±0.55		

LOCF was applied to all randomised subjects. MMRM = mixed effects model for repeated measures.

For MMRM analysis, data from a subject who did not have the baseline ALSFRS-R value was excluded because MMRM required the Baseline value as a covariate for the analysis.

[a] Number of subjects included in MMRM analyses; at Baseline (at end of Cycle 6).

Source: ISE Table 3.5.1 in Module 5.3.5.3.

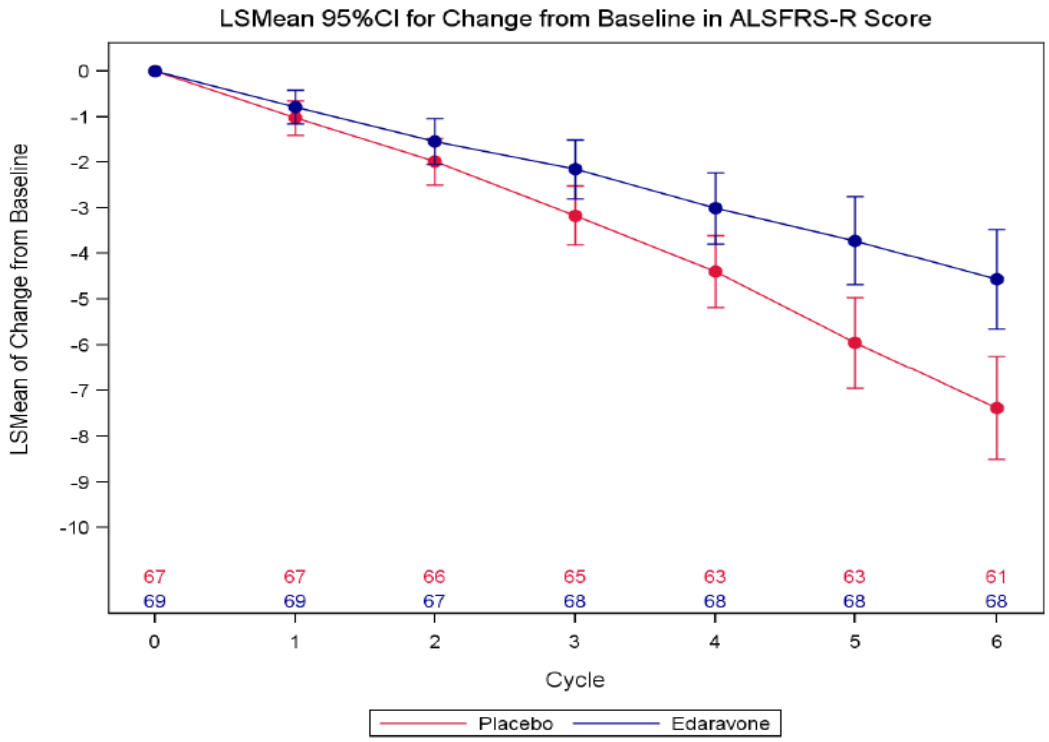


Figure 2.7.3-6: LS Mean Change (±SE) from Baseline in ALSFRS-R Scale Calculated by MMRM (Study MCI186-19 Double-Blind, FAS)

Source: ISE Figure 1.5.1 in Module 5.3.5.3.

Post-hoc analyses were performed to investigate effect of edaravone on individual items of ALSFRS-R score and confirmed consistent effect in all individual items and edaravone appeared to be descriptively favoured in all 4 domains of ALSFRS-R. In an investigation of four-domain data stratified by the onset of disease (bulbar versus limb), edaravone appeared to be consistently favoured in all 4 domains of the ALSFRS-R. Functional decline averages about 1 point per month in untreated patients. The effect of edaravone on individual 4 domains that include bulbar (ALSFRS-R items 1-3), fine motor (items 4-6), gross motor (items 7-9) and respiratory (items 10-12) is being presented in the following Figure.

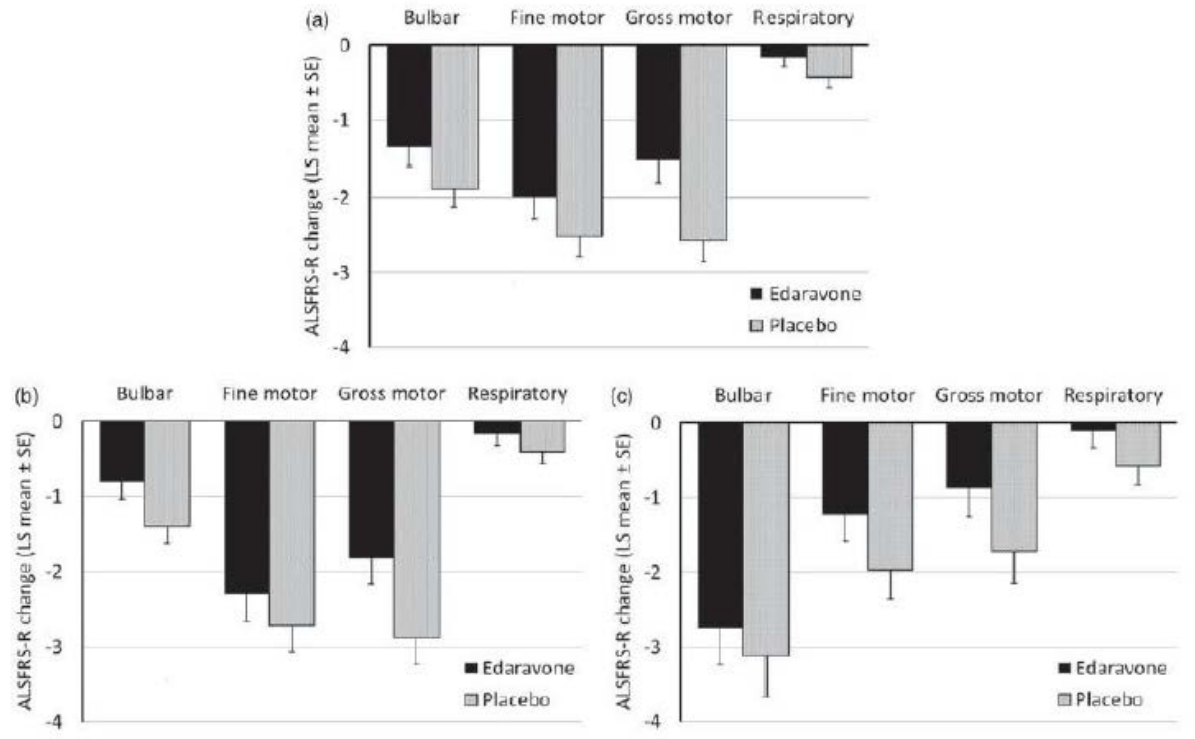


Figure 2.7.3-10 Changes in 4 Domains of the ALSFRS-R Score from Baseline to the End of Cycle 6 (ALL LOCF). Panel (a) All Patients, Panel (b) Patients with Limb Onset, Panel (c) Patients with Bulbar Onset. Source: Takei K et al. 2017

The time course of changes in ALSFRS-R score up to Cycle 12 (12 months) is shown in the following Figure.

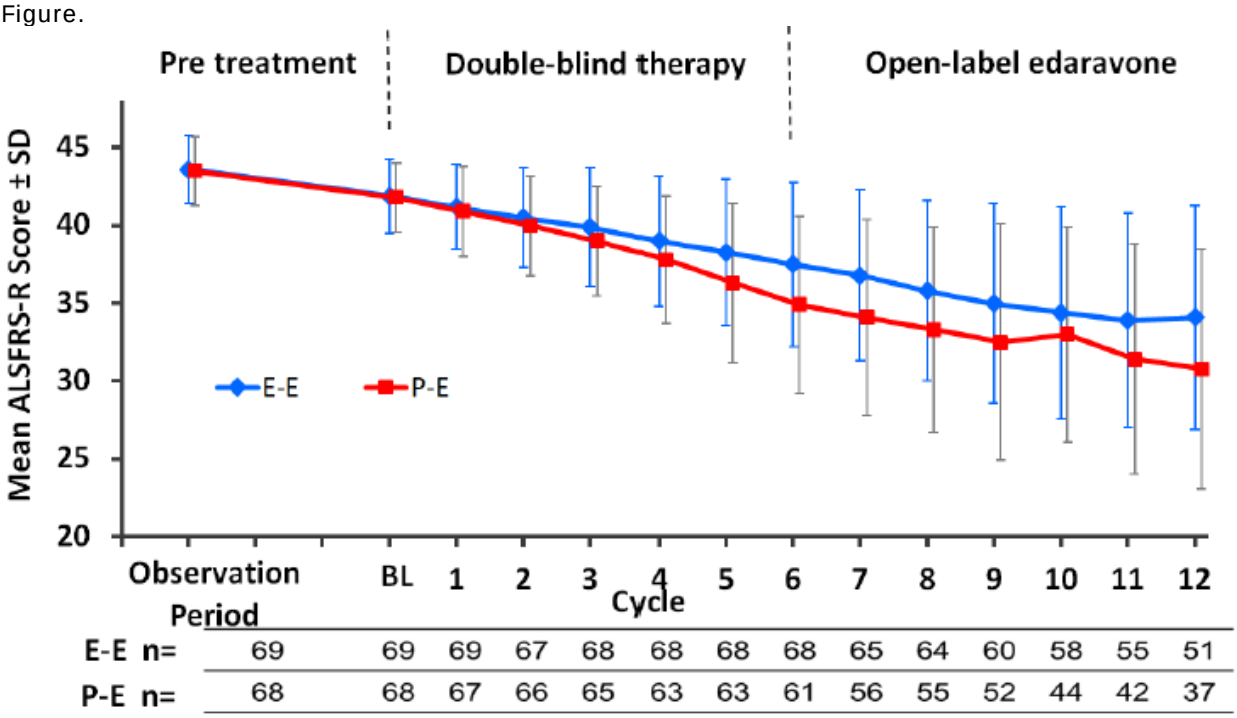


Figure 2.7.3-11: Change in ALSFRS-R Score (Mean ± SD) by Visit up to Cycle 12 (Study MCI186-19, FAS Observed Cases)

Population analysed: FAS in the double-blind period (Cycle 1 to Cycle 6); subjects who participated in the active treatment period (Cycle 7 to Cycle 12).
Abbreviations: E-E = edaravone-edaravone group, P-E = placebo-edaravone group.
Source: MCI186-19 CSR (modified). Takei K et al. 2017.

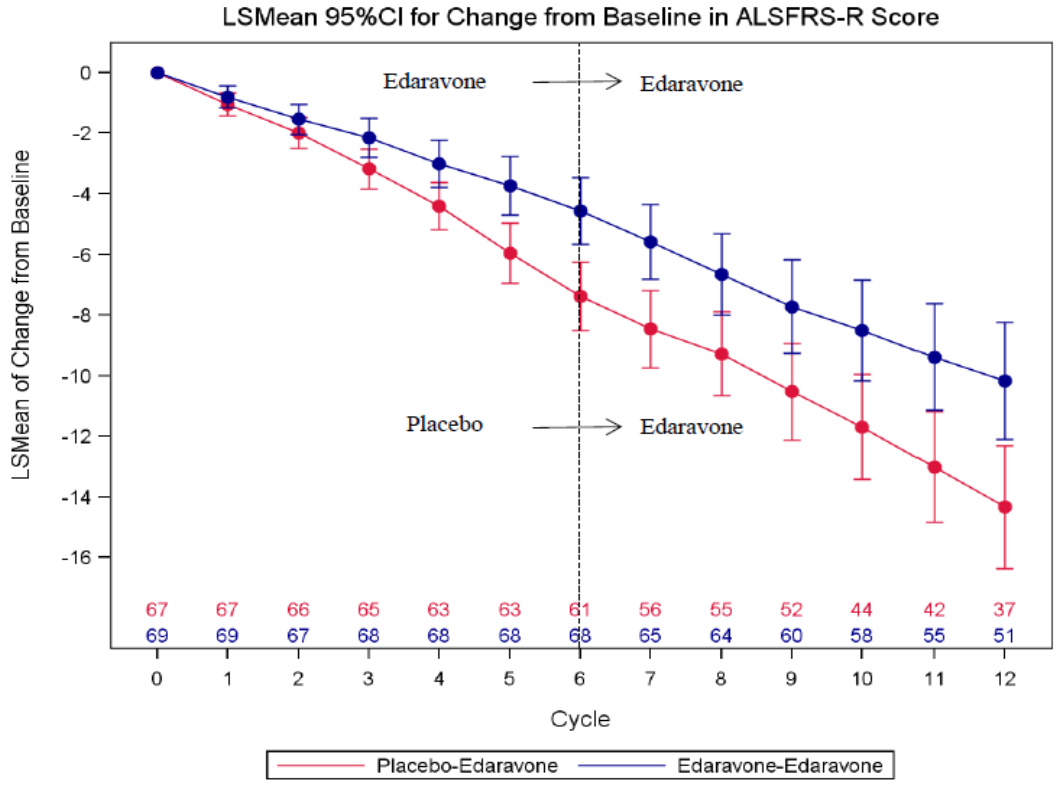
After the end of Cycle 6 in Study MCI186-19, edaravone was administered to subjects who agreed to continue the study in open-label fashion for an additional 6 cycles (24 weeks) up to Cycle 12.

Table 2.7.3-24: MMRM Analysis of ALSFRS-R Score from Baseline in Cycle 1 to the End of Cycle 12 (Study MCI186-19, FAS, Post-hoc)

Time	Treatment group	Number of subjects	Adjusted mean change from Baseline in Cycle 1[a]	Between-group difference in adjusted mean[a]	p-value[a]
			LS mean±SE	LS mean±SE (95%CI)	
End of Cycle 12	P-E group	67 (37)[a]	-14.33 ± 1.02	4.17 ± 1.40 (1.39, 6.95)	p=0.0037
	E-E group	69 (51)[a]	-10.16 ± 0.97		

For MMRM analysis, data from a subject who did not have the baseline ALSFRS-R value were excluded because MMRM required the Baseline value as a covariate for the analysis.
[a] Number of subjects included in MMRM analyses; at Baseline (at end of Cycle 12).
Source: ISE Table 3.5.2 in Module 5.3.5.3.

According to the Applicant, even after Cycle 6, when subjects in both groups received active treatment in open label fashion, the difference in ALSFRS-R score was maintained up to Cycle 12. The results from analysis of ALSFRS-R score in the full 12-month period, including the open-label extension, could be seen as providing support to the clinical benefit of edaravone reported in the 6-month randomised double blind phase of Study MCI186-19.



A dotted line is added to display the end of Cycle 6.
Source: ISE Figure 1.5.2 in Module 5.3.5.3.

Figure 2.7.3-13: LS Mean Changes (±SE) of ALSFRS-R Score to Cycle 12 Calculated by MMRM (Study MCI186-19, FAS)

The Kaplan-Meier curves for each item of the ALSFRS-R have been constructed. A consistent effect favouring edaravone was observed for each item of ALSFRS-R. Among these items, difference between placebo-edaravone and edaravone-edaravone were remarkably larger in Swallowing, Walking, Eating motion, and Climbing stairs. These complicated activities require more body parts and stronger muscle movement compared to Speech, Handwriting, or Walking.

Table 2.7.3-28 MMRM Analysis of %FVC, ALSAQ40 Score and Modified Norris Score (Total) From Baseline to 48 Weeks (Study MCI186-19 FAS, Post Hoc)

Endpoints	Time	Treatment group	Number of subjects	Adjusted mean change from Cycle 1 Baseline[a]	Between-group difference in adjusted mean[a]	p-value[a]
				LS mean±SE	LS mean±SE (95% CI)	
%FVC	End of Cycle 12	PE group	67 (36)	-40.12±3.72	11.88±5.05 (1.85, 21.91)	p=0.0207
		EE group	68 (50)	-28.24±3.52		
ALSAQ40 score	End of Cycle 12	PE group	61(37)	43.40±3.92	-10.71±4.51 (-19.66, -1.76)	p=0.0195
		EE group	68 (51)	32.69±3.54		
Modified Norris Score (Total)	End of Cycle 12	PE group	61 (37)	-36.98±2.97	10.28±3.71 (2.93 , 17.64)	p=0.0066
		EE group	68 (51)	-26.70±2.71		

Abbreviations: ALSAQ40=ALS assessment questionnaire-40 items; CI=confidence interval; E-E group=edaravone group in double-blind phase followed by edaravone group in active phase; FAS=full analysis set; FVC=forced vital capacity; LS=least squares; MMRM=mixed model repeated measures; P-E group=placebo group in double-blind phase followed by edaravone group in active phase; SE=standard error a Adjusted mean value and p-value from an MMRM with treatment group, time, treatment group-by-time interaction, change in ALSFRS-R score during the pre-observation period, El Escorial revised Airlie House diagnostic criteria, and age as fixed effects, and baseline value in Cycle 1 as the covariates. An unstructured covariance matrix.

A post-hoc analysis on the defined survival events conducted following 48 weeks edaravone treatment (see following Tables) confirmed a statistically significant difference between the groups, placebo/edaravone versus edaravone/edaravone (p=0.0193 - Log-rank test). Survival was defined as: Time to death or certain disease progression - death, disability of independent ambulation, loss of upper limbs function, tracheotomy, use of respirator, use of tube feeding, loss of useful speech. The results for death and certain disease progression, which were the prespecified events of functional termination, demonstrated that at the end of 48 weeks there were 19 patients with events in P-E group and 10 patients in E-E group,(p=0.0193 by log-rank test, p=0.0347 by generalized Wilcoxon test). Additionally, the Combined Assessment of Function and Survival (CAFS) endpoint included 4 deaths in the P-E group and 2 deaths in the E-E group, and showed a positive result by a treatment difference in CAFS rank score (32.51±12.24, p =0.0089).

Table 2.7.3-27: Number of Events for Death or Certain Signs of Disease Progression up to Cycle 12 (Study MCI186-19, FAS, Post-hoc)

Name of event	P-E group (N=68)	E-E group (N=69)
Death	2	1
Disability of independent ambulation	2	3
Loss of upper limb function	6	4
Tracheotomy	0	1
Use of respirator	0	0
Use of tube feeding	5	2
Loss of useful speech	5	4
Number of subjects with event[a]	19	10
Between-group comparison	p=0.0193 (log-rank test) p=0.0347 (generalised Wilcoxon test)	

Note: All events are counted for subjects with multiple events. a Includes death, disability of independent ambulation, loss of upper limb function, tracheotomy, use of respirator, use of tube feeding, and loss of useful speech. For subjects in whom multiple events occurred, the date when the first event occurred was used as the date of the survival event's onset. The date of censoring was the last observation day for each patient. Source: MCI186-19 CSR.

Table 2.7.3-26: Survival Analyses for Death or Certain Disease Progression up to Cycle 12 (Study MCI186-19)

Treatment group	Number of patients	Number of events[a]	Between-group comparison
P-E group	68	19	p = 0.0193 (log-rank test)
E-E group	69	10	p = 0.0347 (generalised Wilcoxon test)

a Death, disability of independent ambulation, loss of upper limbs function, tracheotomy, use of respirator, use of tube feeding, and loss of useful speech with respect to the patients in which multiple events occurred, the date when the first event occurred was used as the date of the event's onset. The date of censoring was the last observation day for each patient.
Abbreviations: E-E group = edaravone group in double-blind phase followed by edaravone group in active phase; FAS = full analysis set; P-E group = placebo group in double-blind phase followed by edaravone group in active phase. Source: MCI186-19 post-hoc analysis.

Japan ALS severity classification

A shift table (FAS) was prepared showing the changes in the Japan ALS severity classification from "baseline in Cycle 1" to "baseline in Cycle 7," to "the end of Cycle 12," and to "discontinuation" in the FAS in the active treatment period.

Table 11.4.1.2-15. Shifts in the Japan ALS severity classification (FAS) (Study MCI186-19 CSR)

Table 11.4.1.2-15 Shifts in the Japan ALS severity classification (FAS)

Treatment group	At baseline in Cycle 1	At baseline in Cycle 7							At the end of Cycle 12							At discontinuation						
		1	2	3	4	5	Missing data	Total	1	2	3	4	5	Missing data	Total	1	2	3	4	5	Missing data	Total
Placebo-Edaravone	1	5	6	3	1	0	0	15	2	4	3	2	1	3	15	0	1	0	1	1	12	15
	2	0	16	21	6	0	0	43	0	5	12	7	1	18	43	0	1	4	4	3	31	43
	Total	5	22	24	7	0	0	58	2	9	15	9	2	21	58	0	2	4	5	4	43	58
Edaravone-Edaravone	1	8	11	3	0	0	0	22	2	9	8	1	0	2	22	0	0	0	2	0	20	22
	2	0	16	18	9	0	0	43	0	8	16	6	1	12	43	0	1	2	2	1	37	43
	Total	8	27	21	9	0	0	65	2	17	24	7	1	14	65	0	1	2	4	1	57	65

At baseline in Cycle 7: Data at the end of Cycle 6 were used.
Population analyzed: FAS in the active treatment period

The Applicant provided the percentages of a subgroup of patients whose individual slopes of the ALSFRS-R were improved during the extension phase compared to the double blind phase. This subgroup of patients were classified as being in Japanese ALS Severity Grade 3, or greater, at the initiation of the extension phase of Study MCI186-19 (end of Cycle 6 onwards) ("Grade 3 progressors"). According to the Applicant and based on this post-hoc analysis, thirty patients in E-E group and 30 patients in P-E group were classified as being in Japanese ALS Severity Grade 3, or greater, at the initiation of extension study of Study MCI186-19. However, based on the MCI186-19 CSR baseline data, there were 22 patients with Grade 1 and 47 patients with Grade 2 Japan ALS severity classification in the edaravone group, indicating that 30 out of 69 patients (43.5%) progressed to Grade 3 severity while being on treatment with edaravone. It appears likely that 30 out of 47 (63.8%) of patients in Grade 2 progressed to Grade 3, while being on treatment with edaravone. The Applicant is requested to provide a comparative analysis on the Japanese ALS severity classification (including ALSFRS-R scores) of the patients in the different treatment groups at baseline and at the end of Cycles 6 and 12 in study MCI186-19 (including the ALSFRS-R scores) and discuss the deterioration.

Despite the observation of a substantial proportion of patients on edaravone deteriorating during the first 6 cycles, the Applicant found in a post-hoc analysis that, among patients classified as being in Japanese ALS Severity Grade 3 or greater at the initiation of the extension phase of Study MCI186-19 (end of Cycle 6 onwards), "*20 patients (66.7%) in P-E group showed an improvement (i.e. less decline) in the slope of their ALSFRS-R score after first being initiated on edaravone treatment during the extension phase (from the end of Cycle 6 to Cycle 12) compared to the double-blind phase (from baseline to Cycle 6)*". In the E-E group, 12 patients (40.0%) showed an improved slope of ALSFRS-R when the slope from the end of Cycle 6 through Cycle 12 was compared to the slope of Cycle 1 through Cycle 6. The Applicant presented this using a Bar graph. However, the results need to be presented as a line graph showing the progression of the ALSFRS-R score at all timepoints from baseline to end of Cycle 12.

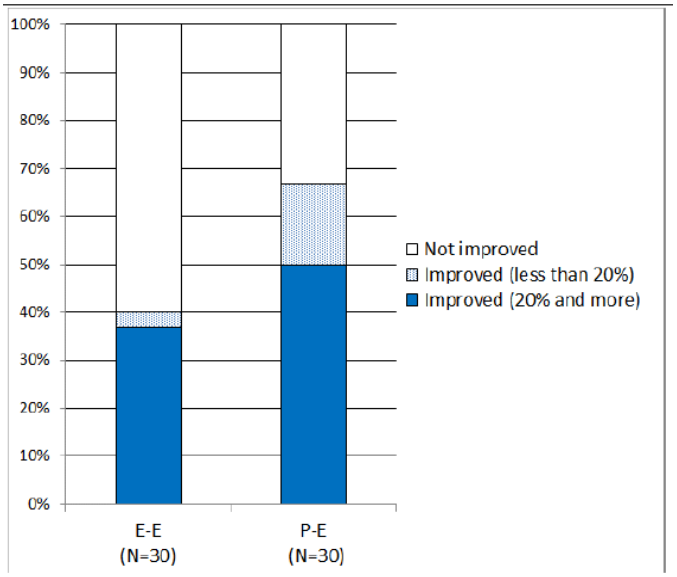


Figure 56-1: Percentages of Patients Whose Slopes of ALSFRS-R were Improved During the Extension Phase Compared to the Double-Blind Phase (Study MCI186-19 Full Analyses Set, Patients Diagnosed as ALS Severity 3 and Greater at the Initiation of Extension Phase)

Subpopulation Analyses in Study MCI186-19

Since Study MCI186-19 is the sole pivotal study prospectively designed with an enriched population, and because the number of subjects meeting Definite or Probable/EESP/2y criteria in Study MCI186-16 is limited, comparisons of change in ALSFRS-R scores by subpopulation are presented based on the results from Study MCI186-19. In Study MCI186-19, ALSFRS-R analyses of the following subpopulations were prospectively defined or requested by PMDA during the Japanese sNDA review (those additional requests by PMDA are marked with *).

- Gender (male versus female)
- Age (<65 years versus ≥65 years)
- Disease duration (<1 year versus ≥1 year)
- Initial symptom (bulbar versus limb)
- El Escorial revised Airlie House diagnostic criteria (definite versus probable)
- Japan ALS severity classification (Grade 1 versus Grade 2)
- Concomitant riluzole (without versus with)
- Comorbidity (without versus with)
- Change in ALSFRS-R score during the 12-week pre-observation period (-4/-3 versus -2/-1)
- Baseline ALSFRS-R score (<Median versus ≥Median)*
- Weight (<Median versus ≥Median)*
- Body mass index (BMI) (<Median versus ≥Median)*
- ALS diagnosis (Sporadic ALS versus Familiar ALS)*
- Baseline %FVC (<Median versus ≥Median).*

According to the Applicant, these analyses demonstrated that the effect of edaravone is consistent across subpopulations defined above and there is no subpopulation showing drastically inconsistent results between edaravone and placebo. Especially due to limited number of subjects (e.g., less than 10 subjects per group in Study MCI186-19), there were limitations of data in subjects without riluzole use, subjects without comorbidity, or familial ALS subjects. For reference, analyses for subpopulations in Definite or Probable/EESP/2y in Study MCI186-16, applying similar criteria as Study MCI186-19 FAS, are also presented in Table 2.7.3-37. With limitations due to smaller number of subjects in each subpopulation and also imbalance observed in the population defined post-hoc, conclusions could not be drawn from the subpopulation analyses in Definite or Probable/EESP/2y in Study MCI186-16. Since all the ALS studies with edaravone were conducted in Japan, there are no study data to directly compare efficacy between Japanese ALS patients and EU ALS patients. Therefore, expected results in the EU patients with ALS have been discussed by the Applicant in detail from viewpoints of PK, treatment practice guideline, actual demographics and treatment, and the course of ALS disease (i.e., ALSFRS-R score changes over time).

Table 2.7.3-37 (page 1) Subgroup Analyses of Changes in ALSFRS-R for 6 Cycles (Study MCI186-19 FAS and Study MCI186-16 Definite or Probable/EESP/2y)

			Study MCI186-19 FAS			Study MCI186-16 Definite or Probable/EESP/2y		
Category	**Subgroup**	**Treatment group**	**Number of subjects**	**Between-group differences in the adjusted mean[a]**		**Number of subjects**	**Between-group differences in the adjusted mean[b]**	
				LS mean ± SE	**95% CI**		**LS mean ± SE**	**95% CI**
Sex	Male	P group	39	2.54±1.06	(0.42, 4.66)	18	0.42±1.56	(-2.75, 3.58)
		E group	38			26		
	Female	P group	27	2.36±1.11	(0.14, 4.58)	11	5.97±2.10	(1.57, 10.36)
		E group	30			13		
Age (years)	< 65	P group	44	2.31±1.00	(0.33, 4.30)	22	2.24±1.30	(-0.36, 4.85)
		E group	46			33		
	≥ 65	P group	22	2.73±1.13	(0.46, 5.01)	7	6.72±5.27	(-5.44, 18.88)
		E group	22			6		
Body Weight[c] (kg)	< Median	P group	31	3.21±1.15	(0.90, 5.51)	14	3.98±1.99	(-0.12, 8.07)
		E group	34			17		
	≥ Median	P group	35	2.05±1.07	(-0.08, 4.18)	15	1.58±1.69	(-1.85, 5.02)
		E group	34			22		
BMI[c] (kg/m^2)	< Median	P group	32	2.97±1.15	(0.66, 5.28)	15	2.09±2.07	(-2.14, 6.32)
		E group	34			18		
	≥ Median	P group	34	2.28±1.05	(0.18, 4.38)	14	3.74±1.77	(0.13, 7.35)
		E group	34			21		
Duration of illness (years)	<1 year	P group	32	2.56±1.17	(0.22, 4.90)	15	4.86±2.41	(-0.12, 9.84)
		E group	27			13		
	≥1 year	P group	34	2.22±1.03	(0.17, 4.28)	14	1.30±1.29	(-1.32, 3.92)
		E group	41			26		
ALS Diagnosis	Sporadic	P group	64	2.41±0.76	(0.90, 3.92)	29	2.98±1.35	(0.28, 5.68)
		E group	67			38		
	Familial	P group	2	-	-	0	-	-
		E group	1			1		
Initial Symptom	Bulbar symptoms	P group	14	2.42±1.46	(-0.60, 5.43)	7	5.65±4.33	(-4.33, 15.63)
		E group	15			4		
	Limb symptoms	P group	52	2.44±0.89	(0.68, 4.21)	22	2.51±1.35	(-0.20, 5.23)
		E group	53			35		
El Escorial revised Airlie House Diagnostic Criteria	Definite ALS	P group	26	2.13±1.19	(-0.25, 4.51)	9	3.69±2.42	(-1.35, 8.73)
		E group	28			17		
	Probable ALS	P group	40	2.85±0.99	(0.88, 4.82)	20	2.08±1.58	(-1.12, 5.28)
		E group	40			22		

Table 2.7.3-37 (page 2) Subgroup Analyses of Changes in ALSFRS-R for 6 Cycles (Study MCI186-19 FAS and Study MCI186-16 Definite or Probable/EESP/2y)

Category	Subgroup	Treatment group	Study MCI186-19 FAS			Study MCI186-16 Definite or Probable/EESP/2y		
			Number of subjects	Between-group differences in the adjusted mean[a]		Number of subjects	Between-group differences in the adjusted mean[b]	
				LS mean±SE	95% CI		LS mean±SE	95% CI
Japan ALS Severity Classification	Grade 1	P group	16	**2.51±1.00**	(0.48, 4.55)	15	0.48±1.32	(-2.21, 3.17)
		E group	22			20		
	Grade 2	P group	50	2.14±0.93	(0.28, 3.99)	14	**7.48±1.87**	(3.64, 11.31)
		E group	46			19		
Comorbidity	Yes	P group	60	2.72±0.80	(1.13, 4.30)	26	3.33±1.44	(0.44, 6.22)
		E group	64			36		
	No	P group	6	1.25±0.87	(-0.87, 3.37)	3	2.33±1.89	(-21.63, 26.29)
		E group	4			3		
ALSFRS-R Score[c]	< Median	P group	27	1.38±1.33	(-1.30, 4.05)	9	**7.73±3.61**	(-0.07, 15.53)
		E group	27			9		
	≥ Median	P group	39	**2.98±0.87**	(1.24, 4.72)	20	1.23±1.19	(-1.16, 3.61)
		E group	41			30		
Pre-observation Period ALSFRS-R Score	-4, -3	P group	10	2.27±2.01	(-1.95, 6.50)	9	7.33±3.57	(-0.45, 15.11)
		E group	12			7		
	-2, -1	P group	56	2.65±0.82	(1.02, 4.28)	20	1.65±1.33	(-1.02, 4.33)
		E group	56			32		
%FVC[c]	< Median	P group	35	2.47±1.23	(0.01, 4.93)	12	6.15±2.75	(0.44, 11.86)
		E group	30			15		
	≥ Median	P group	31	1.98±0.94	(0.10, 3.87)	17	0.90±1.33	(-1.81, 3.60)
		E group	37			24		
Concomitant Riluzole	Yes	P group	61	2.39±0.81	(0.78, 3.99)	24	3.53±1.46	(0.60, 6.45)
		E group	62			36		
	No	P group	5	1.96±2.21	(-3.45, 7.36)	5	-1.75±1.77	(-6.29, 2.79)
		E group	6			3		

a Adjusted mean value and p-value from an analysis of variance model (ANOVA) with treatment group, change in ALSFRS-R score during the prestudy observation period, concomitant riluzole, and initial symptom as fixed effects. LOCF was applied to the subjects who completed Cycle 3 (subjects who reached 81 days after treatment in MCI186-16 Definite or Probable/EESP/2y).

b Adjusted mean value and p-value from an analysis of variance model (ANOVA) with treatment group, change in ALSFRS-R score during the prestudy observation period, El Escorial revised Airlie House diagnostic criteria and age as fixed effects. LOCF was applied to the subjects who completed Cycle 3 (subjects who reached 81 days after treatment in MCI186-19 FAS).

c At Baseline in Cycle 1.

