CLINICAL STUDY PROTOCOL

Title

A multicenter, open-label extension study to investigate the long-term safety of FAB122 in patients with Amyotrophic Lateral Sclerosis

ADOREXT (ALS trial with Daily ORal Edaravone EXTension) study

THE SPONSOR STUDY CODE: FAB122-CT-2201

EudraCT NUMBER: 2022-003050-32

Sponsor:	Ferrer Internacional, S.A. Barcelona, Spain
Study Drug Name:	FAB122
Development Phase:	PHASE III Extension
Date of Protocol:	10/07/2023

DOCUMENT VERSION HISTORY

Date	Version	Reason for Revision
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PROTOCOL APPROVAL SIGNATURES

Sponsor Signatures

Declaration of Sponsor

Study title: A multicenter, open-label extension study to investigate the long-term safety of FAB122 in patients with Amyotrophic Lateral Sclerosis

Version number: 1.1 SWE

Date:

This study protocol was subjected to critical review. The information it contains is consistent with current knowledge of the risks and benefits of the investigational product, as well as with the moral, ethical and scientific principles governing clinical research as set out in the Declaration of Helsinki, the guidelines on Good Clinical Practice (GCP) and other local and national laws and regulations, as well as any applicable guidelines.

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Investigator Signature Page

Declaration of Investigator

Study title: A multicenter, open-label extension study to investigate the long-term safety of FAB122 in patients with Amyotrophic Lateral Sclerosis

Version number:1.1 SWE

Date:

All documentation for this study that is supplied to me and that has not been previously published will be kept in the strictest confidentiality. This documentation includes this study protocol, Investigator's Brochure, Case Report Forms (CRFs), and other scientific data.

The study will not be commenced without the prior written approval of a properly constituted Institutional Review Board (IRB) or Independent Ethics Committee (IEC) and the corresponding Competent Authority. No changes will be made to the study protocol without the prior written approval of the Sponsor and the IRB or IEC, except where necessary to eliminate an immediate hazard to the patients.

I have read and understood and agree to abide by all the conditions and instructions contained in this protocol.

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ABBREVIATIONS

3-NT	3-Nitrotyrosine
4HNE	4-hydroxy-2-nonenal
8-OHdG	8-hydroxyguanosine
ADR	Adverse Drug Reaction
AE	Adverse Event
AIS	Acute Ischaemic Stroke
ALS	Amyotrophic Lateral Sclerosis
ALSFRS-R	ALS Functional Rating Score – revised
ALSAQ-40	ALS Assessment questionnaire 40
ALT	Alanine transaminase
aPTT	Activated partial thromboplastin time
AST	Aspartate transaminase
AUC	Area Under the Curve
BID	Twice Daily
BUN	Blood urea nitrogen
CAFS	Combined Assessment of Function and Survival
CAS	Chemical Abstracts Service
CHMP	Committee for Human Medicinal Products
CI	Confidence Interval
CK	Creatinine kinase
C_{max}	Maximum concentration
CNS	Central Nervous System
CYP	Cytochrome P450
CV	Coefficient of Variation
DSMB	Data Safety Monitoring Board
EC	European Committee
ECAS	Edinburgh Cognitive and behavioural ALS Screen
eGFR	Estimated glomerular filtration rate
EMA	European Medicines Agency
EMG	Electromyography
EQ-5D-5L	EuroQoL – 5 Dimensions – 5 Levels
fALS	familial Amyotrophic Lateral Sclerosis
FBR	Future Biomedical Research
FDA	Food and Drug Administration
FAB122	Ferrer New Product 122* (FNP122)
FTD	Frontotemporal dementia
FVC	Forced Vital Capacity
G93A	G93A-human Cu/Zn superoxide dismutase