Source: ISE Table 9.1-9.14 in Module 5.3.5.3.

Patients with ALS advanced disease

During the double-blind period of study MCI186-19, there was a subgroup of patients who progressed to Grade 3, either being on edaravone treatment or on placebo. A Table and a graphical representation with the individual ALSFRS-R scores (and %FVC values) (from baseline to end of Cycle 12) of these progressing patients should be provided. The changes in ALSFRS-R score and condition of patients having progressed to stage 3 during the double-blind phase needs to be discussed for both the edaravone-edaravone and the placebo-edaravone group, also in comparison to the results of the double-blind phase.

As in the case of Japanese ALS severity classification, similarly for the %FVC, when patients were recruited in study MCI186-19, part of the inclusion criteria was that they had to have a %FVC greater than 80%. Upon visual inspection of Figure 56-2 it appears that 12 patients had their %FVC value dropping to 50%, while these patients were continuously administered edaravone (E-E group). The exact number of these patients, the number of patients in the P-E group who had a significant decline in %FVC, their Japanese ALS severity classification, as well as their ALSFRS-R scores at baseline(s) and at the end of the two cycles need to be provided.

Subgroup analyses and BMI

In the case of study MCI186-16 there are noticeable differences in LS mean difference between placebo and edaravone in the changes of ALSFRS-R score for 6 cycles between subgroups e.g. in body weight for the <median subgroup the LS mean difference in ALSFRS-R score was 3.98±1.99, and 1.58±1.69 for the ≥median subgroup, whilst for the BMI the LS mean difference in ALSFRS-R score for the <median group was 2.09±2.07 and for the ≥median group it was 3.74±1.77. BMI subgroup analysis (<Median versus ≥Median BMI) for study MCI186-19 did not identify significant differences consistently. Between-group differences in the adjusted mean for ALSFRS-R were 2.97±1.15 for <Median BMI subgroup vs 2.28±1.05 for the ≥ Median BMI subgroup in study MCI186-19 (FAS) and 2.09±2.07 for <Median BMI subgroup vs 3.74±1.77 for the ≥ Median BMI subgroup in study MCI186-16 (Definite or probable/EESP/2y). However, it should be noted that the mean (SD) values in the demographic characteristics in the pivotal study MCI186-19 were in the low range of BMI, i.e. 21.8 (2.7) for placebo and 21.9 (3.6) for edaravone, but within the normal range (18.5-24.9) according to WHO criteria [Park et al 2015, WHO webpage].

The following Table summarises the BMI values (Mean and SD) of patients included during the clinical development program of edaravone.

Table E. BMI values of patients included in the Phase 3 clinical studies.

	Study MCI186•19 (FAS) (N=137)	**Study MCI186-16 (Definite or Probable /EESP/2y) (N=72)**	**Study MCI186-16 (EESP) (N=104)**	**Study MCI186-16 (FAS) (N=205)**
BMI, mean (SD) kg/m^2	21.9 (3.2)	21.9 (2.4)	22.2 (2.7)	21.9 (2.8)

	Study MCI186•17 EP+EE (definite or probable /EESP/2y) (N=38)	**Study MCI186-17 EP+EE (EESP) (N=52)**	**Study MCI186•17 EP+EE (FAS) (N=92)**	**Study MCI186-18 (FAS) (N=25)**
BMI, mean (SD) kg/m^2	22.05 (2.14)	22.17 (2.22)	21.90 (2.39)	20.40 (2.80)

Summary of main efficacy results

The following tables summarise the efficacy results from the main studies supporting the present application. These summaries should be read in conjunction with the discussion on clinical efficacy (see later sections).

Table A: Summary of efficacy for trial < **MCI186-16**>

Title: A double-blind, parallel-group, placebo-controlled, phase 3 confirmatory study of MCI-186 (edaravone) for the treatment of amyotrophic lateral sclerosis			
Study identifier	**MCI186-16**		
Design	A multicenter, placebo-controlled, double-blind, parallel-group comparative study [Confirmatory study in ALS grade 1 and 2]		
	Duration of main phase:		Approximately 2 years and 4 months Study initiation date: May 8, 2006 [date of conclusion of the initial clinical trial agreement with medical institution] Study completion date: September 9, 2008 [date of completion of observation (tests the end of Treatment cycle 6) in the last patient (excluding the follow-up of adverse events (AEs))]
	Duration of Run-in phase:		Pre-observation period: A 12-week pre-observation period before the start of Treatment cycle 1 was designed. Treatment cycle 1: The investigational product was administered for 14 consecutive days, followed by a 2-week drug free period. Treatment cycles 2 to 6: The investigational product was administered for a total of 10 days per 2 weeks, followed by a 2-week drug free period after the end of each Treatment cycle.
	Duration of Extension phase:		not applicable
Hypothesis	Superiority to placebo		
Treatments groups	Investigational product, Lot No. (Manufacturing No.): "Edaravone Injection 30 mg," RSV5A03		Edaravone at 60 mg or matched placebo (2 ampules per treatment) was diluted with an appropriate volume of saline before use, and was intravenously infused over 60 min once daily. 101 patients
	Placebo		A placebo injection whose appearance is indistinguishable from "Edaravone Injection 30 mg". 104 patients
Efficacy Endpoints and definitions	Primary endpoint	ALSFRS-R score	The ALSFRS-R was created and validated in the US to measure the degree of daily functional loss in patients with ALS. It is well accepted in the ALS expert community and has been used frequently in clinical trials and also clinical practice. The ALSFRS-R strongly correlates with both objective measures of disease status and level of disability. The Japanese version of the ALSFRS-R has also been validated and is feasible for clinical evaluation in ALS studies.

	Secondary endpoint	Time to death or certain disease progression (death, disability of independent ambulation, loss of upper limb function, tracheotomy, use of respirator, and use of tube feeding)	Time to death or time to certain aspects of terminal disease progress (e.g., ventilator dependence or tracheostomy) can be important and were relevant to the published clinical studies of riluzole in ALS. Death, disability of independent ambulation, loss of upper limb function, tracheotomy, use of respirator (except bilevel positive airway pressure), use of tube feeding, and loss of useful speech were analysed as discrete events. These events were assessed according to the protocols from Baseline to the End of Cycle 6 or 12 (or 2 weeks after the last dose when subjects discontinued the study).
	Secondary endpoint	domain-specific ALSFRS-R score	ALSFRS-R score data were analyzed by its domains (bulbar, limb and respiratory functions).
	Secondary endpoint	%FVC	Respiratory function is one of the most important individual items of measurement in ALS. The evaluation methods for respiratory function in ALS noted in the ALS treatment guidelines (2002), suggest decline of %FVC to 50% or less as a criterion to introduce respiratory support. Respiratory function was also reported as a predictive parameter in ALS of a very rapid decline in functionality and survival. Decreasing percentage represents worsening FVC.
	Secondary endpoint	Modified Norris Scale score	The Modified Norris Scale is a measure of movement disorder for patients with ALS. The Modified Norris Scale has been set as an efficacy endpoint in the 4 Phase 3 clinical studies to evaluate movement disorder associated with ALS. The validity of the Japanese version of the Modified Norris Scale has been confirmed. Decreasing score represents worsening function.
	Secondary endpoint	Amyotrophic Lateral Sclerosis Assessment Questionnaire (ALSAQ40) score	The ALSAQ40 score is a measure of QoL for patients with ALS and was an efficacy endpoint in the 4 Phase 3 clinical studies of edaravone. The ALSAQ40 evaluates domains that include physical mobility, ADL and independence, eating and drinking, communication, and emotional reactions. The validity of the Japanese version of the ALSAQ40 has been confirmed. Increasing score represents worsening QoL.
	Secondary endpoint	grip strength	Grip strength and pinch grip strength were set as an objective measurement to assess muscle weakness as muscle strength decreases in ALS patients as a result of motor neuron dysfunction.
	Secondary endpoint	pinch grip strength	
	Secondary endpoint	ALS severity classification	ALS severity classification as an efficacy endpoint, because this indicated the QOL of ALS patients in terms of the activities of daily living. Patients with severity grade 1 or 2 ALS were included.

Safety endpoints		AEs, adverse drug reactions (ADRs), serious adverse events (SAEs), serious adverse drug reactions (SADRs), laboratory tests (hematology and urinalysis), and sensory test	
Database lock	CRFs and database were locked on December 5, 2008, and the statistical analysis plan (final version) was fixed on December 11, 2008.		

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	Analysis sets were the Full Analysis Set (FAS), Per Protocol Set (PPS), and safety analysis set in the present study. For additional analysis, Efficacy Expected Sub-population (EESP) and definite or probable/EESP/2y were set and similar analysis was performed.

FAS	
Total	205
Placebo	104
Edaravone	101

PPS	
Total	195
Placebo	98
Edaravone	97

Safety analysis set	
Total	206
Placebo	104
Edaravone	102

Descriptive statistics and estimate variability	Treatment group	Edaravone	Placebo
	Number of subject	n=101	n=104
	ALSFRS-R score data (FAS) P=0.3476	35.3	35.1
	S.D.	7.1	7.4
	ALSFRS-R score data (EESP) P=0.0184	39.0	36.5
	S.D.	4.7	8.3
	Treatment group	Edaravone	Placebo
	Number of subject	n=101	n=104
	ALSFRS-R score (definite or probable/ EESP/2y) P=0.0184	38.4	34.7
	S.D.	5.1	8.9
	Primary endpoint: Adjusted mean change in ALSFRS-R score from baseline in Cycle 1 to the end of Cycle 6 (Adjusted mean, Least square [LS] mean)	-5.70	-6.35
	SE (Standard Error)	±0.85	±0.84

	Secondary endpoint: Time to death or certain disease progression (from baseline in Cycle 1 to the end of Cycle 6)	12 events	14 events
Effect estimate per comparison	Primary endpoint ALSFRS-R score data from baseline in Treatment cycle 1 to 2 weeks after the end of Treatment cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	0.65 ± 0.78
		(95% C.I.)	(–0.90, 2.19)
		P-value	P = 0.4108
	Primary endpoint ALSFRS-R score data from baseline in Treatment cycle 1 to the end of Treatment cycle 6 (LOCF) (EESP)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	2.20 ±1.03
		(95% C.I.)	(0.15 , 4.26)
		P-value	p=0.0360
	Primary endpoint ALSFRS-R score data from baseline in Treatment cycle 1 to the end of Treatment cycle 6 (LOCF) (definite or probable/ EESP/2y)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	3.01 ±1.33
		(95% C.I.)	(0.35 , 5.67)
		P-value	0.0270
	Primary endpoint **ALSFRS-R score data from baseline in Treatment cycle 1 to the end of Treatment cycle 6, placebo multiple imputation (PMI) (definite or probable/ EESP/2y)**	**Comparison groups**	**Edaravone vs Placebo**
		Between-group difference **LS Mean**	**3.35**
		(95% C.I.)	**(0.79 , 5.92)**
		P-value	**0.0104**
	Death or certain disease progression (FAS)	Comparison groups	Edaravone (29) vs Placebo (32) (ALSFRS-R score changes during pre-observation period, -4, -3)
		Number of events	12 vs 14
		P-value	0.3814
	Death or certain disease progression (FAS)	Comparison groups	Edaravone (72) vs Placebo (72) (ALSFRS-R score changes during pre-observation period, -2, -1)
		Number of events	20 vs 13
		P-value	0.3992
	ALSFRS-R score (bulbar function) from baseline in Treatment cycle 1 to the end of	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	–0.01 ± 0.24

	Treatment cycle 6 (LOCF) (FAS)	(95% C.I.)	(–0.48, 0.47)
		P-value	P = 0.9761
	ALSFRS-R score (limb function) from baseline in Treatment cycle 1 to the end of Treatment cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	–0.59 ± 0.51
		(95% C.I.)	(–0.42, 1.61)
		P-value	P = 0.2487
	ALSFRS-R score (respiratory function) from baseline in Treatment cycle 1 to the end of Treatment cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	0.06 ± 0.23
		(95% C.I.)	(–0.39, 0.50)
		P-value	P = 0.7950
	%FVC from baseline in Treatment cycle 1 to the end of Treatment cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	2.92 ± 2.24
		(95% C.I.)	(–1.49, 7.33)
		P-value	P = 0.1928
	Limb Norris Scale score from baseline in Treatment cycle 1 to the end of Treatment cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	1.86 ± 1.50
		(95% C.I.)	(-1.11, 4.82)
		P-value	P = 0.2178
	Norris Bulbar Scale score from baseline in Treatment cycle 1 to the end of Treatment cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	0.17 ± 0.66
		(95% C.I.)	(-1.13, 1.48)
		P-value	P = 0.7925
	Modified Norris Scale score from baseline in Treatment cycle 1 to after the end of Treatment cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	2.03 ± 1.89
		(95% C.I.)	(-1.69, 5.75)
		P-value	P = 0.2835
	ALSAQ40 score from baseline in Treatment cycle 1 to the end of Treatment cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	0.48 ± 3.50
		(95% C.I.)	(-6.44, 7.39)

<table>
<tr><td></td><td></td><td>P-value</td><td>P = 0.8921</td></tr>
<tr><td></td><td rowspan="4">Grip strength (mean of left and right) from baseline in
Treatment cycle 1 to the end of Treatment cycle 6 (LOCF) (FAS)</td><td>Comparison groups</td><td>Edaravone vs Placebo</td></tr>
<tr><td>Between-group difference
LS Mean ± S.E.</td><td>0.89 ± 0.64</td></tr>
<tr><td>(95% C.I.)</td><td>(-0.37, 2.16)</td></tr>
<tr><td>P-value</td><td>P = 0.1650</td></tr>
<tr><td></td><td rowspan="4">Pinch grip strength (mean of left and right) from baseline
in Treatment cycle 1 to the end of Treatment cycle 6 (LOCF) (FAS)</td><td>Comparison groups</td><td>Edaravone vs Placebo</td></tr>
<tr><td>Between-group difference
LS Mean ± S.E.</td><td>0.20 ± 0.14</td></tr>
<tr><td>(95% C.I.)</td><td>(-0.08, 0.48)</td></tr>
<tr><td>P-value</td><td>P = 0.1653</td></tr>
<tr><td>Notes</td><td colspan="3">For the above endpoints performed in FAS, analyses were performed for the Efficacy Expected Sub-population, EESP (n=104, placebo 50, edaravone 54) and for the definite or probable/EESP/2y (n=72, placebo 32, edaravone 40).
Table 10.1-2 Reasons for discontinuations (FAS)
<table>
<tr><td>Group</td><td colspan="2">Placebo</td><td colspan="2">Edaravone</td></tr>
<tr><td>n</td><td colspan="2">104</td><td colspan="2">101</td></tr>
<tr><td>Reason for discontinuation</td><td>n</td><td>(%)</td><td>n</td><td>(%)</td></tr>
<tr><td>1. The patient requested study discontinuation</td><td>5</td><td>(4.8)</td><td>5</td><td>(5.0)</td></tr>
<tr><td>2. The patient experienced an AE and it was assessed difficult to continue the study</td><td>6</td><td>(5.8)</td><td>3</td><td>(3.0)</td></tr>
<tr><td>3. The patient underwent tracheotomy due to worsening of the underlying condition</td><td>2</td><td>(1.9)</td><td>1</td><td>(1.0)</td></tr>
<tr><td>5. Protocol deviation was unavoidable and it was assessed difficult to continue the study</td><td>1</td><td>(1.0)</td><td>0</td><td>(0.0)</td></tr>
</table>
Protocol deviations were observed for 18 patients in the Edaravone group and for 22 patients in the placebo.</td></tr>
</table>

Analysis description	**Secondary analysis** Four secondary analyses on the FAS were performed: the analysis of changes from "baseline in Treatment cycle 1" to each time point by patient with the use of the covariates "ALSFRS-R score changes during the pre-observation period," "initial symptom" and "concomitant use of riluzole"; the analyses consisted of the simple regression analysis by patient and the analysis of covariance for the slope of changes with the use of the covariates "ALSFRS-R score changes during the pre-observation period," "initial symptom" and "concomitant use of riluzole"; the analyses using the mixed effects model with the intercept and slope of each group as fixed effects and the intercept and slope of each patient as random effects; and the analyses using the Kaplan-Meier method with the stratified Log-rank test and stratified generalized Wilcoxon test, in which outcome events and censored observations were defined according to decreases in the ALSFRS-R score, and patients were stratified by change in ALSFRS-R score during the prestudy pre-observation period. None of these analyses showed any significant difference between the edaravone and placebo groups. Post-hoc analyses (Adjusted mean [LS mean±SE] and Between-group difference in adjusted mean [LS mean±SE] [95% CI]) for: - EESP (Efficacy Expected SubPopulation) and - Definite or Probable/EESP/2y (for the primary analysis also for non-EESP and non-Definite or Probable/EESP/2y) Change in ALSFRS-R score from baseline in Cycle 1 to the end of Cycle 6 (LOCF): **EESP**: P -7.06±1.13 vs E -4.85±1.24; 2.20±1.03 (0.15, 4.26); P=0.0360 **Definite or Probable/EESP/2y**: P -7.59±1.34 vs E -4.58±1.55; 3.01±1.33 (0.35, 5.67); P=0.0270 **Non-EESP**: P -5.24±1.25 vs E -6.65±1.17; 1.42±1.16 (-3.73, 0.89); P=0.2251 **Non-Definite or Probable/EESP/2y**: P -5.54±1.08 vs E -6.11±1.03; -0.57±1.00 (-3.73, 0.89); P=0.5711

Table B: Summary of efficacy for trial < **MCI186-17**>

Title: A Double-Blind, Parallel-Group, Placebo-Controlled, Phase 3 Confirmatory Study of MCI-186 (Edaravone) for the Treatment of Amyotrophic Lateral Sclerosis (Extension Study)		
Study identifier	**MCI186-17**	
Design	A multicenter, placebo-controlled, double-blind, parallel-group comparative study [extension study]	
	Duration of main phase:	The investigational product was administered on a total of 10 days in 2 weeks, followed by a 2-week drug-free period. The combination of the treatment period and drug-free period was considered 1 cycle, and this was repeated for 9 cycles. The cycles of this study were counted consecutively beginning from the confirmatory study, with "Cycle 7" to "Cycle 15" considered the extension study. Total of 9 cycles, with each cycle consisting of a treatment period followed by a drug-free period. Treatment period: Treatment was given for a total of 10 days of each 2-week period. Drug-free period: An interval of 2 weeks after the treatment in each cycle.
		Cycles 7 to 12 (6 cycles) Edaravone group: 2 ampules of edaravone injection 30 mg administered once daily over 60 minutes by intravenous infusion Placebo group: 2 ampules of edaravone injection placebo administered once daily over 60 minutes by intravenous infusion Cycles 13 to 15 (3 cycles) All patients: 2 ampules of edaravone injection 30 mg administered once daily over 60 minutes by intravenous infusion
	Duration of Run-in phase:	not applicable
	Duration of Extension phase:	not applicable

Treatment period	

Confirmatory study	Registration for the extension study	Investigational product treatment period											
		Edaravone or placebo group								Edaravone			
Cycle 6		Cycle 7		Cycle 8		to		Cycle 12		Cycles 13 and 14		Cycle 15	
Treatment	Drug-free period	Treatment period	Drug-free period	Treatment period	Drug-free period	Treatment period	Drug-free period	Treatment period	Drug-free period	Treatment period	Drug-free period	Treatment period	Drug-free period
10 days (/14 days)	14 Days	10 days (/14 days)	14 Days	10 days (/14 days)	14 Days	10 days (/14 days)	14 Days	10 days (/14 days)	14 Days	10 days (/14 days)	14 Days	10 days (/14 days)	14 Days

Figure 9.4.1.2-1 Summary of treatment periods

Hypothesis	To examine efficacy and safety objectively, the study was conducted as a double-blind, parallel-group comparison.	
Treatments groups	Investigational product, Lot No. (Manufacturing No.): "Edaravone Injection 30 mg," Cycles 7 to 9: RSV6803, Cycles 10 to 12: RSV6805, Cycles 13 to 15: RSV7103, RSV8502	Edaravone at 60 mg or matched placebo (2 ampules per treatment) was diluted with an appropriate volume of saline before use, and was intravenously infused over 60 min once daily. Edaravone-edaravone 48 patients and Placebo-edaravone 88 patients
	Placebo	A placebo injection whose appearance is indistinguishable from "Edaravone Injection 30 mg". Edaravone-placebo 45 patients
Efficacy Endpoints and definitions	PLEASE SEE ABOVE STUDY MCI186-16	
Database lock	September 30, 2009	

Results and Analysis

Analysis description	**Primary Analysis**
Analysis population and time point description	As specified in the statistical analysis plan, efficacy analyses were performed in the efficacy analysis sets, the FAS, PPS and EESP, and also in non-EESP established for confirmation. Homogeneity between the groups was examined using Fisher's exact test. A two-sided significance level of 15% was used as the criterion.

FAS	
Total	180
Edaravone-placebo	44
Edaravone-edaravone	48
Placebo-edaravone	88

PPS	
Total	172
Edaravone-placebo	42
Edaravone-edaravone	46
Placebo-edaravone	84

Safety analysis set	
Total	181
Edaravone-placebo	45
Edaravone-edaravone	48
Placebo-edaravone	88

Descriptive statistics and estimate variability			
	Treatment group	Edaravone-Placebo	Edaravone-Edaravone
	Number of subject	n=41	n=45
	ALSFRS-R score data (FAS) P=0.2336	31.5	32.3
	S.D.	7.7	8.1
	Treatment group	Edaravone-Placebo	Edaravone-Edaravone
	Number of subject	n=41	n=45
	ALSFRS-R score data (EESP) P=0.1762	n=25 34.0	n=27 35.3
	S.D.	7.7	6.6
	Primary endpoint: Adjusted mean change in ALSFRS-R score from baseline in Cycle 7 to the end of Cycle 12 (Adjusted mean, Least square [LS] mean)	-5.58	-4.42

	SE (Standard Error)	±0.74	±0.69
	Secondary endpoints: Not significant except for Change in Modified Norris Scale score (limb function) from baseline in Cycle 7 to the end of Cycle 12 (LOCF)	-10.90	-7.37
	SE	±1.34	±1.27
Effect estimate per comparison	Primary endpoint ALSFRS-R score data from baseline in Cycle 7 to the end of Cycle 12 (LOCF) (FAS)	Comparison groups	Edaravone-placebo vs Edaravone-edaravone
		Between-group difference LS Mean ± S.E.	1.16 ± 0.93
		(95% C.I.)	(–0.70, 3.01)
		P-value	P = 0.2176
	Primary endpoint ALSFRS-R score data from baseline in Cycle 7 to the end of Cycle 12 (LOCF) (EESP)	Comparison groups	Edaravone-placebo vs Edaravone-edaravone
		Between-group difference LS Mean ± S.E.	1.85 ± 1.14
		(95% C.I.)	(-0.45 , 4.15)
		P-value	p=0.1127
	Analysis using the mean change in ALSFRS-R score across all cycles as a summary measure (FAS)	Comparison groups	Edaravone-placebo vs Edaravone-edaravone
		Between-group difference LS Mean ± S.E.	1.02 ± 0.59
		(95% C.I.)	(-0.16 , 2.20)
		P-value	0.0885
	Death or certain disease progression (FAS)	Comparison groups	Edaravone-placebo (11) vs Edaravone-edaravone (13) (ALSFRS-R score changes during pre-observation period, -4, -3)
		Number of events	4 vs 7
		P-value	0.1540
	Death or certain disease progression (FAS)	Comparison groups	Edaravone-placebo (33) vs Edaravone-edaravone (35) (ALSFRS-R score changes during pre-observation period, -2, -1)
		Number of events	7 vs 11
		P-value	0.0684
	ALSFRS-R score (bulbar function) from baseline in Cycle 7 to the end of Cycle 12 (LOCF) (FAS)	Comparison groups	Edaravone-Placebo vs Edaravone-Edaravone
		Between-group difference LS Mean ± S.E.	0.13 ± 0.29
		(95% C.I.)	(–0.45, 0.70)
		P-value	P = 0.6684
	ALSFRS-R score (limb function) from	Comparison groups	Edaravone-placebo vs Edaravone-edaravone

	baseline in Cycle 7 to the end of Cycle 12 (LOCF) (FAS)	Between-group difference LS Mean ± S.E.	1.02 ± 0.61
		(95% C.I.)	(–0.19, 2.24)
		P-value	P = 0.0973
	ALSFRS-R score (respiratory function) from baseline in Cycle 7 to the end of Cycle 12 (LOCF) (FAS)	Comparison groups	Edaravone-Placebo vs Edaravone-Edaravone
		Between-group difference LS Mean ± S.E.	0.01 ± 0.40
		(95% C.I.)	(–0.79, 0.81)
		P-value	P = 0.9801
	%FVC from baseline in Cycle 7 to the end of Cycle 12 (LOCF) (FAS)	Comparison groups	Edaravone-placebo vs Edaravone-edaravone
		Between-group difference LS Mean ± S.E.	-3.17 ± 3.09
		(95% C.I.)	(–9.32, 2.97)
		P-value	P = 0.3074
	Limb Norris Scale score from baseline in Cycle 7 to the end of Cycle 12 (LOCF) (FAS)	Comparison groups	Edaravone-Placebo vs Edaravone-Edaravone
		Between-group difference LS Mean ± S.E.	3.53 ± 1.72
		(95% C.I.)	(0.11, 6.94)
		P-value	P = 0.0430
	Norris Bulbar Scale score from baseline in Cycle 7 to the end of Cycle 12 (LOCF) (FAS)	Comparison groups	Edaravone-placebo vs Edaravone-edaravone
		Between-group difference LS Mean ± S.E.	-0.34 ± 0.91
		(95% C.I.)	(-2.15, 1.47)
		P-value	P = 0.7098
	Modified Norris Scale score from baseline in Cycle 7 to the end of Cycle 12 (LOCF) (FAS)	Comparison groups	Edaravone-Placebo vs Edaravone-Edaravone
		Between-group difference LS Mean ± S.E.	3.19 ± 2.26
		(95% C.I.)	(-1.32, 7.69)
		P-value	P = 0.1634
	ALSAQ40 score from baseline in Cycle 7 to the end of Cycle 12 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	-5.45 ± 3.89
		(95% C.I.)	(-13.19, 2.29)
		P-value	P = 0.1651
	Grip strength (mean of left and right hands) from baseline in Cycle 7 to the end of Cycle	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	0.38 ± 0.58

	12 (LOCF) (FAS)	(95% C.I.)	(-0.77, 1.52)
		P-value	P = 0.5173
	Pinch grip strength (mean of left and right) from baseline in Cycle 7 to the end of Cycle 12 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	0.01 ± 0.16
		(95% C.I.)	(-0.31, 0.33)
		P-value	P = 0.9419

Notes

For the above mentioned endpoints there was also a Repeated measurements analysis of variance. As described in "11.2 Demographic and Other Baseline Characteristics," (MCI-186-17 CSR) there were imbalances in sex, age and height. Therefore, adjusted analyses using these factors as additional covariates were performed in the FAS for the analyses (i) and (2). The analysis results remained unchanged before and after the adjustment.

Table 10.1-2 Detailed reasons for discontinuation (FAS)

Treatment group	Edaravone-placebo	Edaravone-edaravone	Placebo-edaravone
No. of patients	44	48	88
Reason for discontinuation	No. of patients (%)	No. of patients (%)	No. of patients (%)
1. The patient requested discontinuation.	4 (9.1)	2 (4.2)	5 (5.7)
2. The investigator (or subinvestigator) decided it difficult to continue the patient's participation in the study due to an adverse event.	2 (4.5)	3 (6.3)	2 (2.3)
3. Due to worsening of the primary disease, tracheotomoy was needed.	1 (2.3)	7 (14.6)	6 (6.8)
8. It turned out impossible to continue the study for the sake of patient's convenience.	0 (0.0)	0 (0.0)	1 (1.1)
9. The investigator (or subinvestigator) assessed it difficult to continue the study due to reasons other than the above.	0 (0.0)	2 (4.2)	2 (2.3)

Protocol deviations were observed for 15 patients in the Edaravone-placebo group, for 34 patients in the placebo-edaravone and for 18 patients in the edaravone-edaravone.

Analysis description (part 1)	**Secondary analysis** The score at each time point was compared between the groups in the FAS by a repeated measurements analysis of variance using treatment, time, and treatment-by-time interaction as factors and "baseline in Cycle 7" and "change in ALSFRS-R score during the pre-observation period" as covariates. There was no treatment-by-time interaction (P=0.4517), and the LS Mean ± SE in each group was 32.97±0.44 in the edaravone-placebo group and 33.98±0.43 in the edaravone-edaravone group. The LS Mean ± SE of the between-group difference was 1.01±0.57 with the 95% confidence interval of −0.12 to 2.14 (P=0.0788). The following 4 analyses in the FAS were performed: an analysis for the change from "baseline in Cycle 7" to each time point calculated for each patient using "change in ALSFRS-R score during the pre-observation period" as a covariate; an analysis for the slope of time-dependent change after a simple regression analysis for each patient using "change in ALSFRS-R score during the pre-observation period" as a covariate; an analysis using a mixed effect model with the intercept and slope of each group as fixed effects and the intercept and slope of each patient as random effects; and "a stratified log-rank test and a stratified generalized Wilcoxon test by constructing a Kaplan-Meier curve stratified by "change in ALSFRS-R score during the pre-observation period," where events and censored observations were defined based on decreases in ALSFRS-R score. In any of the analyses, the results showed no significant difference between the groups.
Analysis description (part 2)	Post-hoc analyses (Adjusted mean [LS mean±SE] and Between-group difference in adjusted mean [LS mean±SE] [95% CI]) for: - EESP (Efficacy Expected SubPopulation) - Definite or Probable/EESP/2y - non-EESP - non-Definite or Probable/EESP/2y) Change in ALSFRS-R score from baseline in Cycle 7 to the end of Cycle 12 (LOCF) **EESP**: EP -5,86±0.98 vs EE -4.01±0.86; 1.85±1.14 (-0.45, 4.15); p=0.1127 **Definite or Probable/EESP/2y**: EP -7.02±1.39 vs EE -4.22±1.04 2.79±1.51 (-0.26, 5.85); p=0.0719 **Non-EESP**: EP -5.66±1.17 vs EE -5.20±1.17; 0.46±1.61 (-2.83, 3.74); p=0.7790 **Non-Definite or Probable/EESP/2y**: EP -4.96±0.88 vs EE -4.83±0.95; 0.13±1.24 (-2.36, 2.62); P=0.9164 Change in ALSFRS-R score from baseline in Cycle 1 to the end of Cycle 12 (MMRM): **Definite or Probable/EESP/2y**: EP -14.26±1.81 vs EE -7.37±2.06; 6.89±2.71 (1.43, 12.35); p=0.0147

Table C: Summary of efficacy for trial < **MCI186-18**>

Title: A double-blind, parallel-group, placebo-controlled, exploratory study of MCI-186 (edaravone) for the treatment of amyotrophic lateral sclerosis (Japan ALS severity classification: Grade 3)		
Study identifier	**MCI186-18**	
Design	A multicenter, placebo-controlled, double-blind, parallel-group comparative study	
	Duration of main phase:	Treatment period: 14 consecutive days in Cycle 1. A total of 10 days per 2 weeks in Cycles 2 to 6. Drug-free period: 2 weeks after the end of each Treatment period.
	Duration of Run-in phase:	12 weeks before the start of Cycle 1 Pre-observation period: A 12-week observation period before the start of Cycle 1 was designed. Cycle 1: The study drug was administered for 14 consecutive days, followed by a 2-week drug-free period. Cycles 2 to 6: The study drug was administered for a total of 10 days per 2 weeks, followed by a 2-week drug-free period after the end of each cycle.
	Duration of Extension phase:	not applicable

Figure 9.4.1-1 outlines the treatment schedule.

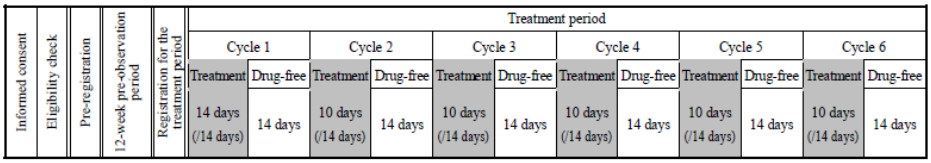


Figure 9.4.1-1 Outline of treatment schedule

Hypothesis	Superiority to placebo	
Treatments groups	Investigational product, Lot No. (Manufacturing No.): "Edaravone Injection 30 mg," RSV6804	Edaravone at 60 mg or matched placebo (2 ampules per treatment) was diluted with an appropriate volume of saline before use, and was intravenously infused over 60 min once daily. 13 patients
	Placebo	A placebo injection whose appearance is indistinguishable from "Edaravone Injection 30 mg". 12 patients
Efficacy Endpoints and definitions	PLEASE SEE ABOVE STUDY MCI186-16	
Database lock	October 17, 2008	

Results and Analysis

Analysis description	**Primary Analysis**		
Analysis population and time point description	Analysis sets were the Full Analysis Set (FAS), Per Protocol Set (PPS), and safety analysis set in the present study. For additional analysis, Efficacy Expected Sub-population (EESP) and definite or probable/EESP/2y were set and similar analysis was performed.		

FAS	
Total	25
Placebo	12
Edaravone	13

PPS	
Total	24
Placebo	12
Edaravone	12

Safety analysis set	
Total	25
Placebo	12
Edaravone	13

Descriptive statistics and estimate variability	Treatment group	Placebo	Edaravone
	Number of subject	n=12	n=13
	ALSFRS-R score data (FAS) P=0.8649	29.2	26.6
	S.D.	4.9	9.9
Effect estimate per comparison	Primary endpoint ALSFRS-R score data from baseline in Cycle 1 to the end Cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	-0.53 ± 2.46
		(95% C.I.)	(–5.62, 4.58)
		P-value	P = 0.8347
	Analysis using the summary measure of the mean changes in ALSFRS-R score throughout all cycles (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	0.04 ±1.01
		(95% C.I.)	(-2.06 , 2.14)
		P-value	p=0.9681

	Analysis using the summary measure of the slope of changes with time in ALSFRS-R score (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	-0.18 ± 0.40
		(95% C.I.)	(-1.02 , 0.66)
		P-value	0.6614
	Treatment group	Placebo	Edaravone
	Number of subject	n=12	n=13
	Death or certain disease progression (FAS)	Comparison groups	Placebo (4) vs Edaravone (4) (ALSFRS-R score changes during pre-observation period, -4, -3)
		Number of events	2 vs 2
		P-value	0.1058
	Death or certain disease progression (FAS)	Comparison groups	Placebo (8) vs Edaravone (9) (ALSFRS-R score changes during pre-observation period, -2, -1)
		Number of events	2 vs 1
		P-value	0.0782
	ALSFRS-R score (bulbar function) from baseline in Cycle 1 to the end Cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	–0.54 ± 0.92
		(95% C.I.)	(–2.46, 1.37)
		P-value	P = 0.5631
	ALSFRS-R score (limb function) from baseline in Cycle 1 to the end Cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	1.50 ± 1.06
		(95% C.I.)	(–0.69, 3.68)
		P-value	P = 0.1706
	ALSFRS-R score (respiratory function) from baseline in Cycle 1 to the end Cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	-1.47 ± 0.93
		(95% C.I.)	(–3.40, 0.45)
		P-value	P = 0.1274
	%FVC from baseline in Cycle 1 to the end Cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	-3.06 ± 6.28
		(95% C.I.)	(–16.12, 10.00)
		P-value	P = 0.6313
	Limb Norris Scale score from baseline in Cycle 1 to the end Cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	3.50 ± 3.31
		(95% C.I.)	(-3.38, 10.38)

		P-value	P = 0.3022
	Norris Bulbar Scale score from baseline in Cycle 1 to the end Cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		LS Mean ± S.E.	-3.92 ± 3.13
		(95% C.I.)	(-10.42, 2.59)
		P-value	P = 0.2242
	Modified Norris Scale score from baseline in Cycle 1 to the end Cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	-0.42 ± 5.22
		(95% C.I.)	(-11.27, 10.44)
		P-value	P = 0.9371
	ALSAQ40 score from baseline in Cycle 1 to the end Cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	-5.42 ± 7.49
		(95% C.I.)	(-21.05, 10.20)
		P-value	P = 0.4773
	Grip strength (mean of left and right) from baseline in Cycle 1 to the end Cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	0.66 ± 1.77
		(95% C.I.)	(-3.00, 4.33)
		P-value	P = 0.7117
	Pinch grip strength (mean of left and right) from baseline in Treatment cycle 1 to the end of Treatment cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	-0.23 ± 0.33
		(95% C.I.)	(-0.91, 0.45)
		P-value	P = 0.4929
Analysis description (part 1)	**Secondary analysis** Data were analyzed for the efficacy of edaravone in the primary analysis set FAS (13 patients in the edaravone group and 12 patients in the placebo group). Only results in the FAS are described below. Differences in the ALSFRS-R score between “baseline in Cycle 1” and “the end of Cycle 6 or at discontinuation (LOCF)” were analyzed with the use of the covariate “ALSFRS-R score changes during the pre-observation period” for comparison between the 2 groups. The LS Mean ± S.E. was –6.52 ± 1.78 points in the edaravone group and –6.00 ± 1.83 points in the placebo group. The LS Mean ± S.E. (95% C.I.) of between-group differences was –0.52 ± 2.46 points (–5.62 to 4.58 points). For the score by time point, the repeated measures analysis of variance was performed using factors of treatment, time, and the treatment×time interaction, and the covariates “baseline in Cycle 1” and “ALSFRS-R score changes during the pre-observation period” for comparison between the 2 groups. There was no interaction between treatment group×time point (P = 0.4850). The LS Mean ± S.E. was 30.32 ± 0.78 points in the edaravone group and 30.39 ± 0.78 points in the placebo group. The LS Mean ± S.E. (95% C.I.) of between-group differences was –0.08 ± 1.08 points (–2.32 to 2.17 points).		

Analysis description (part 2)	In the analysis using the summary measure of the mean of changes from "baseline in Cycle 1" to each time point by patient and the covariate "ALSFRS-R score changes during the pre-observation period", the LS Mean ± S.E. of differences throughout all cycles was –3.15 ± 0.73 in the edaravone group and –3.20 ± 0.75 in the placebo group. The LS Mean ± S.E. (95% C.I.) of between-group differences was 0.04 ± 1.01 points (–2.06 to 2.14 points). In the analysis where the simple regression analysis was performed by patients to calculate the summary measure of the slope of changes with time, and the analysis of covariance was performed with the use of the covariate "ALSFRS-R score changes during the pre-observation period", the LS Mean ± S.E. of the slope was –1.14 ± 0.29 points in the edaravone group and –0.96 ± 0.30 points in the placebo group. The LS Mean ± S.E. (95% C.I.) of between-group differences was –0.18 ± 0.40 points (–1.02 to 0.66 points). In the mixed effects model analysis with the intercept and slope of each group as fixed effects and the intercept and slope of each patient as random effects, the LS Mean ± S.E. of the slope was –1.04 ± 0.35 points in the edaravone group and –0.87 ± 0.15 points in the placebo group. The LS Mean ± S.E. (95% C.I.) of between-group differences was –0.16 ± 0.38 points (–0.91 to 0.58 points).

Table D: Summary of efficacy for trial < **MCI186-19**>

Title: A Phase 3, Double-blind, Parallel-group Study of Edaravone (MCI-186) for Treatment of Amyotrophic Lateral Sclerosis (Second Confirmatory Study)		
Study identifier	**MCI186-19**	
Design	A multicenter, placebo-controlled, double-blind, parallel-group comparative study	
	Duration of main phase:	Approximately 2 years and 9 months Study initiation date: November 28, 2011 (date of first patient enrolment) Study completion date: September 3, 2014 (date of last patient observation [not including the follow-up for adverse events])
	Duration of Run-in phase:	Pre-observation period: A 12-week pre-observation period was set prior to the start of Cycle 1. Cycle 1: Treatment was given for 14 consecutive days, followed by a drug-free period of 2 weeks. Cycles 2 to 12: Treatment was given for a total of 10 days per 2 weeks, followed by a drug-free period of 2 weeks- Cycles 1 to 6: edaravone at 60 mg/day, placebo
	Duration of Extension phase:	not applicable
Hypothesis	Superiority to placebo	
Treatments groups	Investigational product, Lot No. (Manufacturing No.): "Edaravone Injection 30 mg," 110097	Edaravone at 60 mg or matched placebo (2 ampules per treatment) was diluted with an appropriate volume of saline before use, and was intravenously infused over 60 min once daily. 67 patients
	Placebo	A placebo injection whose appearance is indistinguishable from "Edaravone Injection 30 mg". 60 patients
Efficacy Endpoints and definitions	PLEASE SEE ABOVE STUDY MCI186-16	
Database lock	June 10, 2014 for the double-blind period; November 10, 2014 for the entire period including the active period (extension)	
Results and Analysis		

<table>
<tr><td>Analysis description</td><td colspan="3">Primary Analysis</td></tr>
<tr><td>Analysis population and time point description</td><td colspan="3">Analysis sets were the Full Analysis Set (FAS), Per Protocol Set (PPS), and safety analysis set in the present study. For additional analysis, Efficacy Expected Sub-population (EESP) and definite or probable/EESP/2y were set and similar analysis was performed.
<table>
<tr><td colspan="2">FAS</td></tr>
<tr><td>Total</td><td>205</td></tr>
<tr><td>Placebo</td><td>104</td></tr>
<tr><td>Edaravone</td><td>101</td></tr>
</table>
<table>
<tr><td colspan="2">PPS</td></tr>
<tr><td>Total</td><td>195</td></tr>
<tr><td>Placebo</td><td>98</td></tr>
<tr><td>Edaravone</td><td>97</td></tr>
</table>
<table>
<tr><td colspan="2">Safety analysis set</td></tr>
<tr><td>Total</td><td>206</td></tr>
<tr><td>Placebo</td><td>104</td></tr>
<tr><td>Edaravone</td><td>102</td></tr>
</table></td></tr>
<tr><td rowspan="8">Descriptive statistics and estimate variability</td><td>Treatment group</td><td>Edaravone</td><td>Placebo</td></tr>
<tr><td>Number of subject</td><td>n=68</td><td>n=66</td></tr>
<tr><td>ALSFRS-R score data (FAS)
P=0.0016</td><td>37.5</td><td>35.0</td></tr>
<tr><td>S.D.</td><td>5.3</td><td>5.6</td></tr>
<tr><td>Primary endpoint: Adjusted mean change in ALSFRS-R score from baseline in Cycle 1 to the end of Cycle 6 (Adjusted mean, Least square [LS] mean)</td><td>-5.01</td><td>-7.50</td></tr>
<tr><td>SE (Standard Error)</td><td>±0.64</td><td>±0.66</td></tr>
<tr><td>Secondary endpoint: Time to death or certain disease progression (from baseline in Cycle 1 to the end of Cycle 6)</td><td>2 events</td><td>6 events

p=0.1284 [log-rank test], p=0.1415 [generalized Wilcoxon test]</td></tr>
<tr><td>Variability statistic</td><td>NA</td><td>NA</td></tr>
<tr><td rowspan="11">Effect estimate per comparison</td><td rowspan="4">Primary endpoint
ALSFRS-R score data from baseline in Cycle 1 to the end of Cycle 6 (LOCF) (FAS)</td><td>Comparison groups</td><td>Edaravone vs Placebo</td></tr>
<tr><td>Between-group difference
LS Mean ± S.E.</td><td>2.49 ± 0.76</td></tr>
<tr><td>(95% C.I.)</td><td>(0.99, 3.98)</td></tr>
<tr><td>P-value</td><td>P = 0.0013</td></tr>
<tr><td rowspan="4">Primary endpoint
ALSFRS-R score data from baseline in Cycle 1 to the end of Cycle 6, Placebo multiple imputation (PMI) (FAS)</td><td>Comparison groups</td><td>Edaravone vs Placebo</td></tr>
<tr><td>Between-group difference
LS Mean</td><td>2.87</td></tr>
<tr><td>(95% C.I.)</td><td>(1.32, 4.43)</td></tr>
<tr><td>P-value</td><td>P = 0.0003</td></tr>
<tr><td rowspan="2">Death or certain disease progression (FAS)
Decrease of ≥6 points from baseline</td><td>Comparison groups</td><td>Edaravone (12) vs Placebo (11)
(ALSFRS-R score changes during pre-observation period, -4, -3)</td></tr>
<tr><td>Number of events</td><td>6 vs 7</td></tr>
</table>

	in Cycle 1	P-value	0.0338
	Death or certain disease progression (FAS) Decrease of ≥6 points from baseline in Cycle 1	Comparison groups	Edaravone (57) vs Placebo (57) (ALSFRS-R score changes during pre-observation period, -2, -1)
		Number of events	17 vs 26
		P-value	0.0180
	Death or certain disease progression (FAS) Decrease of ≥12 points from baseline in Cycle 1	Comparison groups	Edaravone (12) vs Placebo (11) (ALSFRS-R score changes during pre-observation period, -4, -3)
		Number of events	2 vs 3
		P-value	0.0261
	Death or certain disease progression (FAS) Decrease of ≥12 points from baseline in Cycle 1	Comparison groups	Edaravone (57) vs Placebo (57) (ALSFRS-R score changes during pre-observation period, -2, -1)
		Number of events	3 vs 10
		P-value	0.0208
	Analysis of change in ALSFRS-R score between baseline in Cycle 1 and the end of Cycle 6 (imputed with values predicted from regression line) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	2.67 ± 0.80
		(95% C.I.)	(1.09, 4.25)
		P-value	P = 0.0011
	ALSFRS-R score (bulbar function) from baseline in Cycle 1 to the end of Cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	–0.58 ± 0.29
		(95% C.I.)	(0.01, 1.15)
		P-value	P = 0.0448
	ALSFRS-R score (limb function) from baseline in cycle 1 to the end of cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	1.61 ± 0.61
		(95% C.I.)	(0.42, 2.81)
		P-value	P = 0.0087
	ALSFRS-R score (respiratory function) from baseline in cycle 1 to the end of cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	0.29 ± 0.15
		(95% C.I.)	(–0.01, 0.60)
		P-value	P = 0.0593
	%FVC from baseline in cycle 1 to the end of cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	4.78 ± 2.84
		(95% C.I.)	(–0.83, 10.40)
		P-value	P = 0.0942

	Limb Norris Scale score from baseline in cycle 1 to the end of cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	3.44 ± 1.92
		(95% C.I.)	(-0.36, 7.24)
		P-value	P = 0.0757
	Norris Bulbar Scale score from baseline in Treatment cycle 1 to the end of Treatment cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	1.46 ± 0.90
		(95% C.I.)	(-0.33, 3.24)
		P-value	P = 0.1092
	Modified Norris Scale score from baseline in cycle 1 to after the end of cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	4.89 ± 2.35
		(95% C.I.)	(0.24, 9.54)
		P-value	P = 0.0393
	ALSAQ40 score from baseline in cycle 1 to the end of cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	-8.79 ± 4.03
		(95% C.I.)	(-16.76, -0.82)
		P-value	P = 0.0309
	Grip strength (mean of left and right hands) from baseline in cycle 1 to the end of cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	0.11 ± 0.64
		(95% C.I.)	(-1.15, 1.38)
		P-value	P = 0.8583
	Pinch grip strength (mean of left and right hands) from baseline in cycle 1 to the end of cycle 6 (LOCF) (FAS)	Comparison groups	Edaravone vs Placebo
		Between-group difference LS Mean ± S.E.	0.10 ± 0.16
		(95% C.I.)	(-0.23, 0.42)
		P-value	P = 0.5478

Notes

Table 10.1.1-3 Detailed reasons for discontinuation (FAS)

Group	Placebo	Edaravone
No. of patients	68	69
Reasons for discontinuation	No. of patients (%)	No. of patients (%)
1: The patient requested discontinuation.	2 (2.9)	0 (0.0)
3: The investigator (or subinvestigator) decided it difficult to continue the patient's participation in the study due to an adverse event, etc.	2 (2.9)	0 (0.0)
4: Tracheotomy was needed.	1 (1.5)	1 (1.4)
5: Respiratory support was needed all day long.	1 (1.5)	0 (0.0)
8: The patient showed %FVC of ≤50% and PaCO2 (blood gas) of ≥45 mmHg.	1 (1.5)	1 (1.4)
10: Other cases where the investigator (or subinvestigator) decided that the patient's participation in the study should be terminated.	1 (1.5)	0 (0.0)

Population analyzed: FAS in the double-blind period

Protocol deviations were observed for 21 patients in the Edaravone group and for 17 patients in the placebo.

Analysis description (part 1)

Secondary analysis

(1) For the ALSFRS-R score during each period, a repeated measurements analysis of variance was performed using treatment, time, and treatment-by-time interaction as factors and the score at "baseline in Cycle 1" and the 3 factors used in dynamic allocation as covariates. The groups were compared, and the results are shown in Table 11.4.1.1-3. A compound symmetry structure was used for the covariance matrix.

With a significance level of 15%, treatment-by-time interaction was significant (P<0.0001). Consequently, the evaluation was performed using the end of Cycle 6 as the primary evaluation time point. The LS Mean ± SE in the examination of adjusted mean by time point at the end of Cycle 6 was 37.20±0.42 in the edaravone group and 34.61±0.44 in the placebo group. Thus, the LS Mean in the difference between the treatment groups and the 95% confidence interval of the difference was 2.59±0.52 (1.57 to 3.62), results that were similar to those of primary analysis (Table 11.4.1.1-2).

(2) The mean change in the score from "baseline in Cycle 1" to the various time points was calculated for each patient as a summary measure and analyzed using the 3 factors used in dynamic allocation as covariates. The groups were compared, and the results (FAS) are shown in Table 11.4.1.1-4.

Analysis description (part 2)	(3) The slope of time-dependent change was calculated as a summary measure by performing a single regression analysis for each patient and analyzed using the 3 factors used in dynamic allocation as covariates. The groups were compared, and the results (FAS) are shown in Table 11.4.1.1-5. (4) The results of an analysis (FAS) using a mixed-effects model with the intercept and slope for each treatment group as fixed effects and the intercept and slope for each patient as random effects are shown in Table 11.4.1.1-6. An unstructured covariance matrix was used. (5) A Kaplan-Meier curve was constructed using the "change in ALSFRS-R score during the pre-observation period" as the stratification factor, for which a decrease in the ALSFRS-R score of ≥6 points as compared with baseline in Cycle 1 was defined as an event and the absence of a decrease of ≥6 points was defined as a censored value, and a stratified log-rank test and stratified generalized Wilcoxon test were performed. The censoring date for patients who completed the double-blind period without an event was the end of Cycle 6. The censoring date for patients who discontinued from study was the date when the last observation was performed. A similar analysis was performed with an event defined as a decrease of ≥12 points. The results (FAS) are shown in Fig. 11.4.1.1-2 and Table 11.4.1.1-7. The number of events, in the case where an event was defined as "a decrease of ≥6 points," was determined to be 23 in the edaravone group and 33 in the placebo group, and the difference between the groups was significant (P=0.0338 [stratified log-rank test], P=0.0180 [stratified generalized Wilcoxon test]). The number of events when defined as "a decrease of ≥12 points" was 5 in the edaravone group and 13 in the placebo group, and the difference between the groups was significant (P=0.0261 [stratified log-rank test], P=0.0208 [stratified generalized Wilcoxon test]). (6) The following analyses were performed as sensitivity analyses to determine the robustness of the results of analyses of the ALSFRS-R score, the primary endpoint. 1) Sensitivity analysis for the primary analysis 2) Sensitivity analysis for changes in levels of dynamic allocation factors 3) Sensitivity analysis for the secondary analysis (repeated measurements analysis of variance) Repeated measurement analysis of variance for ALSFRS-R score Adjusted mean (LS mean±SE): P 37.85±0.39 vs E 39.12±0.38 Between-group difference in adjusted mean (LS mean±SE) (95% CI): 1.27±0.44 (0.40, 2.14), P-value 0.0044 Analysis of change in ALSFRS-R score between baseline in Cycle 1 and the end of Cycle 6 (imputed with values predicted from regression line) Adjusted mean (LS mean±SE): P -8.01±0.69 vs E -5.34±0.68 Between-group difference in adjusted mean (LS mean±SE) (95% CI): 2.67±0.80 (1.09, 4.25), P-value 0.0011

Analysis performed across trials (pooled analyses and meta-analysis)

As an exploratory post-hoc analysis for ALSFRS-R, %FVC, ALSAQ40, Modified Norris Score (Total), and Death and Certain Disease Progression results in PE group and EE group consisting of subjects who entered Study MCI186-17 were compared (similar to the comparison of P-E group and E-E group in Study MCI186-19 extension). The statistical results of MMRM in Definite or Probable/EESP/2y populations are shown in Table 2.7.3-12. In line with Study MCI186-16 results in Definite or Probable/EESP/2y, EE group showed favouring trend compared to PE group while the number of subjects were limited.

Table 2.7.3-12: Differences in ALSFRS-R between Baseline in Cycle 1 and the End of Cycle 12 (MMRM) for Study MCI186-16/-17 combined (Definite or Probable/EESP/2y, Post-hoc)

Treatment group	Number of subjects	Adjusted mean change from Cycle 1 Baseline	Between-group difference in adjusted mean	
		LS mean±SE	LS mean±SE (95% CI)	p-value
PE group	29 (25)[a]	-14.26±1.81	6.89±2.71 (1.43, 12.35)	p=0.0147
EE group	22 (21)[a]	-7.37±2.06		

For MMRM analysis, data from subject who entered Study MCI186-17 were included. a Number of subjects included in MMRM analyses; at Baseline (at end of Cycle 12). Source: ISE Table 3.3.3 in Module 5.3.5.3.

Study MCI186-19 was designed prospectively to replicate these results of the MCI186-16 post-hoc by establishing inclusion/exclusion criteria in MCI186-19 FAS set based on the Definite or Probable/EESP/2y criteria in Study MCI186-16. A comparison of treatment differences in change from Baseline in ALSFRS-R scores in Study MCI186-16 ("Definite or Probable/EESP/2y") post-hoc and the prespecified Study MCI186-19 (FAS) populations is shown in Table 2.7.3-31. Least-squares mean differences between the groups are consistent between the 2 studies and between the 2 types of analyses (ALL LOCF and MMRM), showing a consistent short term treatment effect of edaravone between Study MCI186-19 FAS and MCI186-16 Definite or Probable/EESP/2y.

Table 2.7.3-31: Analyses of the Difference in ALSFRS-R Score for Studies MCI186-16 (Definite or Probable/EESP/2y, Post-hoc) and MCI186-19 (FAS, Post-hoc)

Study Number (population)	Group	Change from Baseline in Cycle 1 to the end of Cycle 6 ALL LOCF			Change from Baseline in Cycle 1 to the end of Cycle 6 MMRM		
		No. of subjects	LS mean±SE (95% CI)	p-value	No. of subjects	LS mean±SE (95% CI)	p-value
MCI186-16 (Definite or Probable/EESP/2y	P group	32	3.11± 1.27 (0.57, 5.65)	p= 0.0170	31 (29)[a]	3.44±1.29 (0.86, 6.02)	p=0.0097
	E group	40			40 (38)[a]		
MCI186-19 (FAS)	P group	68	2.37±0.75 (0.89, 3.84)	p= 0.0019	67 (61)[a]	2.81 ±0.78 (1.27, 4.35)	p=0.0004
	E group	69			69 (68)[a]		

a Number of subjects included in MMRM analyses; at Baseline (at end of Cycle 6).
Source: ISE Table 3.1.3 and 3.5.1 in Module 5.3.5.3.

The combined results from studies MCI186-16 and MCI186-19 demonstrate a favourable trend for edaravone at 6 months of treatment. The results were statistically significant in favour of edaravone in the "Definite or Probable/EESP/2y" population of study MCI186-16 and in the FAS population of study MCI186-19 (which included less advanced patients, characterised as Grade 1 or 2 by the Japan ALS severity classification). A post-hoc analysis using MMRM showed statistically significant results with respect to the change from baseline in ALSFRS-R score between edaravone and placebo. Least-squares mean differences between the groups are consistent between the 2 studies and between the 2 types of analyses (ALL LOCF, which included and data from patients who discontinued before Cycle 3 and MMRM), showing a consistent treatment effect of edaravone in the two confirmatory phase 3 studies MCI186-19 and MCI186-16. The issues with the enriched/restricted population have already been discussed above.

In addition, study MCI186-17 displayed a positive trend in favour of edaravone (not statistically significant) and it appeared that the treatment effect from study MCI186-16 was maintained. However, patients who were randomised from placebo in study MCI186-16 and then received edaravone did not show the same level of improvement (did not catch up) in comparison to the EE group. This can hint that the earlier the patients start treatment with edaravone the greater the improvement indicating disease modifying properties. However, this was not statistically significant in the included broad population and definite conclusions cannot be drawn.

Placebo multiple imputation (PMI) analyses of the primary endpoint were performed upon request and the results of these primary endpoint analyses in Study MCI186-19 Full Analysis Set (FAS) and MCI186-16 Definite or Probable/EESP/2y (dpEESP2y), were confirmed as statistically significant. The change from baseline in Cycle 1 to the end of Cycle 6 in ALSFRS-R Score for the edaravone group showed statistical significance when compared to placebo, with a larger treatment difference observed for the edaravone group (least squares mean difference [LSMD]=3.35, p=0.0104 in MCI186-16 dpEESP2y; and LSMD=2.87, p=0.0003 in MCI186-19 FAS).

Table 85-1: Analysis of Primary Endpoint (ALSFRS-R Score) of Change from Baseline in Cycle 1 to the End of Cycle 6 (Placebo Multiple Imputation) (Study MCI186-16 dpEESP2y, Study MCI186-19 FAS)

	MCI186-16 (dpEESP2y)			MCI186-19 (FAS)		
Group	No. of subjects	LS mean ±SE	LSMD (95% CI) p-value	No. of subjects	LS mean ±SE	LSMD (95% CI) p-value
P group	32	-6.97±1.01	3.35 (0.79, 5.92) p=0.0104	68	-7.45±0.58	2.87 (1.32, 4.43) p=0.0003
E group	40	-3.62±0.91		69	-4.58±0.56	

LS = Least Squares; LSMD=Least Squares Mean Difference.

Clinical studies in special populations

There were no dedicated studies performed in special populations i.e. elderly subjects. In Study MCI186-17, an imbalance was noted in age as the EE group included more elderly subjects than the EP group (39.6% versus 15.9%). (Table 11.2-1 in Study MCI186-17 CSR).

Mean age for study MCI-186-16 was approximately 58±10, for study MCI-186-17 was between 55 and 60, for study MCI-186-18 mean age was 58.65±7.3 and for study MCI-186-19 mean age was approximately 60±10. However, the course of the disease is such that onset is expected around the age of 55-60. The incidence of ALS increases with each decade, especially after age 40 years, and it peaks at age 74, decreasing thereafter. In a systematic review, the mean age of ALS onset was 62 years. Median survival times are consistently reported as 2 to 3 years from the diagnosis (or 3 to 4 years from the first onset of symptom). While this progressive fatal course is usually observed in about 90% of ALS patients, about 10% of ALS patients live over 10 years. As a result of these considerations a study in patients over 75 years of age may not have been feasible and if performed may not have yielded useful information.

Supportive study(ies)

A number of studies have been performed in acute ischaemic stroke (AIS) (cerebral thrombosis and cerebral embolism) and for inhibiting cerebral vasospasm after subarachnoid haemorrhage (SAH) (patients with ruptured cerebral aneurysm) and have been submitted with this dossier, but are not considered relevant for the clinical efficacy of the ALS indication.

3.3.6. Discussion on clinical efficacy

Design and conduct of clinical studies

The Applicant is applying for a therapeutic indication for the treatment of amyotrophic lateral sclerosis (ALS), which is a broad indication and includes a disease modifying effect. It should be noted that according to the European ALS guideline (EMA/531686/2015, Corr. 1), functional measurements alone are not considered sufficient to show disease modifying effects and long term survival/mortality data are needed to support the efficacy claims. The clinical program consisted of one phase 2 study (study MCI186-12) and four phase 3 completed studies (studies MCI186-16, MCI186-17, MCI186-18 and MCI186-19). All studies were performed in Japan with Japanese patients and it is currently not clear whether the study results and the posology can be fully transferred to the EU population.