GGT	Gamma-glutamyl transpeptidase
GI	Gastrointestinal
HCT	Haematocrit
HEK	Human Embryonic Kidney
hERG	human Ether-a-go-go-Related Gene
Hgb	Haemoglobin
hOAT	Human Organic Anion Transporter
HSP	Hereditary Spastic Paraparesis
IC_{50}	Half Maximal Inhibitory Concentration
IDMC	Independent Data Monitoring Committee
INN	International Non-proprietary Name
iNOS	Inducible Nitric Oxide Synthase
IV	Intravenous
IUPAC	International Union of Pure and Applied Chemistry
Km	Michaelis constant
LD_{50}	Median Lethal Dose
LDH	Lactate dehydrogenase
LMN	Lower Motor Neurons
MMRM	Mixed Model for Repeat Measures
MND	Motor Neuron Disease
MoA	Mechanism of Action
MOS	Margin of Safety
mSOD1	Mutated Superoxide Dismutase 1
MVV	Maximum Voluntary Ventilation
NAA	N-Acetyl Aspartate
NCS	Nerve Conduction Study
NF	National Formula
NFL	Neurofilament Light
NIPPV	Non-invasive Positive Pressure Ventilation
NMR	Nuclear Magnetic Resonance spectroscopy
NOAEL	No Observed Adverse Effect Level
Nrf2	Nuclear erythroid 2-related factor 2
OAT	Organic Anion Transporter
OD	Once Daily
OLE	Open-label extension
$P75^{EDC}$	Extracellular domain of neurotrophin receptor p75
PAP	Pharmacokinetics Analysis Plan
PEG	Percutaneous Endoscopic Gastrostomy
PEG 400	Polyethylene glycol 400
PK	Pharmacokinetic(s)
PLP	Pyridoxal Phosphate

PLS	Primary Lateral Sclerosis
PMM	Pattern Mixture Model
PNS	Peripheral Nerve System
POC	Proof of concept
PTT	Prothrombin Time
Q1, Q3	First quarter, third quarter
QoL	Quality of Life
RBC	Red blood cell
RDW	Red cell distribution width
RNA	Ribonucleic acid
ROS	Reactive Oxygen Species
SAE	Serious Adverse Event
sALS	Sporadic Amyotrophic Lateral Sclerosis
SAH	Subarachnoid Haemorrhage
SAP	Statistical Analysis Plan
SD	Standard Deviation
SLS	Sodium Laurilsulfate
SOC	Standard of Care
SOD1	Superoxidase Dismutase 1
SULT	Sulfotransferase
SVC	Slow Vital Capacity
$t_{½}$	Half-life
TDP-43	Transactive response DNA/RNA Binding Protein 43
TEAE	Treatment Emergent Adverse Event
TID	Three Times Daily
t_{max}	Time to peak concentration
TW	Treeway
UGT	UDP-glucuronosyltransferases
UMN	Upper Motor Neurons
US	United States of America
VAS	Visual Analogue Scale
WBC	White blood cell
WFN	World Federation of Neurology
WHO	World Health Organisation

* It substitutes prior codification FAB122 (Ferrer Advanced Biotherapeutics 122)

1. SYNOPSIS

TITLE:	A multicenter, open-label extension study to investigate the long-term safety of FAB122 in patients with Amyotrophic Lateral Sclerosis
THE SPONSOR STUDY CODE:	FAB122-CT-2201
EudraCT NUMBER:	2022-003050-32
SPONSOR:	Ferrer Internacional, S.A. Barcelona, Spain
STUDY PHASE:	PHASE III Extension
STUDY DESIGN:	Multicenter, multinational, open-label Phase III extension study to investigate the long-term safety of 100 mg FAB122 once daily as oral formulation in ALS patients. All patients participating in the ADORE study will be invited to roll over to FAB122 and to participate in ADOREXT. Patients that discontinued treatment in the main ADORE study for other than safety reasons, will be also invited to re-start treatment with FAB122 in the OLE study. The duration of this open label extension (OLE) will be until the product is commercially available at each participant country, provided good tolerance and safety is proven. The sponsor could also make the decision to terminate the study at any time, in case the objectives of the main study (ADORE) are not met. Patients not willing to continue receiving active treatment in the extension study or that had already discontinued study treatment during the course of the main ADORE study for safety reasons, will be asked to be contacted by phone and followed up for vital status. Subjects rolling over active treatment will visit the clinic at Baseline (Visit 6 or 8 of the main study (+ 6 weeks in case the OLE is not fully set up) and every 3 months thereafter.
STUDY PARTICIPANTS:	
Study Population	ALS patients from main ADORE study
Inclusion Criteria	Patients who meet all of the following criteria, will be eligible for the study: 1. who completed the full study period in the main ADORE study (FAB122-CT-2001); 2. whom the investigator has no concern and judges tolerable for receiving treatment with FAB122 from a risk and benefit point of view; 3. a female subject should not be able to become pregnant up to 30 days after the last dose of FAB122 and needs to meet at least one of the following criteria: - female subject who is not of reproductive potential is eligible