Patient selection and duration of studies

The patients' selection according to the El Escorial revised Airlie House diagnostic criteria (Airlie House 1998) are in general considered adequate. With respect to the design of the studies, it should be noted that according to the guideline, for disease modifying treatments, study duration of 12-18 months is recommended. Studies MCI186-16 and MCI186-17 combined had a total duration of 60 weeks with 48 weeks placebo controlled, however for study MCI186-17 patients were re-randomized in three groups after 6 months in trial MCI186-16. Study MCI186-19 was a double-blind, placebo controlled trial during the first 24 weeks (6 cycles). After the end of Cycle 6 in study MCI186-19, edaravone was administered to subjects who agreed to continue the study in open-label fashion for an additional 6 cycles (24 weeks) up to Cycle 12, to a total of 48 weeks.

Taking into consideration the epidemiology and the prevalence of the condition the number of patients analysed in the studies can be considered sufficient. From the data, it appears that no specific site had a dominating effect on the recruitment of patients in the pivotal phase 3 studies. In addition in study MCI186-19, the sites that recruited the highest number of patients (12, 10 and 8 patients) have been inspected by FDA and no critical findings were identified.

Long term survival/mortality data for a disease modifying agent

According to the guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis (ALS) (EMA/53168672015, Corr.1), the following study objectives could be considered: increased survival, delay of disease progression and improvement of symptoms of ALS, e.g. muscle strength and related function. For disease-modifying treatments the primary goal is the slowing or even reversal of disease progression. Trials should address the effect on both, functioning and survival. As primary efficacy variable in ALS, trials can use either time to death including other end of life measures that prolong life in ALS patients (e.g. non-invasive ventilation [NIV], ventilation via tracheostomy) or function (ALSFRS-R), or both. For products developed for symptomatic treatment, muscle strength and function are considered the most important endpoints and should show consistency in effects. These can include products with a direct action on muscles or an effect on neuronal conduction that does not affect the neurodegenerative process and would be expected to be reversible on cessation of treatment. According to the expected effect, one should be selected as

primary endpoint and the other as secondary endpoint. However, this only holds true for products that by their mechanism of action do not affect the neurodegenerative process. The Applicant has argued that "*oxidative stress plays a major role in the progression of motor neuron degeneration and astrocyte dysfunction that lead to progressive deterioration in motor function in ALS*" and that " *the development rationale for edaravone in ALS is based upon multiple lines of preclinical evidence affirming protection of neuronal cell damage against high oxidative stress. Studies have confirmed that edaravone scavenges free radical species and peroxynitrite (ONOO-) while other studies confirm that edaravone can ameliorate oxidative stress that damages endothelial and neuronal cells. Taken in context, these studies show that edaravone can protect astrocytes, oligodendrocytes, and endothelial cells from oxidative stress damage*". Hence, edaravone has been submitted for approval in the treatment of ALS as a disease-modifying agent and not as a symptomatic treatment.

However, the design of the studies did not include collection of robust long term survival/mortality data to support the measurement of function, muscle strength, respiratory function or quality of life and provide the required clinical relevance, as described in the European ALS guideline (EMA/531686/2015, Corr.1) and as already discussed in the protocol assistance procedures (EMEA/H/SA/3202/1/2015/PA/III and EMEA/H/SA/3202/1/FU/1/2018/PA/II) (please see below).

Dosing regimen

The rationale for the dosing regimen has not been clarified, either. It is unclear why there is a dosing regimen with 14 days administration and cessation of 14 days in the first cycle and 10 days administration in the second cycle. It is also noted that patients were permitted to receive riluzole concomitantly. It is acknowledged that a substantial amount of data has been generated from the AIS indication with a variety of doses ranging from 0.08 mg/kg bolus +0.2 mg/kg/hr, IV, 24 hr/day and 10 mg, IV, 30 min, BID up to 180 mg, IV, 24 hr/day. However, no dose finding data was provided for the proposed administration scheme (see also relevant section). The Applicant based the justification for the choice of the dosing scheme on exposure from studies with mutant SOD1 transgenic rats (more relevant for familial ALS), the dosing regimen approved for AIS (30 mg/30 min IV infusion) and the investigation of 3NT levels. The Applicant was requested to further discuss which other factors played a significant role for the choice of the specific ALS dosing. The Applicant provided further information on the PPK model and results from the studies MCI186-J22 and MCI186-J25. It is considered that the model underpredicts the concentrations especially in the case of 60mg/60min dosing. The Applicant should include all additionally available data and reconduct a covariate analysis with the enlarged dataset in order to evaluate whether a dose-adjustment is needed with respect to the patient's body weight.

Endpoints

The revised (since 1999) Amyotrophic Lateral Sclerosis Functional Rating Score (ALSFRS-R) is considered the most widely used instrument to measure function in ALS clinical trials. It is a validated disease-specific questionnaire and the most appropriate scale for the evaluation of function in ALS and in line with guideline recommendations.

It is acknowledged that the Applicant has also included muscle strength and respiratory function measurements as secondary endpoints such as percent forced vital capacity, modified Norris Scale (measurement of movement disorder), grip strength and pinch grip strength, as well measurements for the quality of life such as ALSAQ40.

The same efficacy endpoints were analysed in both phase 3 confirmatory studies (studies MCI186-16 and MCI186-19). Efficacy data in the FAS, the primary analysis set, were analysed for the efficacy endpoints of change in ALSFRS-R score (differences between groups in the change of ALSFRS-R from

Baseline to end of treatment cycle), time to death or certain disease progression (analysed as discrete events), %FVC, Modified Norris Scale score, ALSAQ40 score, grip strength, pinch grip strength, Japan ALS severity classification. The Japanese ALS severity grade is a general and simple scale based on daily-living activities. Grade 1 and 2 in the Japan severity classification are patients who can manage without assistance for daily living, "Able to work or perform housework" and "Independent living but unable to work" respectively, compared to grade 3 "Requiring assistance for eating, excretion, or ambulation. It is noted that no grading or classification of disease severity exists in the European guidelines for the diagnosis and clinical care guidelines of ALS.

The Applicant has used as secondary endpoint "time to death or certain disease progression (death, disability of independent ambulation, loss of upper limb function, tracheotomy, use of respirator, and use of tube feeding)". This, however, is considered as a partial replication of the positive effects on function, as demonstrated with changes in the ALSFRS-R scale, and not as an independent survival factor indicative of a disease modifying effect. An additional analysis using only time to death as the endpoint should also be provided to allow evaluation of the consistency of the results.

Efficacy data and additional analyses

Primary endpoint (difference between groups in the change of ALSFRS-R from baseline to end of treatment)

In the open label phase 2 exploratory study MCI186-12, the primary efficacy endpoint, change from Baseline to 24 weeks in ALSFRS-R, was decreased after 6 months by 2.3 ± 3.9 (p = 0.337) in the 30-mg edaravone group and by 2.4 ± 3.5 (p = 0.035) in the 60-mg edaravone group. The secondary endpoint, potential marker of oxidative stress i.e. differences in 3NT levels between Baseline in Cycle 1 and at the end of administration in Cycle 6, was -0.63 ng/mL (p = 0.261) in the 30-mg group (4 subjects) and -1.12 ng/mL (p = 0.007) in the 60-mg group (12 subjects). Several biomarkers have been suggested for their role in oxidative stress, including 3-nitrotyrosine (3NT), but none of them has been established. Statistically significant results were shown with the 60mg dose, which was chosen for the phase 3 studies.

In the phase 3 initial confirmatory study MCI186-16 the analysis in the broader predefined Full Analysis Set did not yield statistically significant results. Only a post-hoc analysis of the results of the primary endpoint differences in the change in ALSFRS-R score from baseline in the two subpopulations EESP and Definite or Probable/EESP/2y showed statistically significant results. The effect size of 2.20±1.03 (p=0.0360) was smaller in the case of EESP population which fulfilled the El Escorial revised Airlie House diagnostic criteria for definite, probable and probable-laboratory supported ALS and had an onset of ALS symptoms within 3 years compared to the effect size (3.01±1.33, p=0.0270) for the Definite or Probable/EESP/2y subpopulation which fulfilled the same criteria for definite or probable ALS only and had onset of ALS symptoms within 2 years. In this Definite or Probable/EESP/2y population, sensitivity analyses such as ALL LOCF (analysis of all randomised subjects including those who discontinued before Cycle 3) and post-hoc MMRM analyses for the primary endpoint ALSFRS-R demonstrated statistically significant results in favour of edaravone: difference in ALSFRS-R mean Scores between Baseline in Cycle 1 and the End of Cycle 6 ALL LOCF 3.11±1.27, p=0.0170 and MMRM 3.44±1.29, p=0.0097. A requested placebo multiple imputation (PMI) analysis showed a difference in ALSFRS-R mean Scores between Baseline in Cycle 1 and the End of Cycle 6 (95% CI) of 3.35 (0.79, 5.92) p=0.0104. Secondary endpoints did not show statistical significance, but a trend in favour of edaravone.

In study MCI186-17, which was the extension of study MCI186-16, the difference in ALSFRS-R mean score between Baseline in Cycle 7 and the End of Cycle 12 (LOCF) was not found statistically significant

in FAS or in any of the two subpopulations: between-group differences in the adjusted mean of ALSFRS-R for the definite or probable/EESP/2y subpopulation was 2.79 ± 1.51, p=0.0719. It was also shown that the difference between treatment and placebo in the ALSFRS-R scale observed in study MCI186-16 was kept during study MCI186-17. Patients who were receiving placebo and were switched to edaravone did not show the same degree of improvement (did not catch up) with patients who received treatment of edaravone continuously from baseline in Cycle 1.

Study MCI186-18 in severe, grade 3, ALS population did not provide any statistically significant results and no meaningful difference between treatment groups in change in the ALSFRS-R score (primary endpoint and measure of ALS) in favour of edaravone treatment. Apart from a small trend in the ALSFRS-R score in favour of placebo, (change in ALSFRS-R Scores from Baseline in Cycle 1 to the End of Cycle 6 (LOCF) was -0.52±2.46, p=0.8347), this study cannot provide useful information. In addition, the number of patients included was low (n=25) so a definite conclusion cannot be drawn to prove or disprove efficacy in a more severely affected population.

Study MCI186-19 can be considered as the main pivotal trial, since study MCI186-16 failed to demonstrate statistically significant results in the predefined Full Analysis Set population. Only a post-hoc analysis of the primary endpoint change in ALSFRS-R score in the two subpopulations EESP and Definite or Probable/EESP/2y showed statistically significant results in study MCI186-16. The patients recruited in the study MCI186-19 had the same condition in comparison to the subgroup Definite or Probable/EESP/2y in study MCI186-16, i.e. Grade 1 or 2 of the Japan ALS severity classification or mild patients. A short-term statistically significant difference of 2.5 points between treatment group and placebo in the change in ALSFRS-R score (from Baseline to end of Cycle 6, duration of 24 weeks) was observed (2.49±0.76, 95% CI: 0.99 to 3.98, p = 0.0013; LOCF) after 6 months and confirmed by a series of pre-specified sensitivity analyses (difference in ALSFRS-R Scores between Baseline in Cycle 1 and the End of Cycle 6, ALL LOCF 2.37±0.75, p=0.0019, MMRM 2.81±0.78, p=0.0004 and PMI 2.87 (95% CI: 1.32, 4.43) p=0.0003).

Clinical relevance and survival data

The difference in the change in ALSFRS-R score was maintained in the active open label-extension over 48 weeks (cycle 12). Functional decline averages about 1 point per month in untreated patients. A difference of 20% has been described in the literature as "*somewhat clinically meaningful*" (based on the rating used in the publication of Castrillo-Viguera 2010). The effect size of 2.4-3.1 was similar in the phase 2 study MCI186-12 and the three phase 3 studies MCI186-16, MCI186-17 and MCI186-19, which provides some degree of consistency in the results. The effect size in main pivotal trial MCI186-19 represents a 33% decline on ALSFRS-R functional scale compared to placebo. Such an effect size might be considered clinically meaningful in the restricted population included. MMRM and PMI analyses, prespecified for the primary endpoint ALSFRS-R and post-hoc for the secondary endpoints, showed statistically significant results in favour of edaravone compared to placebo treatment. Edaravone appeared to be consistently favoured in all 4 domains of the ALSFRS-R, which provides some indication of clinical relevance. Survival analysis of death or certain disease progression provided positive indications for survival. However, consistent effects in secondary endpoints and on survival data would have been expected to support the clinical relevance. Since the results in the primary endpoint are not supported by the results in the secondary endpoints, the clinical relevance of the effect size observed for the primary endpoint and the results in general require still further justification and discussion by the Applicant, therefore it was raised as a major objection.

The Applicant was requested to discuss the clinical relevance and the robustness of the observed effect. A statistically significant difference of the ALSFRS-R score (primary endpoint) between edaravone and placebo group was observed after 6 Cycles of double-blind treatment (PMI): 2.87 (p=0.0003). Statistically significant results were also recorded with respect to Quality of Life

measurement. However, as indicated above and in line with the ALS guideline to demonstrate disease modification at least a clear trend on survival would also have been be expected. Whilst the protocol did not define capture of safety information beyond 4 weeks after the end of last cycle or discontinuation, the Applicant tried to capture all death, tracheostomy or permanent continuous ventilator dependence in available SAE reports/narratives. In a post-hoc analysis, which may have introduced bias in an anti-conservative way (open label and more patients in the P-E group discontinued after cycle 6), the applicant found a favourable trend for survival-related events in the edaravone group compared to that seen in the placebo group: six (6) or eight (8) patients in both phases, double blind and open label, (out of a total of 68 patients; corresponding to 8.8% or 11.8%) in the placebo-edaravone group vs. 3 patients (out of a total of 69 patients; 4.3%) in the edaravone-edaravone group could have been counted as survival-related events, such as death, tracheostomy, or use of respirator (permanent continuous ventilator dependence). These events were not included in the initial analysis. Regarding %FVC, there was a numerically favourable trend after Cycle 6 (5.11 ± 2.92, p=0.0829), and a statistically significant difference after Cycle 12 (11.88±5.05, p=0.0207) (results by MMRM of Cycle 6 and Cycle 12 of Study MCI186-19 in Table 55-2), however again the data were open-label. According to the Applicant, these data would support the hypothesis that edaravone efficacy may be lower if started later, in the more advanced stages of the disease, particularly in terms of preservation of respiratory function and survival. However, in the double-blind periods of studies MCI186-19 and MCI186-16, there were contradictory results reported for grade 1 and grade 2 patients (as well as between patients with <median ALSFRS-R and ≥median ALSFRS-R scores at baseline), which do not support this hypothesis (please see also below).

Robust survival data have not been provided and beneficial effects on a functional scale have only been shown short-term (6 month) in a Japanese population with less advanced ALS. The absence of long term survival/mortality data using time to death or equivalent end-of life measures is a significant limitation of the confirmatory studies (Guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis EMA/531686/2015, Corr.1). As already proposed during the protocol assistance procedure, the ideal approach to generate survival data would be a randomized, double blind, placebo controlled study of longer duration (at least 12 months) and preferably in the Caucasian broader ALS population (EMEA/H/SA/3202/1/2015/PA/III and EMEA/H/SA/3202/1/FU/1/2018/PA/II). However, if the drug would be approved, the feasibility of such a placebo-controlled trial becomes questionable. It is noted that a Japanese registry has been set up not long ago, since October 2017. A protocol for a European registry has been submitted as a proposal to generate survival data. However, there is a major concern that the proposed registry study (cut-off year 2010 for inclusion of historical controls) conducted in two local centers (Ulm and Utrecht) will not be able to capture robust efficacy data in a representative EU population taking into consideration possible biases introduced by more recent changes in standard of care, potential off-label use of medications and food supplements as well as the different approaches with respect to euthanasia in different EU countries. A sound justification in the form of a major objection was raised to the company and further clarification is needed to show that this registry study is really adequate as a condition to provide confirmatory efficacy data.

It is noted that an analysis of the ALSFRS-R domains has been provided which showed consistent effects in the domains of bulbar, fine motor, gross motor and respiratory. In addition, an analysis of the Difference in the change of ALSFRS-R Score between Baseline in Cycle 1 and the End of treatment per medical institute/study center was provided confirming that no study center dominated the results.

In conclusion, a statistically significant short-term effect of edaravone to slow down functional deterioration has been demonstrated in the pivotal study MCI186-19 over a double-blind period of 6 months. The post-hoc analysis in the definite or probable/EESP/2y subpopulation in study MCI186-16 can be regarded as supportive evidence. However, important questions remain unanswered and

maintenance of effect beyond 6 months of edaravone treatment has not been clearly demonstrated. The pivotal study MCI186-19 was double-blind placebo-controlled only up to cycle 6, while the open label “active treatment period” up to cycle 12 with all patients being on edaravone provides difficulties in the interpretation of the results. In addition, there was a selection of patients after cycle 6, as more patients in the P-E group discontinued (18 vs. 12), comparisons are therefore not on randomized groups.

As already mentioned, demonstration of efficacy based on ALSFRS-R alone is not considered sufficiently robust, as described in the European Guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis EMA/531686/2015, Corr.1 and as already discussed in the protocol assistance letter (EMEA/H/SA/3202/1/2015/PA/III). An effect on survival should also be demonstrated using time to death and other end of life measures as endpoints in addition to the effect on functional outcome.

Statistical methods

It is noted that the study programme consists of two confirmatory studies MCI186-16 and MCI186-19, of which only one study can be regarded as pivotal confirmatory evidence, as study MCI186-16 failed in the broad population and was re-analysed in a selected subpopulation with better efficacy results compared to the broad included population. For this view it is irrelevant if the re-analysis as performed by the Applicant was designed with or without input by PMDA as regulatory authority, as the re-analysis was a post-hoc exercise and can only be regarded hypothesis generating and supportive. The discussion of the confirmatory approach in this section is therefore focusing on study MCI186-19. The study population included in this second confirmatory study MCI186-19 is a selected subpopulation of ALS patients. Selection criteria are targeting a population with mild disease and without large changes in ALSFRS-R scores as established in a pre-observation period, motivated by findings of post-hoc analyses of study MCI186-16.

The statistical methods used are considered not acceptable for important parts of the statistical approaches pre-specified in the Statistical Analysis Plan. The impact of inappropriate analyses is assessed in detail in the following.

The primary population for the primary analysis was the FAS with additional conditions, such as availability of efficacy data after randomisation. Inclusion of all randomised patients would have been the preferred definition. However, there is no impact from additional conditions as all randomised patients were included in the FAS.

The primary analysis of ALSFRS-R scores for study MCI186-19 used an ANCOVA model with factors used for dynamic allocation included in the model. Although dynamic allocation is generally not recommended due to limitations of the method itself (e.g. homogeneity of allocations may not be guaranteed in the strata), the analysis model is considered acceptable. The quite complex dynamic allocation procedure is described in detail (Appendix 16.7.1.5, study MCI186-19 CSR) and apparently used a three level group assignment approach with a random element in each level. Since a sufficient contribution of randomness is required to avoid complete predictability of the group allocations, the dynamic allocation approach is considered acceptable. Importantly, robustness of the statistical results with regard to the dynamic allocation method was assessed with a permutation test, and this test also indicated statistical significance of the results.

Usually in studies in the ALS population, analysis of ALSFRS-R scores are hampered by deaths during the study period that lead to unobservable ALSFRS-R scores and missing data. In study MCI186-19 there were only few death cases with 4 in the placebo and 2 in the edaravone group, as the population included had only mild disease. Therefore the impact of deaths on study results is limited. Still, a post-hoc analysis using the Combined Assessment of Function and Survival (CAFS) as endpoint, using a

non-parametric rank based analysis with deaths ranked lowest as worst outcome addresses the issue and leads to the same conclusions as the primary analysis.

Missing data is not a major problem of study MCI186-19, as the number of study withdrawals is limited, but handling of missing data is not acceptable. The LOCF approach to handle missing data for the primary analysis is considered inappropriate due to several issues. Generally, a single imputation method is considered inappropriate as variability could be considerably underestimated and an LOCF approach is considered inappropriate for a progressive disease as ALS. Very relevant is also the concern that patients were excluded from the analysis if they discontinued before Cycle 3. All three issues mentioned give reason to not accept the pre-specified analysis as primary analysis of the study. This was addressed by the Applicant with sensitivity analysis using an MMRM model and an analysis with an LOCF approach for all patients, not just those who reached Cycle 3. However, in principle an analysis with an MMRM model, targeting an estimand as if all patients adhered to treatment and implicitly predicting data for patients discontinuing by data from study completers would not be acceptable with a considerable number of patients withdrawing from the study. The impact of study withdrawals is limited with only 2 withdrawals in the edaravone group and 8 in the placebo group. The Applicant, upon request, provided an analysis based on a placebo multiple imputation approach in order to have an appropriately defined estimate of the treatment effect to be included into the SmPC .

Issues identified with regard to the primary endpoint also pertain to the secondary endpoint analyses, as similar methods were used. Methods for time-to event endpoints and slope analysis performed are acceptable.

The approach to handle multiplicity is acceptable. All secondary endpoints were considered as exploratory endpoints and there was no formal interim analysis in the study planned. Interim analyses were performed by the DSMB and the study continued until the planned termination. DSMB recommendations and protocols are transparent and are included in the documentation.

The Statistical Analysis Plan stated that subgroups analyses would not be performed. This is considered inappropriate as pre-specification of demographic and important other factors would have been expected. Nevertheless, subgroups analysis was performed post-hoc for the primary endpoint and the range of subgroups analysis is considered acceptable.

Use of riluzole

The use of riluzole was permitted if the dosage and administration were not changed and 62 out of 68 patients in the placebo group and 63 out of 69 patients in the edaravone group received riluzole concomitantly.

The negative results in the between-group differences in the adjusted mean for the group of patients without concomitant riluzole (n=8 in total) in Study MCI186-16 Definite or Probable/EESP/2y cannot provide useful information.

The number of patients treated with edaravone without co-administration of riluzole in the pivotal studies was limited. Robust conclusions cannot be reached from subgroup analysis for efficacy in patients with or without riluzole treatment. With respect to the results from subgroup analysis for patients with and without riluzole treatment for the primary endpoint and secondary endpoints, data do not allow to conclude that there is a clear difference between subgroups. Number of events linked to disease progression are low and even more limited than endpoint results and do not permit conclusions concerning subgroup differences. It is therefore recommended to collect as many as possible data on patients not treated with riluzole in the post-marketing setting.

Time to Death or Certain Signs of Disease Progression

Time to Death or Certain Signs of Disease Progression defined as “death, disability of independent ambulation, loss of upper limb function, tracheotomy, use of respirator (except bilevel positive airway pressure), and use of tube feeding” was included as secondary endpoint in the phase 3 studies with inclusion of loss of useful speech only in study MCI186-19. CHMP had already in the same protocol assistance considered the positive effect on “Death or certain disease progression” events to be a partial replication of the positive effects on function, as demonstrated on ALSFRS-R, and not an independent survival factor indicative of a disease modifying effect. No patient died or received ventilation and only one patient in the E group had tracheostomy up to cycle 6.

It is noted that for the endpoint “Time to Death or Certain Signs of Disease Progression” there is a trend favouring edaravone (2 events on edaravone and 6 events on placebo), but the small number of events limited the power of the log-rank test and the generalised Wilcoxon test. In addition, these results can only be considered as a partial replication of the positive effects on function, as demonstrated with ALSFRS-R, and not as an independent survival factor indicative of a disease modifying effect since no patient died or received ventilation and only one patient in the E group had tracheotomy.

However, the results were analysed as combination of events including disability of independent ambulation (2 in Placebo), loss of upper limbs function, loss of useful speech (3 in Placebo and 1 in Edaravone), which are also included in the ALSFR-R and tracheotomy, use of respirator, use of tube feeding, including death. There were no deaths in the first 6 months during the double-blind phase of the study, neither in edaravone, nor in the placebo group. One tracheostomy was recorded in the edaravone group and one use of tube feeding in the placebo group. The number of deaths (n=3) or equivalent events such as tracheotomy or respirator use (n=1) up to cycle 12 in study MCI186-19 was very low or non-existent and did not show a difference between the PE and EE groups (2 vs 2, if death and tracheostomy are counted together) even after 1 year of treatment to allow any definite conclusions. Using death or equivalent end-of life measures as an endpoint from a larger amount of study population and for a long-term period would have been more informative and robust.

As mentioned above, whilst the protocol did not define capture of safety information beyond 4 weeks after the end of last cycle or discontinuation, the Applicant tried to capture all death, tracheostomy or permanent continuous ventilator dependence in available SAE reports/narratives. Robustness of analyses including additional events after the double-blind period cannot be claimed for survival and survival related endpoints. Other functional endpoints could be influenced by the open label nature of the study in Cycles 6-12 and the implementation of comparisons not on randomised patients. Hence, the respective post-hoc analyses have to be interpreted with caution.

Other secondary endpoints

With respect to the remaining secondary endpoints in study MCI186-19, it is noted that differences in the changes of ALSAQ40 measuring quality of life and the modified Norris Scale score assessing movement disorder, which have been widely used in ALS patients, reached statistical significance in favour of edaravone. On the other hand respiratory function %FVC, grip strength and pinch grip strength showed no meaningful effects in favour of edaravone treatment. Despite the lack of statistical significance in some of the secondary endpoints, analysis of these endpoints provided some support for the results of the primary endpoint: double-blind period FAS: differences in the quality of life questionnaire ALSAQ40 score -8.79 ± 4.03, p=0.0309 and Modified Norris Scale score (Total), assessing movement disorder 4.89±2.35, p=0.0393 showed statistical significant results and these measuring instruments are widely used in ALS patients. However statistically significant effects on

%FVC 4.78±2.84, p=0.0942, Grip strength 0.11±0.64, p=0.8583 and Pinch grip strength 0.10±0.16, p=0.5478 were not shown.

The combined assessment of function and survival (CAFS) did not provide meaningful results since there were no deaths over 6 months double-blind treatment period of study MCI186-19 and even at the end of cycle 12 blinded extension treatment with edaravone the number of deaths was very low, as already discussed.

Subgroup analyses and BMI

There was no imbalance observed between <Median BMI and ≥ Median BMI subgroups. However, the BMI values in the edaravone studies were lower than those reported in publications with non-Japanese, non-Asian patients. Researchers [Traxinger et al 2013] analysed a clinic population between 1997 and 2011 and reported BMI values of 18.5–24.9 for 217 patients and ≥25 for 244 patients. The BMI mean value in ALS cases (n=393) was 24.6 (SD 4.2) and in controls (n=791) was 26.5 (4.1), slightly higher values than those recorded in studies MCI186-16 and MCI186-19. It has been also reported that when the BMI is low at the time of identification of the symptoms of ALS, this can affect the severity of the condition and the prognosis, e.g. the lower the BMI, the more severe is the condition of the patients with ALS and with a worse prognosis presenting as higher mortality rate (increase in the risk of death up to 7.7-fold). There is still insufficient information whether differences in BMI could influence exposure. Therefore, describing results on the ALSFRS-R, a subgroup analysis of the results in the four WHO categories (underweight, normal, pre-obese and obese) could provide some useful information on a potential effect of BMI or lack thereof. It should be also noted that for edaravone treatment a flat dose of 60mg/day is proposed instead of a weight based posology. The Applicant was requested to provide an analysis of the ALSFRS-R for the 6 Cycles in Study MCI186-19 FAS and Study MCI186-16 Definite or Probable/EESP/2y with the BMI divided into four groups according to WHO criteria: <18.5, underweight; 18.5 to 24.9, normal; 25.0 to 29.9, pre-obesity; ≥30, obesity. The Applicant has provided this additional analysis and concluded that it is unlikely that edaravone is under-dosed, including, specifically patients with high weight or BMI. However, regardless of body weight/BMI, the Applicant have a plan to conduct a double-blind 3-dose comparison study using an oral formulation of edaravone (comparing the current 2-week on/2-week off cycle, a continuous once daily dosing (without drug holiday), and continuous twice daily dosing (without drug holiday), and will investigate this possibility in the study.

It is agreed that no clear trend of an influence of BMI on efficacy can be seen and that there is some supportive evidence that PK of edaravone is independent from BMI/body weight due to its low distribution to fat.

Subgroup analyses and ALS severity

It is unclear whether the effect of edaravone is generalizable and whether consistent effects have been observed between more and less advanced patients. The hypothesis that could have been generated by the unspecific mechanism of action of edaravone, as a free radical scavenger to reduce oxidative stress, is twofold:

a) that edaravone administration to less advanced patients would have been more beneficial to these patients and larger differences in all endpoints would have been observed.

b) the earlier the start of the treatment, the larger the expected improvement for patients would have been, as seen in other neurological disorders.

However, this hypothesis cannot be confirmed by the results.

In the pivotal study MCI186-19, differences in the patient's classified grade 1 or 2 according to the Japan ALS Severity Classification were observed. For Grade 1 patients the between-group differences

in the adjusted mean change in the ALSFRS-R Score was 0.48±1.32 and for Grade 2 patients it was 7.48±1.87. For <Median ALSFRS-R score at baseline in Cycle 1 the between-group differences in the adjusted mean change of ALSFRS-R was 7.73±3.61 and for ≥Median this difference was 1.23±1.19. For <Median %FVC (at baseline in cycle 1) the between-group differences in the adjusted mean change of ALFRS-R was 6.15±2.75 and for ≥Median this difference was 0.90±1.33. Patients with Grade 2 disease showed greater between group differences than Grade 1 patients. Whilst, the subgroup with less than Median Baseline ALSFRS-R score showed between group differences greater than the subgroup with more than or equal to Median Baseline ALSFRS-R score in study MCI186-16, the opposite can be observed in the case of study MCI186-19, albeit with smaller between group differences.

The results appear contradictory for the subgroups regarding Japan ALS severity and baseline ALSFRS-R score. It would have been expected (based on Applicant's postulation) that patients with less advanced condition would have demonstrated greater improvement and larger differences in all endpoints. Subgroup analysis of the results in grade 1 and 2 ALS severity patients and the subgroups of median ALSFRS-R scores should have pointed in both studies and in these four subgroups towards the same direction: that edaravone efficacy may be lower if started later. However, the short term double blind data cannot support this hypothesis.

The Applicant performed an additional post-hoc analysis, based on the conclusions of the Castrillo-Viguera et al. publication. The results of the analysis showed that 15 patients (50.0%) in P-E group experienced an improvement of the slope of their ALSFRS-R by 20% or more during the extension phase (while being on edaravone from the end of Cycle 6 to Cycle 12) compared to their slope during the double-blind phase (while being on placebo). These comparisons are not placebo-controlled and difficult to interpret.

In addition, during the double-blind period of study MCI186-19, there was a subgroup of patients who progressed to Grade 3, either being on edaravone treatment or on placebo. This further questions the overall efficacy of edaravone. A Table and a graphical representation with the individual ALSFRS-R scores (and %FVC values) (from baseline through to end of Cycle 12) of these progressor patients should be provided. The decline and the deterioration of the condition of patients both for the edaravone-edaravone and the placebo-edaravone group who progressed to Grade 3 from the end of Cycle 6 onwards in the extension of study MCI186-19 needs to be further discussed by the Applicant.

Extrapolation from early stage ALS patients to advanced disease ALS population

It is acknowledged that edaravone is approved in Japan with the following indication: "Inhibition on progression of functional disorder in patients with amyotrophic lateral sclerosis (ALS)" and in US with the indication: "for the treatment of amyotrophic lateral sclerosis (ALS)". However, in EU, the Applicant has received protocol assistance, which was not followed with respect to the lack of clarity on the rationale for the selection of dose and schedule of administration, the potential differences in PK data between Japanese and Caucasians, the potential variability in body weight and BMI and the extrapolation of data from Japanese to EU population as well as, the lack of long term survival data. The issue of the lack of long term data has been discussed above.

With respect to the generalisability of the data from Japanese ALS Patients to European ALS Patients, the Applicant has discussed various aspects such as mechanism of action, PK potentially extrapolatable data and clinical practice and treatment guidelines.

There is consensus across world regions in diagnostic criteria for ALS and very similar recognition of symptoms. Treatment guidelines between US, Japan and Europe do not present differences. Riluzole is the only approved medication with the same posology of 50mg twice daily in the 3 regions. The statement of the Applicant that "non-invasive respiratory and ventilatory support, as well as

tracheostomy-based invasive respiratory support, in addition to various methods of manual and mechanical therapeutic interventions, are in good overall concordance" across regions is valid. The absence of significant differences in ALS treatment between Europe, Japan, and North America in terms of identification, diagnosis, prognosis, culture of care, disease progression of ALS patients and available options for treatment has been acknowledged. The only clear difference is the practice of terminal withdrawal of tracheostomy-assisted ventilation in the final stage of the disease, which is less flexible in Japanese written guidelines. However, there are in standard of care, potential off-label use of medications and food supplements as well as the different approaches with respect to euthanasia in different EU countries, which could also influence treatment in ALS in Europe.

In addition, the following points should be considered. The argument on the mechanism of action and the free radical species scavenging effect is weak, since a direct association between oxidative stress and ALS has not been established. It is acknowledged that there are some publications which implicate oxidative stress, as one of many other factors in the pathophysiology of ALS. The physiological role of free radicals and how they can be affected by administration of edaravone has not been clarified. But even in case the postulated role of oxidative stress in ALS is further substantiated, it does not exclude that race or ethnic differences could have an influence on efficacy of edaravone.

The argument related to the PK data is also weak since the PPK model is quite complex and considered to have some limitations (please see relevant section 2.1.7 and 2.1.12). It is noted, that the IV infusion removes any possible ethnic effects associated with absorption such as rate and extent of absorption, first pass metabolism, etc. However, it remains unclear whether the PPK model predicts adequately the plasma concentrations from the current dosing scheme. It is not clear, either, whether the results would have been better, if another posology scheme had been used. For the dosing regimen 30mg/60 min it can be agreed that the model performance is adequate. But for the dosing regimens 60mg/60 min and 300mg/60min the model is not considered to adequately describe the observed data. In both cases, but even more in the case of 60mg/60min dosing, the model underpredicts the concentrations. The Applicant should include all additionally available data and reconduct a covariate analysis with the enlarged dataset in order to evaluate whether a dose-adjustment is needed with respect to the patient's body weight.

Additional expert consultation

Not applicable

Assessment of paediatric data on clinical efficacy

There are no paediatric data submitted with this dossier

Additional efficacy data needed in the context of a conditional MA

The Applicant has applied for a conditional MA, and a detailed protocol for a registry has been submitted with the responses to the Day 120 LoQ. However, besides, the required clarifications and modifications, a justification that such a registry will be sufficient for collecting high quality data compared to a randomised controlled clinical trial, needs to be further discussed.

3.3.7. Conclusions on clinical efficacy

The primary endpoint differences between treatment group and placebo in the changes of ALSFRS-R score from Baseline to end of treatment cycles used in the studies is an acceptable endpoint for trials

in ALS, as a measurement of function. The ALSFRS-R is a validated questionnaire scale that measures physical function in carrying out activities of daily living (ADL) in ALS patients and in line with the guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis (EMA/531686/2015). Short-term statistically significant results were obtained in study MCI186-19 in a subpopulation of Japanese patients with less advanced disease: patients fulfilling the El Escorial revised Airlie House diagnostic criteria for definite or probable ALS, being of Grade 1 or 2 in the Japan ALS severity classification, having normal respiratory function (%FVC not less than 80%) and having an onset of ALS within 2 years (Definite or Probable/EESP/2y).

Secondary endpoints supported the positive results of the primary endpoint analysis, either with statistical significance (in the case of specific measurements for ALS patients) or a trend in favour of edaravone except for muscle strength measurements.

The following issues have been identified:

a) The association of the unspecific mechanism of action considered to reduce oxidative stress via free radical species scavenging effect and efficacy in ALS is considered weak.

b) From the population pharmacokinetic analyses there are some indications of potential influence of additional covariates, i.e. age on clearance, body weight on clearance and volume of distribution (V1) and race and sex on clearance. But due to the limited database, the impact of these demographic parameters on the PK of edaravone could not be finally clarified. All additionally available data should be included in the PK model and a covariate analysis with the enlarged dataset should be reconducted in order to evaluate whether a dose-adjustment in Caucasian patients is needed with respect to the patient's body weight.

c) The clinical relevance of the effect size for the primary endpoint (difference of 2.5 in the change of ALSFRS-R) and the results in general has not been convincingly shown and findings using sensitive instruments (%FVC, pinch grip strength and grip strength) did not provide support.

d) The studies showed beneficial effects in a restricted population with early stage (less advanced) patients and extrapolation to an advanced disease ALS population is currently questionable.

e) Maintenance of effect and long term survival/mortality data are lacking.

f) Adequacy of the proposed registry as condition to confirm efficacy of edaravone is questionable.

3.3.8. Clinical safety

The clinical trial program for edaravone in the targeted ALS indication includes 1 completed phase 2 (MCI186-12) and 4 completed phase 3 studies (MCI186-16, MCI186-17, MCI186-18, and MCI186-19) conducted in ALS patients in Japan.

Evaluated posology:

Except from exploratory phase 2 study MCI186-12 (in which lower daily doses were applied in 1/3 of study subjects), edaravone posology in all ALS studies was in line with the posology proposed for the SmPC.

Patient exposure

A total of 349 ALS patients received edaravone in the ALS clinical trial program. Among these subjects, 306 subjects received edaravone for at least 6 months (6 cycles), 98 subjects received edaravone for at least 12 months (12 cycles) and 37 patients received edaravone for 15 cycles (representing maximum duration of exposure), respectively.

For the purpose of evaluating safety in the ALS population, 4 integrated data sets were used:

• Safety set 1: (184 edaravone subjects, 184 placebo subjects)

First 6 months of double blind, placebo controlled study periods (included cycles 1-6 of studies Nos. MCI186-16, MCI186-18 and MCI186-19);

• Safety set 2: (349 edaravone subjects)

Safety data from all subjects in the 5 ALS studies who received edaravone at least once;

• Safety set 3: (229 edaravone subjects):

Continuous long-term edaravone exposure ≥ 7 cycles, max. 15 cycles (derived from Studies MCI186-16, MCI186-17, MCI186-19)

• Safety set 4: (45 EP subjects receiving placebo during cycles 7-12 after 6 months of edaravone treatment, 146 PE subjects receiving edaravone during cylces 7-12 after 6 months of placebo, 113 EE subjects receiving edaravone during cylces 7-12 after 6 months of edaravone):

Controlled extension period, i.e. pooled safety data from cycle 7-12 of studies MCI186-17 and MCI-186-19.

Baseline characteristics of pooled safety sets:

In safety set 1, 18.5% (placebo) and 20.1% (edaravone) patients had initially bulbar symptoms. The proportions of patients with ALS severity grade 1, 2, and 3 were 30.4%, 63.0% and 6.5% in the placebo group, and 31.5%, 61.4% and 7.1% in the edaravone group, respectively.

In safety set 4 evaluating cycle 7 through 12, baseline imbalances were found:

- At baseline of cycle 7, patients in the PE and EE groups had worse respiratory function at baseline of cycle 7 compared to the EP group (% of patients with FVC < 70% (< 80%) was 15.6% (24.4%) in EP group, 30.3% (44.1) in PE group and 25.0% (34.8%) in the EE group, respectively)

- At baseline of cycle 7, subjects in the PE and EE groups had more severe ALS (the proportion of subjects with ALS severity grade 3-5 per treatment group were 31.1% (EP), 41.8% (PE), and 39.8% (EE), respectively)

- The proportion of patients with definite ALS was higher in the EE group (35.4 %) compared to the other treatment groups (24.2 % in EP, 26.7 % in PE group), (already present at baseline of cycle 1);

- Further, proportion of subjects with initial bulbar symptoms (15.6 % in EP to 20.4 % in EE group) and proportion of subjects ≥ 65 years (15.6 % in EP to 35.4 % in EE; mean age 55.4 years in EP to 60.0 years in EE group), was lower in the EP group compared to the other groups (already present at baseline of cycle 1).

Adverse events

Overall summary of adverse events

In safety set 1, the main safety set, derived from completely double blinded first 6 months of treatment, incidences of overall TEAEs were very similar in the placebo (87.0%) and edaravone group (87.5%) and incidences of ADRs (14.1% and 10.3%), ADRs leading to drug discontinuation (1.6% and 0.5%) as well as SAEs (22.3% and 17.4%) tended to be lower in the edaravone group. Two patients (1.1%) in the placebo group and 4 patients (2.2%) in the edaravone group died. All death cases were attributed to respiratory failure in subjects with advanced ALS. No SAEs including death cases were considered drug related.

In safety set 4, AEs occurred in 91.1% of EP patients, 84.9% of PE patients, and 85.0% of EE patients, the incidence of drug related AEs was 4.4% in EP, 8.2% in PE and 5.3% in EE patients. The incidence of SAEs was higher in the PE (54/146; 37.0%) as well as the EE groups (36/113; 31.9%), compared to the EP group (7/45; 15.6%). Also in this safety set no SAEs/death cases were considered drug related. Although similar, the proportion of deaths was numerically highest in the EP group receiving placebo during the period of interest (2/45; 4.4%) compared to the PE (5/146; 3.4%) EE groups (4/113; 3.5%).

Adverse events by system organ class

The highest incidences of TEAEs by SOC (≥20 % in any treatment group) concerned infections and infestations (31.0% in placebo and 34.2% in edaravone group), gastrointestinal disorders (37.0 % and 31.0 %), skin and subcutaneous tissue disorders (20.1% and 25.5 %), musculoskeletal and connective tissue disorders (21.2 % and 19.6 %), general disorders and administration site conditions (20.1 % and 22.3 %) and injury, poisoning and procedural complications (19.6 % and 21.2 %) (safety set 1).

Common adverse events

In safety set 1 seven TEAEs (by PTs) were reported with a higher incidence (i.e., +2%) in the edaravone compared to the placebo group: contusion (14.7% versus 8.7%), gait disturbance (12.5% versus 9.2%), headache (8.2% versus 5.4%), eczema (6.5% versus 2.2%), dermatitis contact (6.0% versus 3.3%), respiratory disorder (4.3% versus 1.1%), and glucose urine present (3.8% versus 1.6%).

TEAEs by treatment cycle 1-6 (safety set 1):

The overall incidence of TEAEs by cycle was similar between the 2 treatment groups, ranged from 29.6 % to 38.6 % in the placebo and from 27.5 % to 35.9 % in the edaravone group and did not increase over time in edaravone treated subjects.

TEAEs during cycles 7-12 (safety set 4):

The incidences of TEAEs (by PT) in the EE group were generally similar to and partly even lower than those in the EP group. The TEAEs with more than 2% higher incidence in the EE group compared the EP group were Catheter site infection (0% in EP and 2.7% in EE), Speech disorder (0% and 2.7%), Pneumonia aspiration (0% and 2.7%), Respiratory disorder (0% and 6.2%), Upper respiratory tract inflammation (2.2% and 4.4%), Dysphagia (6.7% and 8.8%), Gastritis (2.2% and 4.4%), Dermatitis contact (0% and 2.7%), Eczema (4.4% and 7.1%), Pruritus (2.2% and 4.4%), Musculoskeletal disorder (6.7% and 9.7%), Nocturia (0% and 2.7%), and Pyrexia (0% and 2.7%).

There were no new types of TEAEs especially observed after Cycle 6.

In study MCI186-17 which had up to 15 treatment cycles, no new significant AEs and no meaningful change in frequency of AEs caused by repeated administration were observed.

Severity of TEAEs

Approx. 75% of subjects of safety set 1 reported “mild” or moderate as highest TEAE severity. 12% edaravone subjects experienced at least one severe TEAE, the proportion being slightly lower as compared to the placebo group (15.2%).

By PT, severe gait disturbance occurred at a higher frequency in the edaravone compared to the placebo group (5.4% vs. 2.7%), no other severe TEAEs by PTs occurred in ≥ 2 % of subjects and at a higher frequency in the edaravone group.

In safety set 4 the proportion of subjects reporting at least 1 severe TEAE was highest in the PE group (28.1%), followed by the EE group (20.4%) and lowest in the EP group (11.1%). The most frequently reported severe TEAEs (i.e., > 2% incidence) in the EE group (by PT) were dysphagia, respiratory failure, and musculoskeletal disorder. Of these 3 PTs, only musculoskeletal disorder occurred at a higher incidence in the EE group (reported as TEAE in 9.7%, as severe TEAE in 8.8% patients), compared to the EP group (reported as TEAE in 4.4 %, as severe TEAE in 2.2% patients). The severe TEAEs reported in safety set 4 were in general compatible with advanced ALS.

Adverse events by causality

In safety set 1 10.3% (19/184) edaravone subjects developed 1 or more drug-related AEs, compared to 14.1% (26/184) subjects in the placebo group.

The most frequently reported drug-related AE (by PT) in the edaravone group were Glucose urine present and Liver function test (LFT) abnormal, both of which occurred in 1.1% (2/184) subjects in the edaravone group and 0.5% (1/184) in the placebo group. In contrast, the most frequently reported drug-related AE (by PT) in the placebo group was hepatic function abnormal (2.2% [4/184] subjects in the placebo group and 0.5% [1/184] in the edaravone group.

In safety set 4, incidence of drug-related AEs was similar in the EE and EP groups (5.3% and 4.4%, respectively) and somewhat higher in the PE group (8.2%); nevertheless, incidence of drug-related AEs in all treatment groups of safety set 4 during cycles 7-12 was lower than that reported during cycles 1-6 in safety set 1 (10.3% in edaravone group, 14.1% in placebo group).

Review of selected Adverse events

Respiratory TEAEs (defined as TEAEs in the Respiratory, thoracic and mediastinal disorders SOC) were reviewed as imbalances were observed in the ALS studies with regard to respiratory TEAEs.

In Safety set 1, there was no significant difference in overall incidences of TEAEs in the Respiratory, thoracic and mediastinal SOC between the placebo group (13.0%) and edaravone group (14.1%).

Of the different TEAEs by PT, only respiratory disorder occurred at (+2% absolute) higher incidence in the edaravone (4.3%) compared to the placebo (1.1%) group. However, the incidence of respiratory failure PT was somewhat higher in the placebo group (2.7%) than edaravone group (1.1%).

The overall incidence of respiratory SAEs was similar between placebo (6.5%) and edaravone (6.0%) patients. In the edaravone group, the most frequent respiratory SAE by PT, was Respiratory disorder, occurring in 3.3% (6/184) subjects, compared to 1.1% (2/184) in the placebo group. Respiratory disorder PT SAEs primarily were reported as “decreased respiratory function.” Respiratory failure SAE, on the other hand, was reported more frequently in the placebo group, occurring in 2.7% (5/184) subjects, compared to 1.1% (2/184) subjects in the edaravone group. Respiratory failure (PT) SAEs were primarily reported as “respiratory insufficiency”. Combined, these 2 PTs were reported with similar frequency in the 2 treatment groups.

Individual case review of the serious respiratory TEAEs did not suggest a difference in the type of events between the 2 treatment groups. None of the serious respiratory TEAEs were considered to have a reasonable possibility of causal association with the IMP; all were attributed to worsening ALS. All of the subjects in the edaravone group who experienced serious Respiratory TEAEs had evidence of ALS progression.

All of the fatal TEAEs in edaravone and placebo patients of safety set 1 were respiratory in nature. The 4 fatal respiratory TEAEs in the edaravone group included 2 events each of Respiratory failure and respiratory disorder. All patients had evidence of ALS progression, none of the death cases was considered to have a reasonable possibility of causal association with the IMP.

Apart from fatal cases, no respiratory TEAEs in the edaravone group led to discontinuation of IMP.

In safety set 4, there were numerical imbalances with regard to overall incidence of respiratory TEAEs/SAEs (SOC) across the three treatment groups. Incidence of respiratory TEAEs and SAEs was highest in the PE group (21.9% respiratory TEAEs and 13.7% respiratory SAEs), followed by the EE group (20.4% and 12.4%) and appeared lower in the EP group (13.3% and 4.4%). The incidences of respiratory TEAEs which were fatal or resulted in discontinuation of IMP were balanced across the 3 treatment groups. Individual case review of the serious and fatal respiratory TEAEs, as well as those leading to discontinuation, indicated that these events occurred in the context of ALS progression.

Comparison of EE and PE subgroups:

In the EE group, the most frequent respiratory SAE, by PT, was respiratory disorder, occurring in 5.3% (6/113) subjects, compared to 3.4% (5/146) in the PE group. Respiratory disorder PT SAEs primarily were reported as “decreased respiratory function”. Respiratory failure, on the other hand, was reported more frequently in the PE group, occurring in 6.2% (9/146) subjects, compared to 2.7% (3/113) subjects in the EE group. Respiratory failure PT SAEs were primarily reported as “respiratory insufficiency”. Combined, these 2 PTs were reported at similar incidences in these 2 treatment groups (EE and PE) but with lower frequency in the EP group, in which respiratory failure in 4.4% (2/45) subjects but no respiratory disorder PT was reported. Further analysis of respiratory TEAEs in EE compared to PE group by individual studies (No. MCI186-17 and MCI186-19), did not reveal consistent trends with regard to overall incidence of respiratory TEAEs/SAEs or incidences of respiratory TEAEs/SAEs by PTs.

Review of skin TEAEs, defined as TEAEs with selected PTs in the Hypersensitivity SMQ, was performed as imbalances were observed in the ALS studies with regard to skin related TEAEs (i.e. dermatitis contact and eczema).

In safety set 1, similar to results derived from evaluation of TEAEs in the skin and subcutaneous tissue disorder SOC, the overall incidence of skin TEAEs in the edaravone group (23.4%) was somewhat higher than that in the placebo group (19.6%). Incidences of dermatitis contact (3.3% in placebo and 6.0% in edaravone) and eczema (2.2% in placebo and 6.5% in edaravone) were higher (i.e., +2% absolute) in edaravone than placebo patients.

None of the Skin TEAEs were serious or severe. The Skin TEAEs were all mild, except for 2 TEAEs that were moderate in severity: Toxic skin eruption PT in a subject in the edaravone group and rash PT in a subject in the placebo group. The IMP was discontinued due to these events; no other skin TEAEs led to discontinuation.

In safety set 4 the incidence of skin TEAEs was somewhat higher in the PE (17.8%) and EE (19.5%) groups compared to EP group (15.6%). None of the skin TEAEs were serious or severe. The Skin TEAEs were all mild, except for 1 event of ekzema PT (moderate; EE group).

Only 1 skin TEAE led to discontinuation of the IMP: rash PT (PE group). An additional skin TEAE led to temporary interruption of the IMP: urticaria PT (EE group).

Six skin TEAEs were assessed as having a reasonable possibility of association with IMP: 3 TEAEs in the EE group (1 event each of rash, rash pruritic, and eczema) 2 TEAEs in the PE group (2 events of rash), and 1 TEAE in the EP group (1 event of rash).

Review of hepatic TEAEs and liver function test abnormalities (LFT):

Based on the post-marketing experience in AIS patients in Japan, hepatic TEAEs (defined as TEAEs in the Drug related hepatic disorders - SMQ) were reviewed.

In safety set 1, hepatic TEAEs developed in 4.3% (8/184) subjects in the edaravone group and 5.4% (10/184) subjects in the placebo group. All of the hepatic TEAEs observed in the edaravone group (9 AEs occurring in 8 subjects) were mild in severity and non-serious, and none led to discontinuation; the hepatic TEAE(s) resolved for 7 of the 8 subjects.

In safety set 4, hepatic TEAEs developed in 2.2% (1/45) subjects in the EP group, 3.4% (5/146) subjects in the PE group, and 0.9% (1/113) subjects in the EE group. No subjects in any treatment group experienced a hepatic TEAE that was serious or that led to discontinuation. All of the hepatic TEAEs were mild in severity.

No subjects in Safety Set 1 or 4, including those with hepatic TEAEs, met the criteria for Hy's law.

In safety set 2 (all edaravone), none of the overall 349 subjects treated with edaravone experienced a SAE of hepatitis, hepatic dysfunction, or jaundice, other than 1 subject who experienced cholecystitis.

Liver function test (LFT) abnormalities

In safety set 1, 8.2% (15/184) subjects in the edaravone group and 9.2% (17/184) subjects in the placebo group had potentially clinically significant LFT abnormalities, incidences of increases in AST, ALT, ALP or T-Bil were similar between placebo and edaravone patients.

In safety set 4, higher incidences of treatment-emergent LFT abnormalities in EE (8.8%) and PE (7.5%) groups were found compared to the EP group (2.2%). This imbalance was primarily driven by increase in ALP (> 400 U/L) which occurred in 5.3% EE, 4.8% PE and 2.2% EP patients, respectively, however, these latter numbers included also patients with ALP increase (> 400 U/L) at baseline which concerned approx. half of the subjects with ALP increase in the PE and EP groups, but not in the EP group.

The incidence of hepatic TEAEs (including LFT abnormalities) in the subset of subjects with concomitant riluzole were comparable in the edaravone and placebo group (Safety Set 1).

Review of renal TEAEs was performed based on post-marketing experience in AIS patients in Japan.

No renal TEAEs, defined as TEAEs in the acute renal failure SMQ (narrow) or chronic kidney disease SMQ (narrow) occurred in the 5 clinical ALS studies.

Renal function test abnormalities:

Whereas in safety set 1 increase in blood urea nitrogen (BUN) ≥ 30mg/dL was found in 3 (1.6%) patients in the edaravone group vs. no patients in the placebo group, in safety set 4, a respective increase in BUN was found in 1 patient of the EP group (2.2%, i.e. during current treatment with placebo) and 1 patient in the EE group (0.9%), but in none of the PE group. Creatinine increase (≥2 mg/lL) was not found in any patient of safety sets 1 and 4, respectively.

Serious adverse events and deaths

Death cases

In Safety Set 1, the incidence of treatment-emergent death was 1.1% (2/184) in the placebo group and 2.2% (4/184) in the edaravone group. All of the fatal TEAE were respiratory in nature of ALS, occurring in cycles 3 through 6.

In Safety Set 4, the incidence of treatment-emergent death was 4.4% (2/45) in the EP group, 3.4% (5/146) in the PE group, and 3.5% (4/113) in the EE group. In set 4 most of the fatal TEAEs were respiratory in nature of ALS, occurring in cycles 7 through 12.

In Safety Set 2 (overall ALS study population) and across all treatment groups, 6 patients died during treatment cycle 1-6 (Set 1), 11 patients died during treatment cycle 7-12 (Set 4) and 2 further patients died after cycle 12 (both in cycle 15 in the EE group and respiratory in nature). None of the death cases were considered to have a reasonable possibility of causal association with the study drug, all were attributed to worsening ALS.

SAEs

In safety set 1 the incidence of treatment-emergent SAEs was 22.3% (41/184) in the placebo group and 17.4% (32/184) in the edaravone group. In both treatment groups, the SOCs with the highest incidence of SAEs were the respiratory, thoracic, and mediastinal disorders SOC and gastrointestinal disorders SOC.

Although the overall incidence of SAEs in respiratory, thoracic, and mediastinal disorders SOC was similar for the 2 treatment groups (6.0% in the edaravone group versus 6.5% in the placebo group), the incidences of dyspnoea PT (1.6% versus 0.5%) and respiratory disorder PT (3.3% versus 1.1%) were higher in the edaravone group, while the incidences of pneumonia aspiration PT (0.0% versus 1.6%) and respiratory failure PT (1.1% versus 2.7%) were lower in the edaravone group.

No other differences in incidence or type of SAEs were observed between the 2 treatment groups (including SAEs in the gastrointestinal disorders SOC or individual PTs within this SOC).

No significant differences in SAEs with respect to timing of onset were observed between the 2 treatment groups.

In safety set 4 the incidence of treatment-emergent SAEs was highest in the PE group (37.0%; 54/146 subjects), followed by the EE group (31.9%; 36/113 subjects) and was lowest in the EP group (15.6%; 7/45 subjects).

These higher incidences were primarily driven by:

• Higher incidences of SAEs in the respiratory, thoracic, and mediastinal disorders SOC for both of these groups (13.7% for the PE group and 12.4% for the EE group, compared to 4.4% for the EP group),

• Higher incidences of SAEs in the musculoskeletal and connective tissue disorders SOC for both of these 2 treatment groups (8.9% for the PE group and 9.7% for the EE group, compared to 4.4% for the EP group), and

• Higher incidence of SAEs in the gastrointestinal disorders SOC for the PE group (19.9% for the PE group, compared to 8.9% and 8.8% for the EP group and EE group, respectively).

Laboratory findings

Liver function test (LFT) abnormalities and renal function laboratory abnormalities of safety sets 1 and 4 have been presented in the context of the review on hepatic TEAEs and renal TEAEs .

No further signal of concern arose from serum chemistry measurements of safety sets 1 and 4, respectively.

Hematology

A higher incidence of decreased platelet count of potential clinical relevance (< 100,000/mm³) was found in the edaravone group (5/184, 2.7%) compared to placebo (no patients) during cycles 1-6 of treatment, however, no further cases of decreased platelet count occurred during cycles 7-12. Further review of these cases and the overall clinical ALS safety data base (safety set 2) revealed a total of 7 subjects with decreased platelet count (< 100.000/mm³). Of these, 4 had CTCAE grade 1-2 decreased platelets prior to first edaravone dose, with unchanged CTCAE grade in 3 subjects and intermittent decrease to grade 3 in one further subject. The remaining 3 subjects had decreased platelets as single occurrences confounded by improper blood draw and haemolysis or coagulation of the blood sample, respectively. Apart from one case of mild and non-serious contusion in a subject with (CTCAE grade 1) decreased platelet count at baseline and throughout the study, no further case of bleeding events were reported in the context of thrombocytopenia.Treatment emergent low hemoglobin occurred with similar rates in edaravone (6.0%) and placebo patients (5.5%) during cycles 1-6 (safety set 1). During cycles 7-12, the incidence was highest in the EE group (5.4%), which nevertheless did not exceed the incidence in edaravone or placebo treated patients in safety set 1.

Urinalyses showed a higher incidence (>5%) of glucosuria in edaravone (23.9%) compared to placebo (17.4%) treated subjects in safety set 1. Similarly, a higher incidence was found in patients treated with edaravone compared to placebo during cycles 7-12 (safety set 4).

Other findings

Apart from body weight, vital signs were not scheduled as an examination parameter in the ALS clinical studies. Body weight decrease (at least one decrease ≥ 7%) was reported in 27.7% placebo and 25.5% edaravone subjects (safety set 1) as well as in 26.7% (EP), 34.9% (PE) and 24.8% (EE) of patients in safety set 1.

ECG examinations were not performed in the ALS clinical studies.

In preclinical studies, the result of hERG assay was negative. In the 5 phase I studies in healthy volunteers, no clinically significant ECG changes were described.

A thorough QTc study will be conducted in Japan (scheduled availability of study report Q4 2019).

Sensory tests

Sensory tests (evaluating presence and severity of numbness and staggering, respectively via patient questioning as well as vibratory sensation via tuning fork placed at malleolus) were performed in the clinical ALS studies. In Safety Set 1, no relevant differences in vibratory sensation and in frequencies of numbness and staggering were observed between edaravone and placebo treated subjects. In Safety Set 4, relevant differences in these 3 parameters were not observed between end of cycle 6 and end of Cycle 12. Available data do not allow to draw conclusions on effects of treatment beyond 12 months.

Safety in special populations

The overall incidence of TEAEs by gender was 85.3% in male and 90.7% in female edaravone patients, compared to approx. 87% of TEAEs in male and also female placebo patients, respectively. Headache (12.0% and 5.5%) and contusion (21.3 % vs. 10.1 %) occurred approx. twice as often in female compared to male edaravone patients, and for both TEAEs, the difference to placebo was also clearly higher in female compared to male edaravone subjects.

The maximum age evaluated in the 5 ALS studies was 75 years. In safety set 1, 53 patients were ≥ 65 years, and 2 subjects were 75 years old. In safety set 1, the overall incidence of TEAEs was slightly lower in older (≥ 65 years) compared to younger subjects in edaravone as well as placebo treatment groups. In the subgroup of elderly (≥ 65-75 years) no significant differences in frequencies of SAEs and AEs leading to discontinuation were observed between the edaravone and placebo group.

Analysis of TEAEs (by PT) by edaravone and age is not considered indicative of an increased safety risk of edaravone with increasing age. No further safety signals with regard to age arose from safety set 4 , however, the number of subjects ≥ 65 per subgroups in safety set 4 was limited (N=7 in EP group).

In study MCI186-18, an exploratory study (including 13 edaravone and 12 placebo subjects) evaluating edaravone in grade 3 ALS (i.e. patients "requiring assistance for eating, excretion, or ambulation"), a higher incidence of SAEs (edaravone group: 23.1%, placebo group: 16.7%) as well as a higher incidence of ADRs (edaravone group 23.1%, placebo group: 8.3%) was reported in edaravone compared to placebo patients. No SAE was considered treatment related.

Ethnicity – Safety in Japanese and EU population

The clinical development program for edaravone in ALS was conducted exclusively in Japanese patients. Overall, 2 phase I studies in healthy volunteers (HV) (MCI186-E01 and MCI186-E02) and 1 phase 2 study in AIS subjects (MCI186-E04) have been performed in European subjects using different posology of edaravone, treatment duration was ≤ 14 days.

In five finalized Japanese and Caucasian HV studies, incidences and types of treatment-emergent AEs and drug-related AEs were similar between the placebo and edaravone groups. There were no clinically significant changes in laboratory parameters, vital signs, ECG, physical examination, and neurological assessments. No safety signals were observed in the 5 studies, no SAEs, AEs resulting in discontinuation, or other significant AEs were reported in these studies. Further phase I studies are ongoing or have recently been conducted, however, only preliminary results have hitherto been submitted (concerning Japanese subjects with mild to moderate renal impairment and hepatic impairment, respectively).

The EU study in AIS subjects (E04) was conducted using continuous infusion regimens for 72 hrs. There were no notable differences in AEs including laboratory abnormalities across treatment groups (placebo and 2 different edaravone doses), no dose-dependent AEs were observed, and no new safety concern was observed in this study.