	without requiring the use of contraception. A woman is considered not having childbearing potential when becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause. - female who is of reproductive potential and has a negative pregnancy test at baseline and is non-lactating. A female subject who is of reproductive potential agrees to use (or have their partner use) adequate birth control methods starting from the time of consent through 30 days after the last dose of study therapy. Longer periods of birth control may be required per local requirements. Acceptable methods of birth control include combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device in place for ≥3 months, intrauterine hormone-releasing system, bilateral tubal occlusion or vasectomised partner. 4. a male patient must: - agree he will not donate sperm during the period he will be using FAB122, AND use a condom during sexual intercourse with pregnant or non-pregnant women of childbearing potential (WOCBP) partner even if he is vasectomized and until 104 days after the last dose, . - in addition WOCBP partner of the male patient must use the following acceptable methods of birth control during the study and until 104 days after the last dose: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device in place for ≥3 months, intrauterine hormone-releasing system, bilateral tubal occlusion or vasectomised partner; 5. providing informed consent.
Exclusion Criteria	Patients who meet any of the following criteria, will not be eligible for the study: 1. Patient who has a medical condition (e.g. cardiac, pulmonary, gastrointestinal, musculoskeletal, or psychiatric illness) or personal circumstances which, in the opinion of the investigator, will make initiation or continuation of treatment with FAB122 not tolerable for them from a risk and benefit point of view. 2. Patient who discontinued study drug prematurely in the double-blind phase of the study (ADORE Study) for safety reasons.

	3. Patient who has received any other investigational drug within the period between last visit of the main study and first visit of the extension study (i.e. another trial, managed access program, open label extension or early access program) 4. - History of known hypersensitivity to edaravone or to any of the excipients. For patients who do not take FAB122 but are only followed up by phone, only inclusion criteria #1 and #5 will apply.
SAMPLE SIZE:	No formal size calculation has been done for the extension study. The main study plans to include approximately 300 patients. It is anticipated that 200-225 patients might be included in this extension study.
PLANNED STUDY PERIOD:	Approximately 3 years (up to the product is commercially available). Product commercialization is country dependent, thus study ending will differ between countries. The sponsor may terminate the study at any moment in case the objectives of the main study (ADORE) are not met)
STUDY SITES	Approximately 38 sites
OBJECTIVES AND OUTCOME MEASURES:	
PRIMARY OBJECTIVE:	To evaluate the long-term safety of FAB122 in patients with ALS.
SECONDARY OBJECTIVES:	1. To evaluate the effect of treatment with FAB122 on overall survival; 2. To evaluate the effect of treatment with FAB122 on disease progression in patients with ALS; 3. To evaluate the effect of treatment with FAB122 on cognitive functioning; 4. To evaluate the effect of treatment with FAB122 on quality of life (QoL).
PRIMARY ENDPOINT:	Nature, frequency and severity of Treatment Emergent Adverse Events.
SECONDARY ENDPOINTS:	1. Mortality-adjusted change from baseline in ALSFRS-R total score until the end of the study; 2. Overall survival, defined as time to death from any cause or respiratory insufficiency (insufficiency defined as tracheostomy or the use of non-invasive ventilation for ≥20 h per day for ≥10 consecutive days); 3. Change from baseline in SVC until the end of the study; 4. Mean change in norm-standardized ECAS total score; 5. Change from baseline in the total score on the ALS Assessment

	Questionnaire-40-Item (ALSAQ-40) until the end of the study; 6. Change from baseline in EuroQoL – 5 Dimensions – 5 Levels (EQ-5D-5L) until the end of the study; 7. Change from baseline in Health related QoL Visual Analogue Scale (VAS) score until the end of the study; 8. Change from baseline in the prognostic ALS biomarker neurofilament light (NFL); 9. Change from baseline in the ALS biomarkers creatinine and creatinine kinase; 10. Change from baseline in the ALS biomarker Urinary extracellular domain of neurotrophin receptor p75 (Urinary P75ECD); 11. Change from baseline of oxidative stress biomarker 8-hydroxyguanosine (8-OHdG); 12. Cost-Utility analysis of treatment with FAB122.
SAFETY ENDPOINTS	1. Parameters derived from in vital signs and 12-lead electrocardiogram (ECG); 2. Parameters derived from laboratory tests (hematology, biochemistry, urinalysis); 3. Proportion of patients that drop out due to adverse events.
INTERVENTION(S):	
IMP(S):	**FAB122:** Fasted daily dose of 100 mg FAB122 granules for oral solution in single sachets, which has to be dissolved in 100 mL water prior to administration.
STATISTICAL METHODS:	All treatment emergent AEs (TEAE) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 23.0) coding dictionary. And all preferred terms (PT) will be tabulated by System organ Class (SOC) and additional tabulations will be made by severity and drug relatedness. A separate table (or listing will be created for serious TEAEs (SAE). Safety variables will be tabulated and presented for all subjects in the Safety Population. Data will be summarized by treatment and time. Exposure to study drug and reasons for discontinuation of study drug will be tabulated. Difference in survival curves will be evaluated using a log-rank test, stratified for randomization factors. The effect of treatment will be expressed as hazard ratio. In case of non-proportional hazards, we will estimate the difference in restricted mean survival time (RMST). Changes in the in ALSFRS-R score, ALSAQ-40, SVC, EQ-5D-5L, and VAS

	score over time will be presented descriptively.

2. INTRODUCTION

2.1. Background and rationale

Disease under investigation

ALS is a devastating and fatal condition (Bruijn et al., 2004; Shook and Pioro, 2009) characterized by progressive degeneration of upper and lower motor neurons (Elbasiouny et al., 2012). Degeneration of lower motor neurons (LMN) results in loss of muscle strength, muscular atrophy, hyporeflexia, hypotonicity, fasciculations, flaccidity and or muscle cramps. If the upper motor neurons (UMN) degenerate, symptoms of spasticity and pathologic hyperreflexia may occur. ALS eventually results in death, usually due to respiratory failure (Brown and Al-Chalabi, 2017; Hardiman et al., 2017; Maurer, 2012; van Es et al., 2017).

Average disease duration is 2-5 years from the first symptoms until death, but it may vary between a few months to over twenty years (Westeneng et al., 2018). About one-third of the patients present with speech and swallowing difficulties, whereas others report progressive weakness in the hands, arms or legs. Respiratory symptoms are the initial signs in 2-3% of the patients and are associated with a poorer prognosis (Gautier et al., 2010; Shoesmith et al., 2007). Respiratory failure is the cause of death in 66-81% of the patients with ALS (Gil et al., 2008; Spataro et al., 2010; Yang et al., 2011).

The crude worldwide ALS prevalence is 4.42 (95% CI 3.92–4.96) per 100,000 population and the worldwide incidence is 1.59 (95% CI 1.39–1.81) per 100,000 person-years. In West Europe the prevalence is 9.62 (95% CI 4.80–16.10); and the incidence is 2.76, (95% CI 2.00–3.64) per 100.000 person-years. (Global variation in prevalence and incidence of amyotrophic lateral sclerosis: a systematic review and meta-analysis - PubMed (nih.gov)).

It occurs mostly in the range of 40-60 years, although ALS can occur at any adult age. Approximately 10% is classified as familial ALS (fALS) and 90% as sporadic ALS (sALS). For the familial form, more than 40 genes have been identified to date, which together account for about 15% of cases (Recent advances in the diagnosis and prognosis of amyotrophic lateral sclerosis - PubMed (nih.gov)).

Aetiology

ALS has been classified as either the sporadic or the familial form. In 5–15% of patients with ALS, the ALS runs in the family (Byrne et al., 2011; Swinnen and Robberecht, 2014; Wingo et al., 2011). In these cases, a single genetic defect is thought to cause disease. Examples of the most common mutations with a large effect (presumably pathogenic) are C9orf72 (40%), SOD1 (20%), FUS (1–5%), and TARBDP (gene for TDP-43 protein) (1–5%) (Renton et al., 2014). However, most patients do not have a family history of ALS, in which case the disease is thought to have sporadically resulted from both environmental and genetic risk factors. Multiple genetic risk factors for sporadic ALS have been identified. However, the environmental risk factors are less clear. Currently, only smoking is established to be a risk factor for sporadic ALS (Armon, 2009), but other environmental risk factors such as pesticides, organic toxins, electromagnetic radiation, and physical exercise have been suggested as well (Al-Chalabi and Hardiman, 2013; Harwood et al.,

2016; Lacorte et al., 2016). Patients with symptom onset before age 45 are more often related to a positive family history of ALS (Turner et al., 2012).