Safety related to drug-drug interactions and other interactions

As it was estimated that the potential of causing drug interactions would be low at clinical dose, no formal interaction studies have been conducted by the Applicant.

In safety set 1, additional analyses of TEAEs for the subset of subjects with concomitant riluzole were in line with the results of the overall study population. Similarly, the incidence of hepatic TEAEs (including LFT abnormalities) in the subset of subjects with concomitant riluzole were comparable in the edaravone and placebo group.

Discontinuation due to AEs

In general, the incidence of discontinuation from study drug due to AEs was low and numerically somewhat lower in the edaravone (2.2%) compared to placebo patients (5.4%) during the first 6 cycles of treatment (safety set 1). In the edaravone group, apart from three death cases, only 1 further patient discontinued IMP due to an AE (safety set 1), “toxic skin eruption” (PT) of moderate intensity.

In safety set 4, discontinuation rate due to AEs was somewhat higher in the PE group (7.5% compared to 4.4% in EE and EP group each). The majority of AEs leading discontinuation occurred in the SOC of respiratory, thoracic and mediastinal disorders across all treatment groups of safety set 4. Further, one possibly related skin reaction during edaravone treatment (mild rash) lead to IMP discontinuation in this safety set.

Safety in non-ALS indications:

Clinical trial experience in the acute ischemic stroke (AIS) indication is available from 5 Japanese studies with a total of 569 edaravone and 125 placebo treated subjects, one European phase 2a study (E-04) with 25 edaravone and 11 placebo subjects and an uncontrolled Korean AIS study (56 edaravone subjects). In these studies, different total daily edaravone doses (administered i.v.) have been divided in two single doses or initial bolus was followed by continuous infusion. Duration of edaravone treatment has been evaluated for up to 14 days.

In the 5 Japanese AIS studies, the overall incidence of drug-related AEs (based on investigator attribution) was 4.6%. In the phase 3 study, incidences of drug-related AEs, hepatic function disorder, and deaths were similar between the 2 treatment groups (edaravone versus placebo): 7.2% versus 11.2% for drug-related AEs; 3.2% versus 5.6% for hepatic function disorder; 3.4% versus 5.5% for death. Incidence of drug-related AEs was similar among older versus non-older subjects (4.0% versus 5.5%). No new safety concerns arose from the EU and Korean studies.

In addition, 3 Japanese studies have been performed in subarachnoidal hemorrhage (SAH) in which a total of 367 subjects received edaravone. In these studies 30-180 mg/day have been administered as continuous i.v. infusion over 24 hours for up to 14 days. In the 2 SAH studies which were placebo controlled, no significant difference in incidences of drug-related AEs and SAEs was observed between the edaravone group and the placebo group.

Post marketing experience

AIS indication

As of 04 November 2017, approximately 1.76 million AIS patients have been exposed to edaravone since first approval. Further, AIS patients treated with edaravone have been evaluated in a post-marketing clinical study and post-marketing survey studies:

• A postmarketing Phase IV clinical study (MCI186-13) conducted in Japan (edaravone: 199, ozagrel sodium: 202 subjects), there was no significant difference between the 2 treatment groups with regard to incidences of drug-related AEs, AEs, SAEs, or AEs of interest (renal disorder, liver disorder, or cerebrovascular disorder).

• A Drug Use-Results Survey was conducted in Japan (survey period: October 2001 to September 2004, subjects enrolled through a central registration system, safety analysis set: 3882 subjects): drug-related AEs developed in 11.1% (431/3882 subjects). Incidences of drug-related AEs were higher in the presence (16.8%) than in the absence (10.6%) of hepatic function disorder, and were higher in

the presence (23.9%) than in the absence (10.4%) of renal impairment. No significant difference was noted in the incidence of drug-related AEs in older (10.9%) versus non-older (11.7%) subjects.

• A Special Drug Use-Results Survey was conducted retrospectively in patients with pediatric cerebral infarction who used edaravone between 04 April 2001 and 31 July 2006 (134 subjects enrolled, safety analysis set: 118 subjects).

From 2001 to 2009, based on post marketing spontaneous reports, the following 8 terms were added to the Japan package insert as clinically significant adverse drug reactions (ADRs) according to local practice:

(a) Fulminant hepatitis, hepatic dysfunction, jaundice; (b) Acute renal failure, nephrotic syndrome; (c) Anaphylactic shock; (d) Thrombocytopenia; (e) Granulocytopenia; (f) Rhabdomyolysis; (g) Disseminated intravascular coagulation; and (h) Acute lung injury.

Information relevant to these 8 ADRs was reviewed in Report No. MCI186-N04 (Safety Specification Assessment Report: Review of Clinically Significant Adverse Reactions for Determination of Risks for Edaravone). This report comprised data (received as of 25 December 2015) from nonclinical, clinical (placebo-controlled trials, survey studies, and postmarketing trials), post marketing, and literature sources. The Sponsor also conducted a quantitative risk analysis of acute kidney injury (AKI), hepatic function disorder (HFD), thrombocytopenia, and leukopenia in acute ischemic stroke (AIS) patients treated with edaravone, using data from an external database (Fukuoka Stroke Registry, consisting of 7459 consecutive AIS patients).

Although in ALS clinical studies, a higher incidence of decreased platelet count of potential clinical relevance was found in the edaravone group (5/184, 2.7%) compared to placebo patients (0%) during cycles 1-6 of treatment, no further cases of decreased platelet counts occurred during cycles 7-12. However, additionally presented evaluation of these cases (and of 3 further cases of the overall clinical ALS safety data base (safety set 2), did not substantiate the risk of decreased platelet counts. No further evidence of a risk of edaravone with regard to these 8 adverse events has been found in the clinical studies (ALS, AIS or SAH indication).

Post-marketing overall 9 serious cases consistent with anaphylactic reaction including events with urticaria, decreased blood pressure and dyspnea, respectively were reported as of 25 Dec 2015. Possible alternative causes were present in the majority but not in all of these cases and a contributory role of edaravone was at least possible in all cases. 5 of these 9 cases occurred on the 1st or 2nd day of edaravone administration, 4 cases occurred between the 5th and 9th day of edaravone administration (recommended treatment duration: up to 14 days overall).

Quantitative risk analysis using the external database (Fukuoka Stroke Registry) revealed that patients who used edaravone had a higher risk of developing white blood cell count abnormality (cutoff < 4000/μL) than those who did not use edaravone, after adjusting for all other confounding factors (adjusted odds ratio 2.62; 95% CI 1.21-5.69), however, secondary analyses did not reach statistical significance.

No further evidence of a causal relationship of edaravone with regard to these 8 AEs was derived from this review, including evaluation of cases revealed through internal global safety database search, however in some cases received post-marketing, a contributory role of edaravone for aggravation of pre-existing or concurrent hepatic function disorder or renal impairment, respectively, as well as for thrombocytopenia, granulocytopenia, DIC and ALI, respectively could not be completely excluded.

ALS indication

Through 04-Aug-2018, the estimated cumulative worldwide post-marketing exposure is 6,603 ALS patients. In addition, 24 (EU) and 197 (Canada) ALS patients have been enrolled in special access

programs through 05-Nov-2018). 277 death cases were received, often with limited information. The most frequently reported fatal AEs (by PT) were compatible with ALS related events. Similarly, the most-frequently reported AEs and SAEs would generally be expected during the natural course of ALS.

The cumulative post-marketing data for ALS patients from all post-marketing sources received through 06-Sep-2018 were reviewed with particular focus on the 8 ADRs added to the Japan package insert based on post-marketing reports in the AIS indication and led to the following findings: One out of 4 cases that matched the search criteria for shock/anaphylactoid reaction described a serious anaphylactoid reaction in which a causal association with edaravone is plausible. The 3 other cases had alternative cause and negative re-challenge with edaravone, were sparsely documented or were consistent with septic shock, respectively. The applicant concludes, that review of the SAE reports does not reveal a signal for edaravone-induced fulminant hepatitis, significant hepatic dysfunction or jaundice. Counfounding factors (e.g. concomitant riluzole, or negative rechallenge) were reported in 15 out of 19 cases, however further information is requested on the remaining cases.

No signal was revealed for edaravone-induced significant renal failure/nephrotic syndrome, thrombocytopenia, granulocytopenia, rhabdomyolysis, DIC, or acute lung-injury, respectively.

The reported AEs from US post-marketing data (through 04-Aug-2018; cumulative exposure 2,999 ALS patients) that may be presumed to reflect the Caucasian population safety profile are generally consistent with the worldwide ALS post-marketing data. With regard to post-marketing data in the ALS indication, the following reports were further provided:

• Implementation Report on Early Post-marketing Phase Vigilance for Radicut@ (covered time period 26 June 2015 - 25 December 2015). According to this 6-month post-marketing report, the following serious cases were reported: anemia (1 case), asthma (1 case), respiratory failure (2 cases), and blood creatine (phospho)kinase (CK) increased (1 case).

• Development Safety Update Report (DSUR) 2 (reporting period: 04 April 2016 – 3 April 2017):

During the reporting period, no SAE were reported for overall 3 subjects participating in one of two ongoing clinical trials; no trials were completed.

3.3.9. Discussion on clinical safety

ALS is a rare disease with a prevalence of 3.85 per 100,000 in the EU (Orphanet 2018) or 5.4 (4.06–7.89) per 100,000, based on the publication of Chio et al. (2013). According to the CHMP Guideline on clinical investigation of medicinal products for the treatment of ALS, the recommendations in ICH E1 should be followed with regard to clinical safety exposure. The presented safety data base for edaravone in ALS with a total of 349 Japanese ALS patients receiving edaravone, 98 of which have been treated for at least 12 months is of borderline size but acceptable for the orphan condition of ALS. The maximum duration of treatment of 15 months is limited considering, that edaravone in ALS is scheduled as long-term treatment.

Clinical trial experience is also available in the AIS indication from 5 Japanese studies with a total of 569 edaravone treated subjects, one European phase 2a study (E-04) with 25 edaravone subjects and an uncontrolled Korean study, as well as from 3 Japanese studies in subarachnoidal hemorrhage (SAH) with a total of 367 edaravone treated subjects. No additional safety signals arose from these studies. However, as posology in all these studies was different from the ALS posology (including total daily doses, infusion velocity and/or division of total daily dose and partly continuous infusion), duration of treatment was short-term (14 days at most) in all these studies, and as further AIS and SAH patient populations clearly differ from ALS patients, the informational value resulting from available non-ALS safety data is limited.

Except from exploratory phase 2 study MCI186-12 (in which lower daily doses were applied in 1/3 of study subjects), edaravone posology in all ALS studies was in line with the posology proposed for the SmPC.

Clinical safety assessment in ALS is based on 4 safety sets, of which set 1 evaluating the first 6 months of treatment represents the main safety set, as it comprises the double blind, placebo controlled phases of all phase 3 studies (except for extension study MCI186-17). Controlled follow up during months 7-12 (set 4) was not blinded for all subjects, this safety set included also a (rather small) placebo (EP) group and further allowed for direct comparison of patients with longer (EE) compared to shorter (PE) edaravone exposure. Continuous treatment ≥ 7 months was captured in set 3, set 2 comprised all edaravone treated ALS patients.

Overview of TEAEs during the first 6 month of treatment (safety set 1) indicates a favourable safety profile of edaravone: Incidences of overall TEAEs were very similar in the placebo (87.0%) and edaravone group (87.5%). The incidence of drug-related AEs was low (14.1% and 10.3% in placebo and edaravone subjects) and incidences of ADRs, AEs/ADRs leading to drug discontinuation as well as SAEs tended to be lower in the edaravone group. No SAEs were considered drug related. Two patients (1.1%) in the placebo group and 4 patients (2.2%) in the edaravone group died, all death cases were considered attributable to advanced ALS.

The most common TEAEs by SOC were infections and infestations (31.0% in placebo and 34.2% in edaravone group), gastrointestinal disorders (37.0 % and 31.0 %), skin and subcutaneous tissue disorders (20.1% and 25.5 %), musculoskeletal and connective tissue disorders (21.2 % and 19.6 %), general disorders and administration site conditions (20.1 % and 22.3 %) and injury, poisoning and procedural complications (19.6 % and 21.2 %).

In safety set 1 seven TEAEs (by PTs) were reported with a higher incidence (i.e., +2% absolute) in the edaravone compared to the placebo group (ordered by frequency): contusion (14.7% versus 8.7%), gait disturbance (12.5% versus 9.2%), headache (8.2% versus 5.4%), eczema (6.5% versus 2.2%), dermatitis contact (6.0% versus 3.3%), respiratory disorder (4.3% versus 1.1%), and glucose urine present (3.8% versus 1.6%).

In general, it is not considered plausible, that intravenously administered IMP would cause contact dermatitis (except for local reaction at the injection site), and none of these cases of contact dermatitis was regarded an adverse drug reaction. Instead dermatitis is proposed to be labelled in section 4.8 of the SmPC with frequency calculation based on grouping of similar PTs. All other of these TEAEs which occurred at a (≥ 2 %) higher frequency in the edaravone vs. placebo group of safety set 1 are proposed to be labelled in section 4.8 of the SmPC by the Applicant.

In Safety Set 4, the incidences of TEAEs (by PT) in the EE group were generally similar to and partly even lower than those in the EP group. However, TEAEs with (>2% absolute) higher incidence in the EE group compared to EP group were catheter site infection (0% in EP and 2.7% in EE), speech disorder (0% and 2.7%), pneumonia aspiration (0% and 2.7%), respiratory disorder (0% and 6.2%), upper respiratory tract inflammation (2.2% and 4.4%), dysphagia (6.7% and 8.8%), gastritis (2.2% and 4.4%), dermatitis contact (0% and 2.7%), eczema (4.4% and 7.1%), pruritus (2.2% and 4.4%), musculoskeletal disorder (6.7% and 9.7%), nocturia (0% and 2.7%), and pyrexia (0% and 2.7%). The majority of these TEAEs could also be attributable to the underlying disease (and treatment thereof). In contrast, ALS per se is not considered to adequately explain skin associated TEAEs.

In safety set 1, 12% edaravone subjects experienced at least one severe TEAE, the proportion being slightly lower compared to the placebo group (15.2%). By PT, severe gait disturbance occurred at a higher frequency in edaravone compared to the placebo group (5.4% vs. 2.7%), no other severe TEAEs by PTs occurred in ≥ 2 % of subjects and at a higher frequency in the edaravone group.

The majority of TEAEs which occurred during cycles 1-6 (safety set 1) and 7-12 (safety set 2), respectively were considered not related to IMP. The only drug-related AEs reported in safety set 1 in more than 1 patient of the edaravone group were glucose urine present (proposed to be labelled) and liver function test (LFT) abnormal, reported in 2 (1.1%) edaravone patients each. In contrast, drug-related hepatic function abnormal occurred in 4 (2.2%) placebo but only 1 (0.5%) edaravone patients.

In safety set 4, incidence of drug-related AEs was similar in the EE and EP groups (5.3% and 4.4%, respectively) and somewhat higher in the PE group (8.2%); nevertheless, incidence of drug-related AEs in all treatment groups of safety set 4 during cycles 7-12 was lower than that reported during cycles 1-6 in safety set 1 (10.3% in edaravone group, 14.1% in placebo group).

Overall 17 death cases were reported in safety set 1 plus safety set 4. Whereas the incidence of death was numerically higher in the edaravone (4/184; 2.2%) compared to placebo group (2/184; 1.1%) in safety set 1, the incidence of death in safety set 4 was numerically highest in the EP group (4.4%), i.e. in patients who received placebo during the period of interest, compared to the PE (3.4%) and EE (3.5%) group, respectively. Two further patients of the EE group died after cycle 12 (both in cycle 15). In line with respiratory failure being reported in literature to be the most frequent cause of death from ALS (Gil, 2008), the majority of death cases in the ALS studies (placebo and edaravone subjects) were respiratory in nature and all death cases were compatible with and attributed to ALS worsening.

The frequency of SAEs was somewhat lower in the edaravone (17.4%) compared to the placebo group (22.3%). In both treatment groups, SAEs occurred most frequently in the Respiratory, thoracic and mediastinal disorders and the Gastrointestinal disorders SOCs (Safety Set 1). In contrast in safety set 4, imbalances were seen with regard to SAEs which occurred with a frequency of 37.0%, 31.9% and 15.6% in the PE, EE and EP group, respectively. These imbalances were primarily driven by higher incidences in the SOCs of respiratory disorders, musculoskeletal disorders and in the PE group also by dysphagia (PT). No SAE in safety sets 1or 4 was considered related to treatment but all seemed related to ALS progression. The imbalances in SAEs of safety set 4 may be explained by baseline imbalances of safety set 4 in favour of the EP group which concerned (most importantly) % FVC and ALS severity, but also initial bulbar symptoms, certainty of diagnosis and age, and may have impacted the rate of ALS progression and thus have increased the occurrence of events caused by the underlying disease. Further, the subgroup of EP patients (who showed the most favourable results) was small (N=45). In this context, it is considered particularly reassuring, that safety results for the EE group (which had a longer edaravone exposure) were generally more favourable than those of the PE group.

Respiratory TEAEs (defined as TEAEs in the Respiratory, thoracic and mediastinal disorders SOC) were reviewed, as imbalances were observed in the ALS studies. Progressive respiratory disorder usually occurs during the course of ALS, in particular in advanced disease stages.
In safety **set 1**, the incidence of respiratory disorder (PT) TEAEs was +2% (absolute) higher in edaravone (4.3%) versus placebo patients (1.1%). However, respiratory failure (PT), which implies a more severe stage of a similar event compared to respiratory disorder, occurred at somewhat lower incidence in edaravone vs. placebo patients (1.1% vs. 2.7%). Overall, respiratory TEAEs by SOC occurred at similar incidence and no further imbalances by PT were found. A generally similar reporting pattern was found with regard to respiratory SAEs. In contrast, in safety **set 4**, numerical imbalances occurred in the overall incidence of respiratory TEAEs and SAEs which were highest in the PE group (21.9% respiratory TEAEs and 13.7% respiratory SAEs), followed by the EE group (20.4% and 12.4%) and appeared generally lower in the EP group (13.3% and 4.4%). Again, these imbalances may be explained by the baseline imbalances of safety set 4 in favour of the EP group which included respiratory function (%FVC). Further, comparison of the PE and EE groups (also by individual studies) showed no consistent trend of a higher frequency of any individual respiratory serious/TEAE (by PT) in the EE group (which had a longer edaravone exposure) compared to the PE group. For safety **sets 1 and 4**, individual case review suggested that respiratory SAEs and deaths were of similar type and

respective events clinically appeared to occur in the context of ALS progression. In summary, no clear serious safety concern can be derived from safety set 1 regarding respiratory TEAEs or SAEs. The imbalances in SAEs and respiratory SAEs of safety set 4 may be explained by baseline imbalances of safety set 4 in favour of the EP group, further, the subgroup of EP patients (who showed the most favourable results regarding SAEs) was small (N=45).

Nevertheless, the results of safety set 4 may also be interpreted as a less favourable safety profile of edaravone in patients with more advanced ALS in particular with regard to respiratory TEAEs, and a potential neurotoxic effect of edaravone might provide a possible explanation for this.

Based on pre-clinical findings of axonal nerve fibre degeneration attributed to reduced vitamin B6 plasma levels, neurotoxicity is considered an important potential risk.

As degeneration of motor neurons caused by IMP would presumably not have been distinguishable from clinical ALS symptoms, sensory tests were performed, which did not reveal clear differences between edaravone and placebo groups. However, the sensitivity of the tests applied to detect possible degeneration of sensory neurons is unclear. Severe TEAEs of Gait disturbance developed at a higher incidence in the edaravone group compared to the placebo group (5.4% versus 2.7%, safety set 1) and in safety set 4, 2 EP (4.4%), 10 PE (8.9%), 11 EE (9.7%) subjects experienced a serious TEAE in the Musculoskeletal and connective tissue disorders SOC. However, further analyses of the available clinical data regarding gait disturbance and musculoskeletal disorders do not allow to conclusively differentiate between possible edaravone induced neurotoxicity and worsening of ALS due to natural history of the disease.

Unfortunately, vitamin B6 blood levels have not been evaluated in clinical studies. The applicant is therefore requested to retrospectively measure vitamin B6 blood levels, if retention samples of the ALS clinical studies are still available and to evaluate appropriate recommendations for vitamin B6 plasma determination and supplementation, respectively as well as for electrophysiological monitoring (e.g. by testing of motor or sensory nerve conduction) in order to allow for early detection of neurotoxicity during treatment with edaravone.

Based on the postmarketing experience in AIS patients in Japan, hepatic TEAEs (defined as TEAEs in the Drug related hepatic disorders - comprehensive search Standardised MedDRA Query [SMQ]) were reviewed. In safety set 1, the incidence of hepatic TEAEs, defined as TEAEs in the drug related hepatic disorders SMQ, was similar between treatment groups, and numerically even slightly higher in the placebo (5.4%) compared to the edaravone (4.3%) group. In safety set 4, the incidence of hepatic TEAEs was highest in the PE group (3.4%), nevertheless the incidence in the PE group was still lower as compared to the incidence in the placebo group of safety set 1 (5.4%). In safety set 4 the incidence of hepatic TEAEs was lowest in the EE group (0.9%). None of the hepatic TEAEs in edaravone treated subjects of safety set 1 or 4 was serious or severe.
The incidence of potentially clinically significant LFT abnormalities in safety set 1 was rather low and similar between placebo and edaravone patients without imbalances. In safety set 4, higher incidences of treatment-emergent LFT abnormalities in EE (8.8%) and PE (7.5%) groups were found compared to the EP group (2.2%). This imbalance was primarily driven by increase in ALP (> 400 U/L) which occurred in 5.3% EE, 4.8% PE and 2.2% EP patients, respectively. However, these latter numbers included also patients with ALP increase (> 400 U/L) at baseline which concerned approx. half of the subjects with ALP increase in the PE and EP groups, but not in the EP group. No hepatic toxicity was identified in nonclinical studies and the presented data from ALS studies do not raise safety concerns with regard to hepatic impairment.
However, it should be taken into consideration, that a high proportion (approx. 90%) but not all patients in the edaravone ALS studies took concomitant riluzole, which is associated with abnormal liver function tests (very common) and hepatitis (unknown frequency). The incidence of hepatic TEAEs

(including LFT abnormalities) in the subset of subjects with concomitant riluzole was comparable in the edaravone and placebo group, however, further safety analyses in the subset of using concomitant riluzole of safety set 1 is requested regarding related AEs including hepatic impairment.

Based on post-marketing experience in AIS patients in Japan, renal TEAEs (defined as TEAEs in the Acute renal failure SMQ [narrow] or Chronic kidney disease SMQ [narrow]) were reviewed.
No renal TEAEs defined as TEAEs in the acute renal failure SMQ (narrow) or chronic kidney disease SMQ (narrow) occurred in the 5 clinical ALS studies and renal function test abnormalities do not raise further concerns.

Currently safety data of edaravone in patients with severe hepatic or renal impairment is missing. Preliminary results of phase I studies in Japanese subjects with mild to moderate renal or hepatic impairment require further clarification but indicate, that caution is required in patients with moderate renal or hepatic disease. Further, in a Drug Use-Results Survey conducted in Japan including 3882 subjects, incidences of drug-related AEs were higher in the presence (16.8%) than in the absence (10.6%) of hepatic function disorder, and were higher in the presence (23.9%) than in the absence (10.4%) of renal impairment. Appropriate recommendation should be added to section 4.2 of the SmPC (as specified in the attached document).

Further safety in ALS patients with decreased respiratory function (%FVC < 80%), in ALS severity grade >3, and in AIS patients > 75 years is missing.

Review of skin related TEAES based on selected PTs from Hypersensitivity SMQ was performed based on imbalances with regard to skin related TEAEs. A higher frequency of skin related TEAEs in safety sets 1 and 4 appeared mainly driven by a higher frequency of eczema and dermatitis contact. Eczema (6.5% vs. 2.2%) and dermatitis have been identified as adverse drug reactions by reason of higher frequency of occurrence of respective TEAEs in Safety Set 1. In safety sets 1 and 4, no skin TEAEs were serious or severe; except for 1 moderate event of eczema (EE group, set 4) and 1 moderate toxic skin eruption PT (edaravone group, set 1), all skin TEAEs during edaravone exposition were mild. Review of potentially important skin TEAES derived from the clinical ALS studies did not suggest an increased risk for development of edaravone induced skin effects that would impact the benefit-risk profile of edaravone. However, taking into consideration that rash was assessed as drug related in overall 5 patients exposed to edaravone in safety sets 1 and 4 combined, the Applicant is still requested to discuss addition of rash as ADR to section 4.8 of the SmPC including frequency calculation as appropriate .

Overall, no safety signals were derived from clinical chemistry findings.
A higher incidence of decreased platelet count of potential clinical relevance (< 100,000/mm³) was found in the edaravone group (5/184, 2.7%) compared to placebo (no patients) during cycles 1-6 of treatment, however, no further cases of decreased platelet count occurred during cycles 7-12. However, additionally presented evaluation of these cases (and of 3 further cases of the overall clinical ALS safety data base (safety set 2), did not substantiate the risk of decrease platelet count from clinical ALS studies.

A higher incidence (>5%) of glucosuria was found in edaravone (23.9%) compared to placebo (17.4%) treated subjects in safety set 1. Similarly, a higher incidence was found in patients treated with edaravone compared to placebo during cycles 7-12 (safety set 4). Blood glucose and glycated hemoglobin (HbA1c) were not collected in the 5 ALS studies. Glucosuria is proposed to be labelled in section 4.8 of the SmPC.

In preclinical studies, the result of hERG assay was negative. ECG examinations were not performed in the ALS clinical studies. In the 5 submitted phase I studies in healthy volunteers, no clinically significant ECG changes were described, however, only one of these studies (No. E02) was designed to

determine ECG effects. This latter study raised no concerns regarding ECG changes however due to limitations in study design it is not suitable in order to exclude small effects of edaravone on QTc. The study report of a Japanese thorough QT study is scheduled to be available Q4 2019.

The overall safety profile appeared not to differ by gender, however a higher occurrence of headache (12.0% and 5.5%) and contusion (21.3 % vs. 11.8%) in females compared to males was found. Most contusion events were mild, none of the contusion events of safety set 1 was serious or resulted in study drug discontinuation, nevertheless, as contusion could potentially also result in more severe consequences, the clearly higher incidence in female compared to male subjects should be given in section 4.8 of the SmPC.

Analysis of TEAEs and SAEs by edaravone and age is not considered indicative of an increased safety risk of edaravone with increasing age (safety set 1). No further safety signals with regard to age arose from safety set 4, however, the number of subjects ≥ 65 per subgroups in safety set 4 was limited (N=7 in EP group.

Edaravone has been marketed in Japan since 2001 in the AIS indication and since 2015 in the ALS indication. In May 2017 edaravone was approved in the ALS indication in the US. Comprehensive review of available safety information (including pre-clinical data, post-marketing AIS and literature data) has been performed with regard to 8 adverse events which had been added to the Japanese package insert due to post-marketing reports in the AIS indication:

(a) Fulminant hepatitis, hepatic dysfunction, jaundice; (b) Acute renal failure, nephrotic syndrome; (c) Anaphylactic shock; (d) Thrombocytopenia; (e) Granulocytopenia; (f) Rhabdomyolysis; (g) Disseminated intravascular coagulation (DIC); and (h) Acute lung injury (ALI).

In addition, the cumulative post-marketing data for ALS patients from all post-marketing sources received through 06-Sep-2018 were reviewed with particular focus on these 8 adverse events.

No clear evidence of a risk of edaravone with regard to these 8 adverse events has been found in the clinical studies (ALS, AIS or SAH indication).

Although no evidence of risk for anaphylaxis associated with edaravone was found in the clinical trial data, post-marketing overall 9 serious cases consistent with anaphylactic reaction including events with urticaria, decreased blood pressure and dyspnea, respectively were reported as of 25 Dec 2015 in the AIS indication. Possible alternative causes were present in the majority but not in all of these cases and a contributory role of edaravone was at least possible in all cases. In addition, post-marketing data in the ALS indication (through 06-Sep-2018) revealed one further case of serious anaphylactoid reaction in which a causal association with edaravone is plausible. None of these events were fatal. Information and warning regarding anaphylactic reaction, anaphylactic shock and hypersensitivity is proposed for SmPC sections 4.2, 4.3, 4.4 and 4.8, respectively. The number of respective post-marketing reports was low taking exposure into consideration (estimated ALS patient exposure 6,603); estimated AIS patient exposure approx. 1.7 million). The applicant's argumentation that additional information collected during the registry study for hypersensitivity-related events would not be expected to necessitate further changes to the currently proposed risk minimization measures (via PI labelling) can therefore be followed. No further evidence of a causal relationship of edaravone with regard to the remaining 7 AEs was derived from the review of AIS data, however in some cases of the Internal global database (ARISg), a contributory role of edaravone for aggravation of pre-existing or concurrent hepatic function disorder or renal impairment, respectively, as well as for thrombocytopenia, granulocytopenia, DIC and ALI, respectively could not be completely excluded. Similarly, the available post-marketing experience in AIS does not reveal a signal for edaravone-induced significant renal failure/nephrotic syndrome, thrombocytopenia, granulocytopenia, rhabdomyolysis, DIC, or acute lung-injury, respectively. Further information regarding 4 of the 19

hepatic dysfunction SAEs reported in ALS post-marketing is requested. With the exception of anaphylaxia, these AEs will be further evaluated in the ALS registry post-marketing as AESI and reports of respective adverse events will be evaluated as cumulative reviews in PSURS.

Available post-marketing US safety data are not indicative of safety differences between Caucasian and Japanese patients.

The clinical development program for edaravone in ALS was conducted exclusively in Japanese patients. 2 EU studies in healthy volunteers and 1 phase 2a study in European AIS subjects (25 edaravone, 11 placebo) do not suggest different safety profiles of edaravone in European vs. Japanese subjects. However, these 3 studies were small, different posology was used and duration of administration was short (up to 14 days). The limited clinical data in European healthy and AIS subjects provides only supportive evidence of a similar edaravone safety profile in Japanese and European ALS patients.

3.3.10. Conclusions on clinical safety

The safety database derived from the 5 clinical ALS studies in support of conditional approval of edaravone with a total of 349 exposed ALS subjects of whom 98 subjects have received edaravone for ≥ 12 months is acceptable for an orphan indication. However, information on safety of edaravone in ALS patients with decreased respiratory function (< 80% FVC), with ALS severity > 3, ALS patients > 75 years, long-term safety data beyond 15 months. Also safety in patients with severe renal or hepatic impairment is missing; preliminary results of phase I studies in Japanese subjects with mild to moderate renal or hepatic impairment require further clarification but indicate, that caution is required in patients with moderate renal or hepatic disease.

The only clinical studies performed in the EU population (2 studies in healthy volunteers and one study in AIS patients) do not suggest a different safety profile of edaravone in European vs. Japanese subjects, however the informational value of these data regarding safety in European ALS patients is clearly limited as all three studies were small, included patients with less advanced disease, different edaravone posology was used, and the AIS patient population generally differs from the ALS patient population.

Additional collection of safety data is therefore essential. The applicant has submitted a protocol for the planned EU Registry study (Version 1.1, dated 17 Aug 2018), which needs further clarification/modification (specified in detail in a separate document). In this registry besides efficacy long-term safety of edaravone will be addressed. However, feasibility of collecting data in more advanced patients from the registry study in Europe in case use of edaravone in these patients is considered off-label use based on a restricted approved indication is still under discussion. Seven adverse events (i.e. fulminant hepatitis, hepatic dysfunction, jaundice; acute renal failure, nephrotic syndrome; thrombocytopenia; granulocytopenia; rhabdomyolysis;d Disseminated intravascular coagulation (DIC); and acute lung injury) which have been added to the Japanese package insert of edaravone based on post-marketing reports in the AIS indication, but for which further review of the available safety information in the AIS and ALS indication did not show further evidence of a causal relationship with edaravone, will be evaluated as Adverse Events of Special Interest and reports of respective events will be evaluated as cumulative reviews in PSURs. However, regarding post-marketing reports of hepatic dysfunction in ALS further information is requested.

Currently, the most relevant safety issues associated with edaravone relate to

- anaphylaxis which has not been reported in clinical studies with edaravone (all indications), however, post-marketing overall 9 serious cases consistent with anaphylactic reaction including events with urticaria, decreased blood pressure and dyspnea, respectively were reported as of 25 Dec 2015 in the

AIS indication. Possible confounding factors were present in the majority of but not in all cases. One additional case of serious anaphylactoid reaction in which a causal association with edaravone is plausible resulted from post-marketing reports in the ALS indication through 03-6-Sep-2018. None of these cases were fatal and anaphylaxis is considered adequately manageable via appropriate PI labelling.

- neurotoxicity. Based on pre-clinical findings of axonal nerve fibre degeneration attributed to reduced vitamin B6 plasma levels, neurotoxicity is considered an important potential risk. Available clinical data do not allow to conclusively differentiate between possible edaravone induced neurotoxicity and worsening of ALS due to natural history of the disease. Retrospective measurements of vitamin B6 blood levels are therefore requested if retention samples of ALS clinical studies are still available. Evaluation of recommendations for vitamin B6 plasma determination and supplementation as well as for appropriate electrophysological monitoring (e.g. by testing of motor or sensory nerve conduction) to allow for early detection of neurotoxicity during treatment with edaravone is requested.
Further collection of post marketing data regarding neurotoxicity is considered necessary.

During study treatment cycles 7-12 (Safety Set 4), higher rates of ALS associated SAEs (including respiratory TEAEs) was found in the PE and EE groups compared to the EP group (i.e. the subgroup receiving placebo during the period of interest). These findings may be explained by baseline imbalances indicating more advanced ALS (including decreased respiratory function) in the PE and EE groups. Interpretability of data derived from the EP group is further limited due to the low subject numbers of this particular subgroup (N=45). In this context, it is considered reassuring, that results for the EE group (which had a longer edaravone exposure) in respect of AEs leading to withdrawal, drug related AEs as well as SAEs generally tended to be more favourable than those of the PE group. Nevertheless, the results of safety set 4 may also be interpreted as a less favourable safety profile of edaravone in patients with more advanced ALS in particular with regard to respiratory TEAEs, and a potential neurotoxic effect of edaravone might provide a possible explanation for this.

The overall safety profile resulting from treatment cycles 1-6 of ALS studies (Safety Set 1) appears favourable with very similar TEAE rates (87.5% edaravone, 87.0% placebo), low incidences of AEs considered drug-related (10.3% and 14.1%), and incidences of ADRs, AEs/ADRs leading to discontinuation and SAEs not being higher in the edaravone vs. placebo group. The most frequent TEAEs which occurred at (more than 2%) higher rate in edaravone patients were contusion (14.7% in edaravone, 8.7% in placebo group; mostly of mild severity) and gait disturbance (12.5% vs. 9.2%).

3.4. Risk management plan

3.4.1. Safety Specification

Summary of safety concerns

The applicant identified the following safety concerns in the RMP:

Table SVIII.1: Summary of safety concerns

Summary of safety concerns	
Important identified risks	• None
Important potential risks	• Hypersensitivity reaction, anaphylactic reaction

Missing information	• Patients with renal impairment • Patients with hepatic impairment • Patients with ALS severity grade > 3 and/or decreased respiratory function (%FVC < 80%) • Effect of edaravone on QT/QTc interval • Use in pregnancy and lactation • Long-term safety • Use in patients > 75 years-old

Having considered the data in the safety specification the rapporteur considers that Neurotoxicity should also be a safety concern.

Neurotoxicity was observed after 24-hour continuous IV infusion in dogs at ≥60 mg/kg/day and in monkeys at 1000 mg/kg/day for 28 days. The projection path of the sensory nerve was found to be affected in the spinal cord and the brain.

Even though in clinical trials sensory tests showed no significant differences in vibratory sensation, numbness or staggering over the course of the conducted treatment cycles or between different treatment groups, it is currently unclear how sensitive and appropriate such tests might be for detection of neurotoxicity in ALS patients. In clinical trials severe gait disturbance occurred at a higher frequency in the edaravone compared to the placebo group (5.4% vs. 2.7%). The applicant argues that the events of severe gait disturbances were considered not related to edaravone by the study investigators but rather reported as worsening of ALS. However, this would not explain the higher frequency of severe gait disturbances observed in edaravone-as compared to placebo-treated patients. Of note, differentiation between edaravone-induced gait disturbances/neurotoxicity and worsening of ALS is currently nearly impossible in clinical trials as well as in assessment of post-marketing spontaneous case reports. A contributory role of edaravone in the development or worsening of gait disturbances/neurotoxicity can therefore not be excluded. The same holds true for TEAEs in the Musculoskeletal disorders SOC.

Considering all data from non-clinical, clinical and post-marketing settings there is sufficient scientific evidence to suspect the possibility of a causal relationship between neurotoxicity and edaravone. Therefore, **Neurotoxicity should be added to the RMP as important potential risk** and further post-marketing data collection (including sensory nerve conduction studies and vitamin B6 supplementation) is considered necessary in order to address the uncertainties regarding neurotoxicity.

3.4.2. Pharmacovigilance Plan

Summary of additional PhV activities

Table Part III.1: On-going and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Not applicable				
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				
Category 3 - Required additional pharmacovigilance activities				
PK study in subjects with severe hepatic impairment (MCI-186-E05) Planned	To identify unexpected serious risks resulting from altered PK of edaravone in patients with severe hepatic impairment after administration of edaravone	Patients with hepatic impairment	Final report	June 2020
PK study in subjects with mild or moderate hepatic impairment (MCI-186-J23) Ongoing	To identify unexpected serious risks resulting from altered PK of edaravone in patients with mild or moderate hepatic impairment after administration of edaravone	Patients with hepatic impairment	Final report	Q2 2019
PK study in subjects with mild or moderate renal impairment (MCI-186-J22) Ongoing	To identify unexpected serious risks resulting from altered PK of edaravone in patients with mild or moderate renal impairment after administration of edaravone	Patients with renal impairment	Final report	Q2 2019
Effect of edaravone on QT/QTc interval (MCI-186-J25) Planned	To identify unexpected serious risks of QT prolongation after administration of edaravone in order to comply with standard safety package for a NCE as per ICH E14 [ICH, 2015[40]].	Effect of edaravone on QT/QTc interval (No safety concern identified from preclinical studies)	Final report	November 2019
European ALS Registry Study Planned	To prospectively collect long-term data on edaravone-treated patients (including survival outcome) in a real-world setting and to compare outcomes against relevant control data in order to demonstrate the effectiveness and the safety of edaravone.	Long-term safety (> 12 cycles) Patients with ALS severity grade > 3 and/or decreased respiratory function (%FVC < 80%).	Final report	Q4 2027

ALS: amyotrophic lateral sclerosis; FVC: forced vital capacity; ICH: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use; NCE: new chemical entity; PK: pharmacokinetic(s); Q: quarter; QTc: QT interval corrected for heart rate.

The applicant has proposed both routine and additional pharmacovigilance activities. From the proposed list of additional pharmacovigilance activities, the applicant is requested to remove ALS registry study since it is going to be included in Part IV of the RMP as a condition of marketing authorisation (PAES).

Overall conclusions on the PhV Plan

The PRAC Rapporteur, having considered the data submitted, is of the opinion that both routine and additional pharmacovigilance are needed to identify and characterise the risks of the product. The proposed post-authorisation PhV development plan should be modified according to the comments raised.

The PRAC Rapporteur also considered that routine PhV remains sufficient to monitor the effectiveness of the risk minimisation measures.

3.4.3. Plans for post-authorisation efficacy studies

Summary of Post authorisation efficacy development plan

Table Part IV.1: Planned and on-going post-authorisation efficacy studies that are conditions of the marketing authorisation or that are specific obligations.

Study Status	Summary of objectives	Efficacy uncertainties addressed	Milestones	Due dates
Efficacy studies which are conditions of the marketing authorisation				
European ALS Registry Study *Note: this study is also included as an additional pharmacovigilance activity in Pharmacovigilance Plan [Section III.2].*	To prospectively collect long-term data on edaravone-treated patients (including survival outcome) in a real-world setting and to compare outcomes against relevant control data in order to demonstrate the effectiveness and the safety of edaravone.	Long-term efficacy including survival outcome	Final report	TBD
Efficacy studies which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable				

ALS: amyotrophic lateral sclerosis; TBD: to be determined.

3.4.4. Risk minimisation measures

Summary of risk minimisation measures

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hypersensitivity reaction, Anaphylactoid reaction	Routine risk minimisation measures: • SmPC section 4.3 Contraindication; • SmPC section 4.4 Special warnings and precautions for use; • SmPC section 4.8 Undesirable effects; • PL section 2; • Recommendation to immediately discontinue edaravone if a hypersensitivity reaction occurs (SmPC sections 4.2 Posology and method of administration and section 4.4 Special warnings and precautions for use); • Instructions regarding monitoring and treatment (SmPC section 4.4 Special warnings and precautions for use). Additional risk minimisation measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • None.
Patients with renal impairment	Routine risk minimisation measures: • SmPC section 5.2 Pharmacokinetic properties. Additional risk minimisation measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • Study MCI-186-J22 in subjects with mild or moderate renal impairment.
Patients with hepatic impairment	Routine risk minimisation measures: • SmPC section 5.2 Pharmacokinetic properties. Additional risk minimisation measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • Study MCI186-E05 in subjects with severe hepatic impairment; • Study MCI-186-J23 in subjects with mild or moderate hepatic impairment.

Patients with ALS severity grade > 3 and/or decreased respiratory function (%FVC < 80%)	Routine risk minimisation measures: • None. Additional risk minimisation measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • European ALS Registry Study.
effect of edaravone on QT/QTc Interval	Routine risk minimisation measures: • None. Additional risk minimisation measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • MCI-186-J25 to identify unexpected serious risks of QT prolongation after administration of edaravone.
Use in patients > 75 years of age	Routine risk minimisation measures: • SPC section 5.2 Pharmacokinetic properties. Additional risk minimisation measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • None.
Use during pregnancy and lactation	Routine risk minimisation measures: • SPC section 4.6 Fertility, pregnancy, and lactation; • Recommendation not to use edaravone during pregnancy or in women of childbearing potential not using contraception (SmPC section 4.6, PL section 2); • Recommendation to discontinue breast-feeding or discontinue edaravone, taking into account the benefit of breast feeding and the benefit of therapy (SmPC section 4.6, PL section 2); • Instruction to patients who are pregnant, may be pregnant, are planning to have a baby, or are breast-feeding to ask their doctor for advice before taking edaravone (PL Section 2). Additional risk minimisation measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • None.
Long-term safety (> 12 cycles)	Routine risk minimisation measures: • None. Additional risk minimisation measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None Additional pharmacovigilance activities: • European ALS Registry Study.

ALS: amyotrophic lateral sclerosis; FVC: forced vital capacity; PL: package leaflet; QTc: QT interval corrected for heart rate; SmPC: Summary of Product Characteristics.

No additional risk minimisation measures are needed to minimise the risks of this product. The applicant is requested to link registry study to all safety concerns that will be monitored through and

present it in part V.3 *Summary table of pharmacovigilance activities and risk minimisation activities by safety concern*.

Table Part V.3: Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Hypersensitivity reaction, Anaphylactoid reaction	Routine risk minimisation measures: • SmPC section 4.3 Contraindication; • SmPC section 4.4 Special warnings and precautions for use; • SmPC section 4.8 Undesirable effects; • PL section 2; • Recommendation to immediately discontinue edaravone if a hypersensitivity reaction occurs (SmPC sections 4.2 Posology and method of administration and section 4.4 Special warnings and precautions for use); • Instructions regarding monitoring and treatment (SmPC section 4.4 Special warnings and precautions for use). Additional risk minimisation measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • None.
Patients with renal impairment	Routine risk minimisation measures: • SmPC section 5.2 Pharmacokinetic properties. Additional risk minimisation measures: • None.	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • None. Additional pharmacovigilance activities: • Study MCI-186-J22 in subjects with mild or moderate renal impairment.

Overall conclusions on risk minimisation measures

The PRAC Rapporteur having considered the data submitted was of the opinion that the proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

3.4.5. Summary of the risk management plan

The public summary of the RMP requires a revision. The applicant is requested to updated it to reflected changes made in Part III and V of the RMP regarding registry study.

PRAC Outcome

During the plenary meeting held on 11-14 February 2019, the PRAC, having considered the above, supported by consensus decision the PRAC rapporteur's position on the pharmacovigilance plan and risk minimisation measures proposed for Radicava.

3.4.6. Conclusion on the RMP

The CHMP and PRAC considered that the risk management plan version 0.2 could be acceptable if the applicant implements the changes to the RMP as detailed in the endorsed Rapporteur assessment report.

3.5. Pharmacovigilance system

It is considered that the pharmacovigilance system summary submitted by the applicant fulfils the requirements of Article 8(3) of Directive 2001/83/EC.

Periodic Safety Update Reports submission requirements

The active substance is not included in the EURD list and a new entry will be required. The new EURD list entry uses the {EBD} or {IBD} to determine the forthcoming Data Lock Points. The applicant should indicate if they wish to align the PSUR cycle with the international birth date (IBD).

4. Significance / Non-Conformity of paediatric studies

Significance of paediatric studies

There are no paediatric studies submitted with this application.

Conformity with agreed Paediatric Investigation Plan

Not applicable

5. Benefit risk assessment

5.1. Therapeutic Context

5.1.1. Disease or condition

The proposed indication with this application is:

RADICAVA is indicated for the treatment of amyotrophic lateral sclerosis (ALS).

Radicava is claimed to be a disease-modifying treatment for ALS.

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive muscular paralysis reflecting degeneration of motor neurons in the primary motor cortex, corticospinal tracts, brainstem and spinal cord. ALS affects nerve cells in the brain and the spinal cord. Rapid progression of symptoms directly results from degeneration in upper and lower motor neurons causing the loss of motor function. Impairment of the motor neurons that control the muscles involved in speech and swallowing results in dyslalia and dysphagia, while impairment of the motor neurons that innervate the respiratory muscles results in respiratory disorders. Eventually, respiratory failure develops as ALS progresses and is a leading cause of death in ALS.

The estimated mortality is 30,000 patients a year worldwide. Incidence is ranging from 0.3 to 2.5 cases per 100,000 per year. The prevalence varies in different regions of the world but has been

reported to be 5.40 (4.06-7.89) per 100,000 individuals in the EU, which is equivalent to a total of around 40,000 people (29971-58244) (Chio et al 2013).

Sporadic ALS (SALS) accounts for the vast majority of cases (90-95%) whereas only a small fraction of cases are familial, with a Mendelian pattern of inheritance (FALS). Although FALS is clinically and genetically heterogeneous, the clinical presentation of FALS and SALS is very similar.The mean age of onset for sporadic ALS is between 55 and 60 years.

The pathogenesis of amyotrophic lateral sclerosis (ALS) is uncertain. A number of potential mechanisms have been proposed including abnormal RNA processing, SOD1-mediated toxicity, excitotoxicity, cytoskeletal derangements, mitochondrial dysfunction, viral infections, apoptosis, growth factor abnormalities, inflammatory responses, oxidative stress and others.

The aims of the treatment of ALS are to delay disease progression and functional deterioration and to prolong survival.

5.1.2. Available therapies and unmet medical need

Amyotrophic lateral sclerosis (ALS) is a progressive, incurable and fatal neurodegenerative disease.

Current treatment of ALS consists primarily of supportive measures (such as treatments for pain, limb stiffness, depression, anxiety, cramps, incontinence, sleeping disorders, ventilatory support, dietary considerations); no curative therapies exist. Sanofi Aventis' Rilutek (riluzole) was approved centrally for ALS in the EU in 1996. Several generic versions containing the active ingredient riluzole are also authorized nationally in different EU countries. The indication of riluzole is, "to extend life or the time to mechanical ventilation for patients with ALS". Riluzole remains the only available disease-modifying treatment to have shown a modest beneficial impact on survival in ALS but it has no effect on function. There is a lack of follow-on clinical studies of riluzole in ALS/Motor Neuron Disease (MND) and the true effect remains difficult to define. There is no other available treatment that can either alter the progressive decline in motor function or improve ALS symptoms. There has been no advance in efficacy of available therapeutic agents over the last 20 years since registration of riluzole and there remains an urgent and significant unmet medical need for effective treatments for this ultimately fatal disease.

5.1.3. Main clinical studies

The clinical development program for Radicava consisted of one phase 2 study (MCI186-12) and four completed phase 3 studies. There were two confirmatory studies in an ALS population with less advanced disease (MCI186-16 and MCI186-19), one extension of the first confirmatory study (MCI186-17) and one study in advanced disease (Japan ALS severity grade 3) (MCI186-18). All studies were performed in Japan with Japanese patients. The diagnostic criteria for ALS used for the enrolment of patients were the revised El Escorial research diagnostic criteria for ALS (Airlie House 1998), as mentioned in the European ALS Guideline (EMA/531686/2015, Corr.1) or as the Applicant mentions them, "El Escorial revised Airlie House diagnostic criteria". These are widely accepted criteria for the diagnosis of ALS.

The data from these studies were used for the approval of Edaravone in Japan and South Korea in 2015 and in May 2017 in the USA:

In Japan the approved indications for edaravone (Radicut) are:

1. Improvement of neurological symptoms, disorder of activities of daily living, and functional disorder associated with acute ischaemic stroke (AIS)

2. Inhibition of progression of functional disorder in patients with amyotrophic lateral sclerosis (ALS)

FDA approved edaravone (Radicava) for the broad indication “treatment of amyotrophic lateral sclerosis (ALS)”.

Study MCI186-12 was a phase 2 study in a total of 20 patients, which served as proof of concept and compared two doses of edaravone, i.e. 30mg and 60mg. MCI186-12 was an open label study and treatment duration was for cycle 1: 14 days and for cycles 2 to 6: 10 days.

547 patients with ALS participated in the four phase 3 studies, of whom 363 patients received at least one administration of edaravone and 184 patients received placebo.

Study MCI186-16 was a 24-week double-blind, parallel-group, placebo-controlled Phase 3 trial to evaluate the efficacy and safety of 60 mg/day edaravone in 101 subjects in the edaravone (E) group compared to 104 subjects in the placebo (P) group.

Study MCI186-17 was a 24-week double-blind, parallel-group, placebo-controlled, Phase 3 study to investigate the sustainability of effects of edaravone as well as its long-term efficacy and safety in ALS subjects who completed Study MCI186-16. Patients who completed Cycle 6 (24 weeks) of Study MCI186-16 continued to receive treatment on the same schedule during Cycles 7 to 15 in study MCI186-17. Patients were randomized in a 1:1:2 ratio to the following 3 treatment groups: a) Study MCI186-16 edaravone – Study MCI186-17 placebo (EP group), b) study MCI186-16 edaravone – Study MCI186-17 edaravone (EE group) and c) Study MCI186-16 placebo – Study MCI186-17 edaravone (PE group).

A total of 181 subjects were enrolled in the extension study MCI186-17. The main analyses were performed in the FAS, consisting of a total of 180 subjects: 44 subjects in the EP group, 48 subjects in the EE group, and 88 subjects in the PE group.

In studies MCI186-16 and MCI186-17, patients were enrolled according to the to the EL Escorial revised Airlie House diagnostic criteria for definite, probable or probable-laboratory supported ALS, were grade 1 or 2 based on the Japan ALS severity classification and had normal respiratory function %FVC ≥70%. Retrospective sub-group analysis was undertaken in an “efficacy expected subpopulation” (EESP) as no statistical significance was demonstrated for the broad population. The EESP population was defined as a population who fulfilled the El Escorial revised Airlie House diagnostic criteria for definite or probable ALS, were of Grade 1 or 2 in the Japan ALS severity classification, had normal respiratory function expressed as forced vital capacity (%FVC) not less than 70%, had an onset of ALS within 3 years and had a change of -1 up to -4 points in the ALSFRS-R score during 12-week pre-observation period. The “Definite or Probable /EESP/2y” patient population subset was a population that differed from the EESP in that the forced vital capacity was greater or equal than 80% and had within 2 years of initial ALS symptom onset at preregistration.

Study MCI186-18 was a 24-week randomised, placebo-controlled, exploratory study in a limited number of more advanced ALS patients (Japan ALS severity grade 3) (n=25) who were administered study drug at 60 mg/day for 6 cycles performed as part of a request by the Japanese Pharmaceutical and Medical Devices Agency (PMDA).

Study MCI186-19 was a placebo-controlled, double-blind, parallel-group study to prospectively confirm the efficacy and safety of edaravone 60 mg/day versus placebo in a total of 137 patients with ALS (68 received placebo and 69 received edaravone) meeting “Definite or Probable /EESP/2y” criteria as retrospectively defined in study MCI-186-16 and described above. This study was double blind for 24 weeks (first cycles 1-6) and then from cycle 7 to 12 it was an open label extension with all patients receiving active treatment with edaravone.

The dosage regimen evaluated in the Phase 2 and Phase 3 studies in Japan defined the following treatment cycles:

- Cycle 1: IV administration of the study drug once each day for 14 consecutive days, followed by a 2-week drug-free period
- Cycle 2 and thereafter: IV administration of the study drug once a day for any 10 days within a 2-week period, followed by a 2-week drug-free period.

This dosage regimen is proposed for approval.

The use of riluzole was permitted if the dosage and administration were not changed and the majority of the patients in studies MCI186-16 (n=182/205) and MCI186-19 (n=112/123) and the extension study MCI186-17 (n=161/180) received concomitantly riluzole.

The following endpoints were used in the four phase 3 studies: primary endpoint: change from baseline in the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) score to the end of treatment cycles and difference between edaravone treatment group and placebo. The secondary endpoints were: time to death or certain signs of disease progression(analysed as discrete events), respiratory function %FVC, quality of Life ALSAQ40 score, Modified Norris Scale, ALSFRS-R score for each domain, muscle strength such as grip strength and pinch grip strength and Japanese ALS severity classification. The ALSFRS-R score is a validated scale widely used in the clinical studies for ALS and is recommended by the EU ALS guideline for the evaluation of function in ALS.

5.2. Favourable effects

Whereas study MCI186-16 failed to meet its primary objective in the overall study population, statistically significant results on the change from baseline in the ALSFRS-R score versus placebo at 6 months have been observed in ALS patients with less advanced disease, defined retrospectively as Definite or Probable/EESP/2y [difference between groups in the adjusted mean change from baseline in ALSFRS-R score of 3.01±1.33, (0.35, 5.67), p=0.0270].

A population with the same characteristics as this specific subgroup of study MCI186-16 was prospectively defined as the Full Analysis Set population for study MCI186-19. This population had the characteristics of “Definite or Probable /EESP/2y” subpopulation described above. In this enriched population a statistically significant effect on the change from baseline in the ASLFRS-R score versus placebo was also shown. The change (mean ± SD) from "baseline in Cycle 1" to "the end of Cycle 6 (or discontinuation, LOCF)" was −4.4±3.8 in the edaravone group and −6.8±4.9 in the placebo group. The LS Mean (±SE) of the between-group difference and its 95% CIs were 2.49±0.76 (0.99, 3.98) with a statistically significant difference between the groups in favour of edaravone (p=0.0013).

Sensitivity analysis performed for the primary endpoint ‘change from baseline in the ALSFRS-R score’ confirmed the statistically significant results for short term efficacy. The difference versus placebo in ALSFRS-R Scores between Baseline in Cycle 1 and the End of Cycle 6 (MMRM) in Study MCI186-16 (Double-blind, Definite or Probable/EESP/2y, Post-hoc) was 3.44±1.29 (0.86 , 6.02), p=0.0170.

In study MCI186-19 (double-blind period, FAS) a short-term statistically significant difference of 2.5 points between treatment group and placebo in the change in ALSFRS-R score (from Baseline to end of Cycle 6, duration of 24 weeks) was observed (2.49±0.76, 95% CI: 0.99 to 3.98, p = 0.0013; LOCF, primary analysis) after 6 months and confirmed by a series of pre-specified sensitivity analyses (difference in ALSFRS-R Scores between Baseline in Cycle 1 and the End of Cycle 6, ALL LOCF 2.37±0.75, p=0.0019, MMRM 2.81±0.78, p=0.0004 and PMI 2.87 (95% CI: 1.32, 4.43) p=0.0003). The most relevant analysis is considered to be the placebo multiple imputation analysis, as the

originally provided analyses used inappropriate imputation methods or targeted an estimand as if all patients adhered to treatment.

Some of the secondary endpoints were supportive of the positive results with the primary endpoint. Assessment of endpoints specific for ALS patients such as differences in the changes of ALSAQ40 score, which is measuring quality of life and the modified Norris Scale score, assessing movement disorder reached statistical significance (double-blind period, FAS: ALSAQ40 score -8.79 ± 4.03, p=0.0309 and Modified Norris Scale score (Total) 4.89±2.35, p=0.0393).

Subgroup analyses showed that decrease in the ALSFRS-R score was inhibited significantly and consistently in the edaravone group; in particular, a statistical significant difference between edaravone and placebo was achieved regardless of sex, age (<65 vs ≥65 years), disease duration (<1 vs ≥1 years), baseline grade of disease severity, in patients with BMI ≥median values, diagnosis of sporadic ALS, with initial limb symptoms or probable ALS diagnosis, in patients under concomitant therapy with riluzole, in those with concomitant complications, and finally in patients with change in ALSFRS-R score of -2, -1.

5.3. Uncertainties and limitations about favourable effects

The mechanism of action of edaravone is rather unspecific. Edaravone is believed to eliminate the hydroxyl radicals and peroxynitrite free radicals that are increasingly produced by glutamate excitotoxicity, mitochondrial dysfunction, etc., in the condition of ALS. A number of pharmacological actions can be associated with edaravone, according to the Applicant. Edaravone is considered to suppress lipid peroxidation, ameliorate oxidative stress that damages endothelial and neuronal cells and protect vascular endothelial cells and neurons against oxidative stress. In addition, it has been reported that glial cells also benefit from the cell protective action against oxidative stress. However, the clinical relevance of the mode of action for a disorder without elucidated pathogenesis is unknown. No pharmacodynamic biomarker for oxidative stress has been established as a validated surrogate parameter for efficacy in ALS.

A formal dose response study is missing. The non-clinical data, the dosing regimen approved for AIS (30 mg/30 min IV infusion) and the investigation of 3NT levels as marker of oxidative stress cannot appropriately justify the proposed cyclic dosing regimen. The Applicant has recognized that the currently proposed dosing regimen may not be optimal and that there is the possibility that efficacy of edaravone may be enhanced through an exploration with more frequent dosing without drug-free period. Therefore, the Applicant is planning and committing to the conduct of post-marketing study to investigate more frequent doses (every day dosing without drug-free period) using an oral formulation as a more convenient formulation to reduce burden for every day dosing as mentioned later in this response. A more thorough investigation of dose-response data and of the time-concentration profile of edaravone in CSF should be done by the Applicant during the further development of the oral formulation.

It should be also noted that a discussion of the physiological role of free radicals has not been provided. Higher doses might potentially be more effective but could also be more harmful to physiological processes. Even at the dose of 60 mg/60 min harmful effects to the nervous system might exist that are masked by the underlying disease.

Extrapolation of clinical data from early stage ALS patients to an advanced disease ALS population

In the first confirmatory study MCI186-16 the analysis of the results from ALSFRS-R for the Full Analysis Set did not provide statistically significant results. A post-hoc analysis was then performed in a restricted ALS population with less advanced disease and the results were prospectively confirmed in

this population in study MCI186-19 after 6 months of treatment. As data in ALS severity grade 3 are sparse and do not suggest a beneficial effect and are lacking in ALS severity grade > 3 (based on Japan ALS severity classification), it is currently unclear, how long patients may profit from edaravone treatment. It is noted that in the approved Japanese translated label of edaravone the following warning exists:

The efficacy and safety of this product in patients with Japan ALS severity classification of grade 4 or above and patients with forced vital capacity less than 70% of theoretical normal value have not been established, since there is little clinical experience in such patients. Administration of this product in such patients should be judged carefully in consideration of risks and benefits.

Data from patients at a more advanced stage of disease such as longer disease duration (>2 years), and/or higher baseline disease severity (Grade ≥3) and respiratory function impairment are not available using a placebo controlled approach. Hence, the results from a restricted enriched Japanese population with a less advanced ALS condition used in the confirmatory studies for edaravone, cannot at present support a broad indication for the EU ALS population, without further justification and discussion.

The Applicant provided the percentages of patients in the subgroup classified as being in Japanese ALS Severity Grade 3, or greater, at the initiation of the extension phase of study MCI186-19 (end of Cycle 6 onwards) ("Grade 3 progressors"), whose individual slopes of the ALSFRS-R were improved during the extension phase of study MCI186-19 compared to the double blind phase. According to the Applicant and based on this post-hoc analysis, thirty patients in EE group and 30 patients in PE group were classified as being in Japanese ALS Severity Grade 3, or greater. However, based on the MCI186-19 CSR baseline data in the edaravone group there were 22 patients with Grade 1 and 47 patients with Grade 2 Japan ALS severity classification, indicating that 30 out of these 69 (43.5%) patients progressed to Grade 3 severity while being on treatment with edaravone. Most likely, 30 out of the 47 patients (63.8%) of patients in Grade 2 progressed to Grade 3, while being on treatment with edaravone. These data appear somewhat contradictory. Due to their post-hoc nature, prone to bias, these data are difficult to interpret.

Clinical relevance of treatment benefit

With respect to the effect size of the primary endpoint in the pivotal study MCI186-19, a between-group difference of 2.5 points in the change in ALSFRS-R score (from Baseline to end of Cycle 6) (approximately 33% compared to placebo) can be considered encouraging based on published reports and knowledge from other studies. The average functional decline was reported to be about 1 point per month in untreated patients (EMA/531686/2015, Corr.1, Castrillo-Viguera 2010). However, the magnitude of treatment effect could have been more limited than what suggested by the primary analysis as this was based on LOCF imputation, which could have led to an overestimation of the edaravone effect, and a smaller effect size is suggested by secondary analysis of the primary endpoint. Sensitivity analysis using the MMRM approach confirmed the statistically significant results. However, the handling of missing data was not appropriate and a placebo multiple imputation approach was used and provided a more realistic estimate of the treatment effect (difference of 2.87, p=0.0003).