Specific characteristics; pathophysiological, histopathological, clinical characteristics

ALS is a clinically and genetically heterogeneous, multidomain neurodegenerative syndrome of motor and extra-motor systems with multiple underlying pathophysiological mechanisms and different clinical subphenotypes (Swinnen and Robberecht, 2014). The mechanisms underlying neurodegeneration in ALS are still not fully understood. Many cellular and molecular processes have been implicated, including mitochondrial dysfunction, axonal transport, toxic protein aggregation, impaired protein degradation (involving the proteasome or autophagy, or both), prion-like spreading, excitotoxicity, decreased neurotrophic support from non-neuronal cells, oxidative stress, hypermetabolism, inflammation, RNA metabolism defects, and RNA toxicity (Robberecht and Philips, 2013). Defects in some of these pathways could be secondary phenomena, and genetics would be the logical initial approach to identifying the primary pathophysiological processes underlying ALS.

Clinically, ALS is characterized by muscle weakness and functional decline. Disease onset is usually focal, but the disease eventually spreads to other body regions. The progression and spread of the disease appear to be both local (within the same region; eg, from hand to upper arm) and between neuro-anatomically linked regions (contra-lateral or rostral-caudal) (Ravits and La Spada, 2009). In addition, muscle weakness and functional decline may be accompanied by significant reductions in weight and a poor nutritional status (Moglia et al., 2019).

Moreover, extra-motor symptoms such as cognitive or behavioral impairments occur in up to 50% of the patients, whereas 5-15% fulfill the criteria for frontotemporal dementia (FTD) (Goldstein and Abrahams, 2013; Hardiman et al., 2017; van Es et al., 2017).

Classification

ALS is one of the Motor Neuron Diseases (MNDs), as it is a condition that affects both the UMN as well as the LMN. However, during the first stage of the disease only the UMN or the LMN is affected which can blur the diagnosis of the disease with regard to other MNDs. Example(s) of disease by which the LMN is affected is progressive spinal muscular atrophy and by which the UMN is affected are Primary Lateral Sclerosis (PLS) and Hereditary Spastic Paraparesis (HSP) (Ludolph et al., 2015; Shook and Pioro, 2009). ALS is classified as a neuromuscular disorder and is heterogeneous.

Diagnosis and symptoms

The diagnosis of ALS depends on the criteria-set developed by the World Federation of Neurology (WFN) and are also known as the El Escorial criteria. The criteria-set contains the requirement of both affected LMN and UMN. The clinical part of the diagnosis is made based on signs and symptoms of motor neuron dysfunction of both the lower and upper part of the body confirmed by electromyography (EMG) (Gordon, 2013). The El Escorial criteria have been updated and have been renamed into the Airlie House criteria in 2000 (Brooks et al., 2000). The most widely used instrument to measure function in ALS clinical

trials is the Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS) and the revised version that includes respiratory function (ALSFRS-R) (Cedarbaum et al., 1999), which is a validated disease-specific questionnaire (see Annex 1).

Pharmacological and non-pharmacological treatment options

There are limited pharmacological options in the treatment of ALS; the mainstay of management is symptomatic treatment. ALS patients who receive care at a multidisciplinary clinic may have a better prognosis than patients attending a general neurology clinic. Median survival is up to 7.5 months longer for the patient group treated at a multidisciplinary clinic and was up to two months more for patients with bulbar dysfunction. The data suggest that active management enhances survival (Gordon, 2013).

A variety of compounds have been investigated for their potential in the management of ALS (Zoccolella, 2009), but the only existing, authorised medicine for the treatment of ALS in the European Union is riluzole (INN: riluzole; chemical name: riluzole (2-amino-6-(trifluoromethoxy) benzothiazole) (“Rilutek SmPC,” n.d.). Although riluzole reduces glutamate-induced excitotoxicity, its precise mechanism in ALS is unknown.