The clinical relevance of the effect size for the primary endpoint is not supported by relevant effects on important secondary endpoints as %FVC, pinch grip and grip strength (%FVC 4.78±2.84, p=0.0942, Grip strength 0.11±0.64, p=0.8583 and Pinch grip strength 0.10±0.16, p=0.5478). Also, the survival analysis for death or certain disease progression did not show significant changes between treatment groups (p=0.1284, log-rank test). The clinical relevance of these results still remains unclear and needs to be further justified.

In addition, only short-term controlled data over 6 months were provided in one pivotal study and it is unclear whether the effect is maintained if taken for more than 6 months. The Applicant is applying for

a therapeutic indication for the treatment of amyotrophic lateral sclerosis (ALS), which is a broad indication and suggests a disease modifying effect of edaravone. However, controlled long term survival/mortality data as required by the respective EMA guideline (Guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis EMA/531686/2015, Corr.1) have not been provided. Alternatively, a time-to-event endpoint with the event defined as death or a predefined deterioration on the ALSFRS-R scale should be considered. The combined assessment of function and survival (CAFS) did not yield meaningful results since there were no deaths during the 6 months double-blind treatment period of study MCI186-19 and the same small number of survival events (death and tracheostomy) in the 6 months open label extension, that is even after 12 months treatment with edaravone. The number of deaths was also very low with 4 deaths in the placebo group and 2 deaths in the edaravone group in a safety follow-up until 4 weeks after last dose.

It is noted that for the secondary endpoint "Time to Death or Certain Signs of Disease Progression" there is a trend favouring edaravone (2 events on edaravone and 6 events on placebo up to Cycle 6, 24 weeks), but the small number of events limits the power of the statistical tests. Apart from death or equivalent end of life measures such as tracheotomy (1 on edaravone), use of respirator (0 events) or tube feeding (1 on placebo) certain other symptoms of disease progression were considered such as disability of independent ambulation, loss of upper limb function, and loss of useful speech. No patient died or received ventilation up to cycle 6 (24 weeks). In the open-label phase (cycle 7 to 12) there were 2 deaths in the Placebo-Edaravone (PE) group and 1 in the Edaravone-Edaravone (EE) and 1 tracheotomy in the EE group. The "use of tube feeding events" were 5 for PE and 2 for EE. So the results on this endpointderived from a post-hoc analysis with all the limitations and events were too few to draw meaningful conclusions. Hence, they cannot be considered as supportive for a positive effect on survival indicative of a disease modifying effect.

Whilst the protocol did not define capture of safety information beyond 4 weeks after the end of last cycle or discontinuation, the Applicant tried to capture cases of death, tracheostomy or permanent continuous ventilator dependence in available SAE reports/narratives retrospectively beyond that time. However, the number of these events recorded by the Applicant was small and was derived from a post-hoc analysis with the known limitations. In addition, since capturing of survival and survival related events was not foreseen after 4 weeks past last dose or discontinuation, capturing of such events may not be complete, specifically for patients having withdrawn from the study. The cleanest and best comparison is the one between edaravone and placebo during the first 6 Cycles, but this observation period was too short (only 24 weeks) and produced very limited data on survival-related endpoints. Even after 12 cycles, data are very limited. In addition, judging the effect on survival after all patients had proceeded to active extension and received edaravone is difficult and a respective benefit needs to be demonstrated post-marketing, in case approval is granted.

There are relevant concerns regarding the clinical relevance of the observed treatment effect on the primary functional endpoint taking into account the lack of support from important secondary endpoints. It is also unclear that the data from less advanced ALS population (Grade 1 or 2) can be extrapolated to patients with advanced disease.

Proposed condition to generate long-term efficacy and survival-related endpoints data

The Applicant has applied for a conditional approval and suggests a registry study as condition to provide confirmatory long-term survival/mortality data post–approval. As pointed out during the protocol assistance procedures (EMEA/H/SA/3202/1/2015/PA/III, and EMEA/H/SA/3202/1/FU/1/2018/PA/II), the ideal approach to generate survival data would be a randomized, double blind, placebo controlled study of longer duration (at least 12 months) and that any data generated using a registry will be considered inferior to clinical trial data. The Applicant,

however, has decided to propose a registry in the EU as condition to generate long-term survival data. The study protocol and statistical analysis plan for the EU registry have been submitted.

According to the Applicant, this European study will be a multi-source, multi-country, non-interventional, longitudinal cohort study based on prospective data collection in European ALS centres of excellence, and the use of historical data captured in European ALS registries. The ENCALS network has established a standardised core clinical dataset defined with input from European ALS researchers. This complete feasibility assessment should be made available by the Applicant. However, the outstanding issues on efficacy are not expected to be clarified through non-randomised comparisons and therefore the REGISTRY study is not expected to provide comprehensive data to fulfill the condition. In addition, there is a major concern that the proposed registry study conducted in two local centers will not be able to provide robust efficacy data on survival in a representative EU population taking into consideration possible biases introduced by more recent changes in standard of care, potential off-label use of medications and food supplements as well as the different approaches with respect to euthanasia in different EU countries. In addition, there are a number of issues with the proposed REGISTRY Study that require clarifications and modifications (see separate REGISTRY Study assessment report).

5.4. Unfavourable effects

The safety data set comprises a total of 349 ALS patients, of whom 98 were exposed for ≥ 12 months and some up to 15 months. This is considered acceptable for a life-threatening orphan condition. In addition, through 04-Aug-2018, the estimated postmarketing experience is 6,603 ALS patients from Japan, south Korea and the US, where the ALS indication has already been approved.

It is noted that Safety set 1 (main safety set) includes Cycle 1 through 6 of studies Nos. MCI186-16, MCI186-18 and MCI-186-19, i.e. first 6 months of double blind, placebo controlled study periods. Safety set 4 (controlled extension period; cycle 7-12) includes pooled safety data from the blinded extension period of study MCI186-17 and the active extension period of study MCI186-19.

In the ALS studies (safety set 1), contusion was the most frequently reported TEAE that occurred at a higher frequency in edaravone (14.7%) compared to placebo subjects (8.7%). The incidence of contusion was approx. twice as high in female compared to male edaravone patients (21.3% vs. 11.8%). Two subjects in the edaravone group experienced contusion of moderate severity. All other cases of contusion were mild. In safety set 4, the incidence of contusion was lower in the PE (13/146; 8.9%) and EE (9/113; 8.0%) compared to the EP group (6/45; 13.3%), only few cases were of moderate and all other cases were of mild severity. In safety sets 1 and 4 combined, 1 subject in the placebo group (Set 1) and 1 subject in the PE group (Set 4) experienced contusion as SAE, both were considered not related.

Gait disturbance, which has also been found in pre-clinical studies, occurred in 12.5% edaravone compared to 9.2% placebo subjects in safety set 1. Similarly, severe or serious gait disturbance occurred at a somewhat higher frequency in edaravone compared to the placebo subjects (5.4% vs. 2.7% severe and 1.6% vs. 1.1% serious gait disturbance). Gait disturbance was not among AEs that led to discontinuation of study medication. In safety set 4, gait disturbance also occurred with higher incidence in edaravone vs. placebo treated subjects (13.7% in PE, 9.7% in EE and 8.9% in EP group).

Anaphylactic reactions, although not reported in clinical studies with edaravone (all indications), have been reported post-marketing in overall 9 serious cases including events with urticaria, decreased blood pressure and dyspnea as of 25 Dec 2015 in the AIS indication. Possible confounding factors were present in the majority of but not in all cases. One additional case of serious anaphylactoid reaction in

which a causal association with edaravone is plausible resulted from post-marketing reports in the ALS indication through 03-6-Sep-2018. None of these cases were fatal.

Analysis of TEAEs and SAEs by edaravone and age is not considered indicative of an increased safety risk of edaravone with increasing age (safety set 1).

5.5. Uncertainties and limitations about unfavourable effects

Information is very limited in ALS severity grade 3 and missing in ALS severity grade > 3 and/or in patients with decreased respiratory function (< 80% FVC), in ALS patients > 75 years, regarding long-term exposure > 15 months as well as in patients with severe renal or hepatic impairment. Preliminary results of phase I studies in Japanese subjects with mild to moderate renal or hepatic impairment require further clarification but indicate increasing exposure with decreases in renal and hepatic function.

The clinical development program of edaravone in ALS has exclusively been performed in Japanese patients. The only clinical studies performed in the EU population (2 studies in healthy volunteers and one study in AIS patients) do not suggest a different safety profile of edaravone in European vs. Japanese subjects, however the informational value of these data regarding safety in European ALS patients is clearly limited as all three studies were small, different edaravone posology was used, and the AIS patient population generally differs from the ALS patient population. Nevertheless, available post-marketing data from the US are not indicative of safety differences between Caucasian and Japanese patients.

During study treatment cycles 7-12 of study MCI186-17 (safety set 4) higher rates of SAEs were found in the edaravone groups (37.0% in PE, 31.9% in EE) vs. the placebo treated group (15.6% in EP). These imbalances were primarily driven by higher incidences in the respiratory disorders SOC and musculoskeletal disorders SOC as well as in the PE group also by dysphagia (PT). SAEs were generally attributed to ALS progression with no SAE considered treatment related and the respective imbalances in SAEs may be explained by baseline imbalances favouring the EP group (also concerning respiratory function and ALS severity grade) which would explain a higher rate of disease related events due to advanced ALS in the PE and EE group. Nevertheless, there is uncertainty, whether these findings might also be indicative of a less favourable safety profile of edaravone in patients with more advanced ALS and a potential neurotoxic effect of edaravone might provide a possible explanation for this. Further evaluation of SAEs of safety set 4 are therefore requested for the subset of subjects with ALS severity ≥ 3, which is raised as a major objection.

Axonal nerve fibre degenerations were observed in dogs and monkeys that initiated in the PNS and subsequently progressed to the CNS. In dogs, nerve fibre degenerations even developed after cessation of dosing and were accompanied by decreases of PLP, the active form of vitamin B6, which coincides with the known association of vitamin B6 deficiency and neurodegenerative disorders. Similar axonal degenerations were also reported for clinical treatment with the antibiotic isoniazid, hence, necessitating either supplementation with pyridoxal, another form of vitamin B6, or the use of approved fixed dose isoniazid/pyridoxal combination products. Thus, the causal relationship of nerve fibre degenerations during edaravone treatment due to the reduction of vitamin B6 is reasonable.

Based on the non-clinical finding of neurotoxicity, sensory examination (evaluating presence and severity of numbness and staggering, respectively via patient questioning as well as vibratory sensation via tuning fork placed at malleolus) were performed in all ALS trials. These tests did not show relevant differences across treatment groups up to 12 months of treatment, however, the sensitivity of the sensory test applied to detect possible neurodegeneration caused by edaravone is unclear.

Furthermore, in light of the non-clinical findings, there is the concern that the severe TEAEs of gait disturbance, that occurred at a higher incidence in the edaravone group compared to the placebo group (5.4% versus 2.7%), were due to somatosensory nervous system damage. Further analyses of the available clinical data regarding gait disturbance or musculoskeletal disorder SAEs do not allow to conclusively differentiate between possible edaravone induced neurotoxicity and worsening of ALS due to natural history of the disease.

Therefore, vitamin B6 levels should be retrospectively determined in edaravone-treated patients, if retention samples are still available. In addition, appropriate instructions for vitamin B6 supplementation should be proposed considering the extensive clinical experience from licensed vitamin B6 products. As it is difficult to distinguish treatment-related neurodegenerations from ALS disease progression, electrophysiological monitoring should be implemented to facilitate early detection of deficient motor and sensory nerve function.

Review of the overall post-marketing experience in the ALS indication (since 2015 in Japan and Korea and since May 2017 in the US) through 06-Sep-2018 did not raise additional important safety concerns, however further information is requested regarding some SAE reports of hepatic dysfunction.

5.6. Effects Table

Table F. Effects Table for [Radicava (edaravone) for the treatment of ALS].

Effect	Short Description	Unit	Treatment	Control	Uncertainties/ Strength of evidence	References
Favourable Effects						
ALSFRS-R score (definite or probable/ EESP/2y) Adjusted mean change from Baseline	Adjusted mean change from baseline in ALSFRS-R score (measurement of disease status and level of disability) Decrease in ALSFRS-R score translates into worsening of the condition and disease progression	N/A	Edaravone -4.58 ± 1.55	Placebo -7.59 ± 1.34	Difference in ALSFRS-R between Baseline in Cycle 1 and the End of Cycle 6 (LOCF) (Definite or Probable/ EESP/2y) 3.01±1.33, (0.35 , 5.67), p=0.0270, Placebo Multiple imputation (PMI): 3.35 (0.79, 5.92) p=0.01404 In a restricted, enriched, population, fulfilling the El Escorial and revised Airlie House diagnostic criteria for definite or probable ALS, were of Grade 1 or 2 in the ALS severity classification, within 2 years after the onset of ALS, having forced vital capacity (%FVC) not less than 80% (MCI186-16 and MCI186-19) and had a change of -1 up to -4 points in the ALSFRS-R score during 12-week pre-observation period	Study MCI186-16
ALSFRS-R score (definite or probable/ EESP/2y) Adjusted mean change from Baseline	Adjusted mean change from baseline in ALSFRS-R score (measurement of disease status and level of disability) Decrease in ALSFRS-R score translates into worsening of the condition and disease progression	N/A	EE group -4.22 ± 1.04	EP group -7.02 ± 1.39	Differences in ALSFRS-R between Baseline in Cycle 7 and the End of Cycle 12 (LOCF) (Definite or Probable/EESP/2y) 2.79 ± 1.51 (-0.26, 5.85), p=0.0719	Study MCI186-17
ALSFRS-R score data (FAS) Adjusted mean change from Baseline	Please see above for ALSFRS-R score	N/A	-6.52 ± 1.78	-6.00 ± 1.83	Change in ALSFRS-R Scores from Baseline in Cycle 1 to the End of Cycle 6 (LOCF) (FAS) -0.52±2.46 (-5.62, 4.58), p=0.8347 in severe Grade 3 ALS population. Placebo performed better.	Study MCI186-18

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
ALSFRS-R score data (FAS) Adjusted mean change from Baseline	Please see above for ALSFRS-R score	N/A	-5.01 ± 0.6	-7.50 ± 0.66	Change in ALSFRS-R Scores from Baseline in Cycle 1 to the End of Cycle 6 (LOCF) (Double-blind FAS) 2.49±0.76 (0.99, 3.98), p=0.0013 FAS was the same restricted enriched population as in the case of study MCI186-16	Study MCI186-19
ALSFRS-R score data (FAS), ALL LOCF Adjusted mean change from Baseline	Please see above for ALSFRS-R score	N/A	-5.04 ± 0.64	-7.41 ± 0.65	Sensitivity Analyses of the Difference in ALSFRS-R Scores between Baseline in Cycle 1 and the End of Cycle 6 (ALL LOCF) (Double-blind, FAS, Post-hoc) 2.37±0.75 (0.89, 3.84), p=0.0019 FAS was the same restricted enriched population as in the case of study MCI186-16.	Study MCI186-19
ALSFRS-R score data (FAS), MMRM Adjusted mean change from Baseline	Please see above for ALSFRS-R score	N/A	-4.56 ± 0.55	-7.37 ± 0.57	Sensitivity Analyses of the Difference in ALSFRS-R Scores between Baseline in Cycle 1 and the End of Cycle 6 MMRM (Double-blind, FAS, Post-hoc) 2.81±0.78 (1.27, 4.35), p=0.0004 FAS was the same restricted enriched population as in the case of study MCI186-16.	Study MCI186-19
ALSFRS-R score data (FAS), Placebo Multiple Imputation (PMI) Adjusted mean change from Baseline	Please see above for ALSFRS-R score	N/A	Edaravone -4.58 ± 0.56	Placebo -7.45 ± 0.58	Sensitivity Analyses of the Difference in ALSFRS-R Scores between Baseline in Cycle 1 and the End of Cycle 6 PMI (Double-blind, FAS, Post-hoc) 2.87 (1.32, 4.43), p=0.0003 FAS was the same restricted enriched population as in the case of study MCI186-16.	Study MCI186-19
%FVC Adjusted mean change from Baseline	Percent Forced Vital Capacity, the higher the values the better the condition	%	-15.61 ± 2.41	-20.40 ± 2.48	Change in from Baseline in Cycle 1 to the End of Cycle 6 (LOCF) (Double-blind, FAS) 4.78±2.84 (-0.83, 10.40), p=0.0942 in a restricted, enriched population as above	Study MCI186-19

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
ALSAQ40 score Adjusted mean change from Baseline	ALSAQ40 score is a measure of Quality of Life for patients with ALS The higher the score the better the condition	N/A	17.25 ± 3.39	26.04 ± 3.53	Change in from Baseline in Cycle 1 to the End of Cycle 6 (LOCF) (Double-blind, FAS) -8.79 ± 4.03 (-16.76, -0.82), p=0.0309 in a restricted, enriched population as above	Study MCI186 -19
Modified Norris Scale score (Total) Adjusted mean change from Baseline	Modified Norris Scale is a measure of movement disorder for patients with ALS. The higher the score the better the condition	N/A	-15.91 ± 1.97	-20.80 ± 2.06	Change in from Baseline in Cycle 1 to the End of Cycle 6 (LOCF) (Double-blind, FAS) 4.89±2.35 (0.24, 9.54), p=0.0393 in a restricted, enriched population as above	Study MCI186 -19
Grip strength Adjusted mean change from Baseline	Grip strength and pinch grip strength were set as an objective measurement to assess muscle weakness as muscle strength decreases in ALS patients as a result of motor neuron dysfunction The higher the score the better the condition	N/A	-4.08 ± 0.54	-4.19 ± 0.56	Change in from Baseline in Cycle 1 to the End of Cycle 6 (LOCF) (Double-blind, FAS) 0.11±0.64 (-1.15, 1.38), p=0.8583 in a restricted, enriched population as above	Study MCI186 -19
Pinch grip strength mean change from Baseline		N/A	-0.78 ± 0.14	-0.88 ± 0.14	Change in from Baseline in Cycle 1 to the End of Cycle 6 (LOCF) (Double-blind, FAS) 0.10±0.16 (-0.23, 0.42), p=0.5478 in a restricted, enriched population as above	Study MCI186 -19
Unfavourable Effects						

Effect	Short Description	Unit	Treatment	Control	Uncertainties / Strength of evidence	References
Hypersen-sitivity/ Anaphylactic reaction	Cases consistent with Anaphylactic reaction (including events with urticaria, decreased blood pressure, dyspnea)	N	9 SAE 1 SAE (consistent with anaphylaxia and plausible causality; 4 SAEs matched search criteria)	N/A	Cases from ARISg database as of 25 Dec 2015 retrieved post-marketing (AIS indication); exposure: 1.7 M AIS patients; Not reported in clinical studies (any indication) Cases retrieved post-marketing in ALS indication through 06-Sep-2018; exposure: 6,603 ALS patients;	Report No. MCI186-N04
Contusion	Incidence of TEAEs Safety set 1	%	14.7	8.8	In set 4 highest incidence in placebo treated (EP) group	ISS
Neuro-toxicity	Imbalances in: e.g. gait dis-turbance (see below), SAEs in safety set 4, including respiratory SAEs (see below; events compatible with ALS worsening)				Non-clinical findings of axonal nerve fibre degeneration after continuous treatment attributed to reduced vitamin B6 levels; Clinical ALS studies: ALS worsening or indication of neurotoxicity? -SAE imbalances may be explained by baseline imbalances; -no signal from sensory testing in clinical ALS studies – sensitivity? -Vit. B6 levels not evaluated	
Gait distur-bance	Incidence of TEAEs Safety set 1	%	12.5	9.2	Also finding from pre-clinical studies	ISS
Respira-tory (SOC) SAEs	Incidence Safety set 1 Safety set 4	%	6.5 12.4 (EE) 13.7 (PE)	6.0 4.4 (EP)	No clear overall imbalances in set 1, but in set 4; SAEs attributed to progressive ALS, explained by baseline imbalances of set 4 indicating more advanced ALS in EE/PE; less favorable safety in advanced ALS ?	ISS

Abbreviations:
Notes:

5.7. Benefit-risk assessment and discussion

5.7.1. Importance of favourable and unfavourable effects

According to the guideline on clinical investigation of medicinal products for the treatment of amyotrophic lateral sclerosis (ALS) (EMA/53168672015, Corr.1), the following study objectives could be considered: increased survival, delay of disease progression and improvement of symptoms of ALS, e.g. muscle strength and related function. For disease-modifying treatments as claimed for edaravone the primary goal is the slowing or even reversal of disease progression. As primary efficacy variable in ALS trials aimed at disease modification, trials can use either time to death including other end of life measures that prolong life in ALS patients (e.g. non-invasive ventilation [NIV], ventilation via tracheostomy) or function (ALSFRS-R), or both.

Study MCI186-16 was the initial confirmatory trial, but failed to demonstrate statistically significant results in the predefined Full Analysis Set. Post-hoc analysis in a less advanced ALS subpopulation (Definite or probable/EESP/2y) showed statistically significant effects in favour of edaravone based on the primary and sensitivity analyses of the primary endpoint i.e. difference between edaravone treatment and placebo in the adjusted mean change for ALSFRS-R score from baseline to end of treatment cycle.

The data submitted in this dossier distil down to the existence of prespecified analyses of data from a restricted patient population with Japanese ALS severity Grade 1 or 2 for 6 months in the pivotal study MCI186-19. This analysis showed a difference of 2.87 ($p=0.0003$ using placebo multiple imputation analysis) between edaravone and placebo group in the change of the ALSFRS-R score from baseline to end of treatment cycle at 24 weeks. The very small numbers of survival events and the lack of a statistically significant effect in other important secondary endpoints (lung function, muscle strength) as well as the absence of long-term controlled data, especially those on survival, do not allow to appropriately evaluate the clinical relevance of the observed effects. Furthermore, the maintenance of efficacy beyond 6 months which would be expected for a disease modifying treatment was not demonstrated.

It is acknowledged that the Applicant has also included other secondary endpoints. Differences in the changes of ALSAQ40 (measurement of quality of life) and the modified Norris Scale score (movement disorder) reached statistical significance, whilst the respiratory function %FVC and muscle strength (grip strength and pinch grip strength) did not show meaningful differences. Furthermore, subgroup analysis of the results in grade 1 and 2 ALS severity patients and the subgroups of median ALSFRS-R scores should have pointed in both studies (MCI186-16 and MCI186-19) towards the same direction: that edaravone efficacy may be lower if started later. However, the short term double blind data cannot support this hypothesis and render the results difficult to interpret.

Another relevant limitation of the studies was the dosing regimen. A formal dose response study in ALS patients is missing. The proposed cyclic dosing regimen is not soundly justified on the basis of the available pre-clinical and clinical data, particularly because the latter were initially derived from studies performed in AIS patients and there seems to be no biological plausibility to support the extrapolation of dosage schedule from AIS to ALS. It is not clear whether the results would have been better if another posology scheme had been used.

Another caveat is that the clinical trials have shown functional benefits only in patients with less advanced disease (stage 1 and 2). The effect on the functional aspects of the disease cannot be applied to the broad ALS population, because there are no robust data to support such an extrapolation. In a broader population participating in study MCI186-16 the difference between

edaravone and placebo was minimal and not statistically significant and when a severely affected population was studied (MCI186-18) no meaningful results could be obtained.

All of the above impair the generalizability of the results of the pivotal study MCI186-19 to the whole ALS patient population, including patients at a more advanced stage of disease and it is considered that the broad ALS indication as proposed by the applicant is currently not sufficiently justified.

The safety profile derived from the clinical trial programme in Japanese patients appears generally acceptable, however, information is limited in ALS severity grade 3 and missing in ALS severity grade > 3, in patients with decreased respiratory function (< 80% FVC), respectively, in ALS patients > 75 years and regarding long-term exposure > 15 months. The limited available clinical data in European subjects performed in healthy volunteers and AIS patients, respectively provide only supportive evidence of a similar safety profile of edaravone in Japanese and European ALS patients. Additional collection of safety data is therefore essential. The applicant has submitted a protocol for the planned EU Registry study (Version 1.1, dated 17 Aug 2018), which needs further clarification/modification (specified in detail in separate document). In this registry besides efficacy long-term safety of edaravone will be addressed. However, feasibility of collecting data in more advanced patients from the registry study in Europe in case use of edaravone in these patients is considered off-label use based on a restricted approved indication is still under discussion.

Available clinical trial data do not indicate a less favorable safety profile with longer edaravone exposure, but a less favourable safety profile of edaravone in patients with more advanced ALS cannot be excluded. As efficacy and safety in ALS severity grade > 2 has not been shown/evaluated, it is currently unclear, how long patients may profit from edaravone treatment.

At present, the most relevant safety issues attributed to edaravone relate to:

- anaphylactic reaction. Post-marketing, overall 9 serious cases consistent with anaphylactic reactions including events with urticaria, decreased blood pressure and dyspnea, respectively, were reported as of 25 Dec 2015 in the AIS indication (estimated exposure > 1.7M). Possible confounding factors were present in the majority of but not in all cases. Out of 4 cases, that matched the search criteria, one additional case of serious anaphylactoid reaction in which a causal association with edaravone is plausible resulted from post-marketing reports in the ALS indication through 6-Sep-2018 (estimated exposure 6,603). However, as anaphylactic reaction has not been reported in the clinical edaravone studies (of all indications comprising approx. 100 healthy volunteers, 860 AIS patients and 390 SAH patients exposed to edaravone), the frequency of anaphylactic reaction is presumably very low. None of the reported cases were fatal and anaphylaxis is considered adequately manageable via appropriate PI labelling.

- neurotoxicity. Based on pre-clinical findings of axonal nerve fibre degeneration attributed to reduced vitamin B6 plasma levels, neurotoxicity is considered an important potential risk. Available clinical data do not allow to conclusively differentiate between possible edaravone induced neurotoxicity and worsening of ALS due to natural history of the disease. Appropriate instructions for vitamin B6 monitoring and supplementation should be evaluated considering the extensive clinical experience from licensed vitamin B6 products. As it is difficult to distinguish treatment-related neurodegenerations from ALS disease progression, electrophysiological monitoring should be implemented to facilitate early detection of deficient motor and sensory nerve function.

Of the TEAEs which occurred at a higher frequency in edaravone compared to placebo subjects in the ALS studies (in safety set 1), contusion occurred with the highest incidence (14.7% edaravone vs. 8.7% placebo). Contusion occurred more frequently in female compared to male patients (21.3% vs. 11.8%). The majority of cases were of mild severity, no severe contusion occurred. It is further

considered reassuring, that the incidence of contusion in safety set 4 was highest in the placebo group (13.3% EP) and comparably low in the edaravone groups (8.9% PE, 8.0% EE).

Gait disturbance, which has also been found in pre-clinical studies, occurred in 12.5% edaravone compared to 9.2% placebo subjects in safety set 1. Similarly, severe or serious gait disturbance occurred at a somewhat higher frequency in edaravone compared to the placebo subjects (5.4% vs. 2.7% severe and 1.6% vs. 1.1% serious gait disturbance). Gait disturbance was not among AEs that led to study discontinuation however, gait disturbance can hardly be distinguished from ALS symptoms in individual patients.

Safety of edaravone in patients with severe renal or hepatic impairment is currently not known, and edaravone should not be used in these patients. Preliminary results of phase I studies in Japanese subjects with mild to moderate renal or hepatic impairment require further clarification but indicate, that caution is required in patients with moderate renal or hepatic disease, and the SmPC should be amended accordingly. In a Drug Use-Results Survey conducted in Japan including 3882 subjects, incidences of drug-related AEs were higher in the presence (16.8%) than in the absence (10.6%) of hepatic function disorder, and were higher in the presence (23.9%) than in the absence (10.4%) of renal impairment.

5.7.2. Balance of benefits and risks

Short-term statistically significant results in a validated and widely accepted functional scale for ALS have been demonstrated. Sensitivity analyses suggest robustness of these results and some secondary endpoints have provided support of these positive results. However, placebo-controlled results are only available for 6 months.

A number of limitations have been identified, such as unspecific mechanism of action of edaravone, not adequately justified proposed dosing scheme, effects only shown in a restricted less advanced ALS population, questionable extrapolability to the broad European ALS population and lack of long term survival/mortality data to further support the clinical relevance of the observed effect on function. There are concerns that an ALS patient population which will relevantly benefit from edaravone would not be identified in the clinical practice.The clinical relevance of the results should be further justified before a discussion of a conditional approval can be held. In addition, it is not clear that the registry study proposed as condition by the applicant is suitable to provide confirmatory evidence of efficacy of edaravone.

Whereas the risks of edaravone currently recognized with regard to the evaluated ALS population could be considered manageable, there are uncertainties regarding the safety profile of edaravone, which pertain predominantly to the limited ALS safety data base with missing information regarding long-term exposure > 15 months, patients with ALS severity grade > 3 and/or patients with decreased respiratory function. ALS study results derived from treatment cycles 7-12 may be explained by baseline imbalances of safety set 4 but may also be interpreted as a less favourable safety profile of edaravone in patients with more advanced ALS in particular with regard to respiratory TEAEs, and a potential neurotoxic effect of edaravone might provide a possible explanation for this.

The benefit-risk balance for a broad indication in ALS, as proposed by the Applicant, is therefore currently negative.

5.7.3. Additional considerations on the benefit-risk balance

Riluzole is the only known drug to have a beneficial impact on survival in ALS, but is has been considered as safe and effective for slowing ALS progression to only a modest degree. There has been no advance in disease modifying treatment that can stop disease progression and/or prolong survival,

over the last 20 years since registration of riluzole. An unmet medical need can therefore clearly be identified.

Short-term beneficial effects on a functional endpoint have been demonstrated. With respect to efficacy, long-term data to support the maintenance of effect and survival/mortality data (with time to death and other end of life measures as an endpoint) as well as efficacy data in more advanced ALS are not available. With respect to safety long-term exposure data and safety in patients with more advanced ALS and/or decreased respiratory function are missing. It is not clear at this stage whether the Applicant will be able to provide such comprehensive data post-approval within acceptable time periods and whether these data will adequately address the remaining uncertainties regarding efficacy and safety. A protocol for an efficacy and safety REGISTRY study for post-marketing data collection of uncontrolled data in the Caucasian population has been submitted. However, a sound justification is needed that a registry study is really adequate as a condition to provide the missing confirmatory efficacy data.

In addition, already several issues have been identified which will require modifications of the protocol for the REGISTRY study.

Conditional marketing authorisation

As comprehensive long-term data on survival for the product are not available, a conditional marketing authorisation was requested by the applicant in the initial submission.

The product does not fulfil the requirements for a conditional marketing authorisation, at present.

The product is not recommended for a conditional marketing authorisation since it cannot be decided without a convincing proposal for post-authorisation work whether the Applicant will be able to provide comprehensive data after authorisation.

Marketing authorisation under exceptional circumstances

Not applicable

5.8. Conclusions

The overall B/R of Radicava (edaravone) is currently considered negative.

A SAG meeting is recommended in order to discuss the clinical relevance of the results, the most appropriate population for edaravone and to justify the adequacy of the registry to provide confirmatory evidence of efficacy of edaravone.