All other pharmacological treatment options which are commonly used in the management of ALS in clinical practice are additional palliative treatments aiming at improving the quality of life and at reducing signs and symptoms associated with the disease but which on their own are not specifically indicated for ALS (e.g. treatment of muscle spasms, pain, insomnia, dysphagia and emotional instability; see below) (Hardiman et al., 2017). In addition, supportive non-pharmacological treatments may be required, like mechanical ventilation for the management of respiratory insufficiency.

Quinine sulphate 325 mg BID is the most effective treatment option for muscle spasms and cramps. Baclofen and tizanidine are used for excess muscle spasticity that causes incoordination and discomfort. Sialorrhea (excess salivation) may respond to amitriptyline, atropine, botulinum toxin injection, glycopyrronium or hyoscyamine. Insomnia should be managed by addressing underlying problems (e. g. depression, dyspnoea, dysphagia, pain). This may obviate the need to use sedatives. Pain management includes the use of non-steroidal anti-inflammatory agents, anticonvulsants (e.g. carbamazepine) and later opiates if/when the former treatments fail.

Emotional lability is often treated with amitriptyline or fluvoxamine. A combination of dextromethorphan and quinidine (30 mg/30 mg) were assessed in a randomized, double-blind, controlled trial. The combination was effective for reducing the frequency and severity of pathologic laughter and crying compared with either drug alone. It also resulted in improved quality of life. Longer-term studies regarding side effects of this combination are awaited (Phukan and Hardiman, 2009; Pioro et al., 2010).

Management of respiratory insufficiency in ALS is guided by the American Academy Practice Parameter (Miller et al., 2009). Deciding when to initiate non-invasive mechanical ventilation is critical because of the risk of either sudden death or ventilator dependence without proper advance planning. The recommendations are as follows:

1. Be vigilant for symptoms indicating hypoventilation. Serial measures of pulmonary function (especially vital capacity) are recommended to guide management and to

determine prognosis with the understanding that no single test can detect hypoventilation reliably.

2. Offer non-invasive ventilatory support as an effective initial therapy for symptomatic chronic hypoventilation and to prolong survival in patients with ALS.

3. When long-term survival is the goal, offer invasive ventilation and fully inform patient and family of burdens and benefits.

4. In accordance with the principle of patient autonomy, physicians should respect the right of the patient with ALS to refuse or withdraw any treatment, including mechanical ventilation.

5. When withdrawing ventilation, use adequate opiates and anxiolytics to relieve dyspnoea and anxiety.

Non-invasive positive pressure ventilation (NIPPV) is particularly useful if patients have nocturnal respiratory symptoms but also can be used during waking hours as the disease progresses (Gordon, 2013; Phukan and Hardiman, 2009).

NIPPV has been shown to extend survival, particularly in those compliant with ≥ 4 hours use each day and those without severe bulbar dysfunction. It also improves quality of life in patients without increasing caregiver burden or stress. In some studies, it improves cognitive impairment due to sleep disruption (Lo Coco et al., 2012).

Management of dysphagia includes modification of food and fluid consistency, postural advice (e.g. chin tuck: flexing the neck forward on swallowing to protect the airway), and parenteral feeding. A PEG (percutaneous endoscopic gastrostomy) placement is indicated for those who have symptomatic dysphagia or significant weight loss. Patients and their families should be suitably counselled regarding the benefits and risks of the procedure (Phukan and Hardiman, 2009).

Product under investigation (edaravone)

As described above, ALS is a progressive neurodegenerative disease with multiple underlying pathological mechanisms of neuronal cell death, and most of the possible current therapeutic interventions were developed basically against a specific route of ALS disease progression. Distinguishing pathogenic features of neurodegenerative diseases as ALS include high reactive oxygen species (ROS) levels and mitochondrial dysfunction (Barber, 2006 and Smith, 2019).

From the various published non-clinical and clinical studies described below, the mechanism of action of edaravone in the treatment of ALS is thought to be multifactorial, comprising, but not limited to, inhibition of oxidative damage of motor neurons, inhibition of motor neuron death caused by inflammatory processes, the inhibition of neuronal damage caused by the accumulation of aggregated SOD1 particles, and the inhibition of apoptosis induced protein aggregation (Shin and Lee, 2013). (See Figure 1).

Edaravone is one of three metabolites resulting from antipyrine biotransformation in mammals and is also referred to as norphenazone or norantipyrine. Edaravone is a free

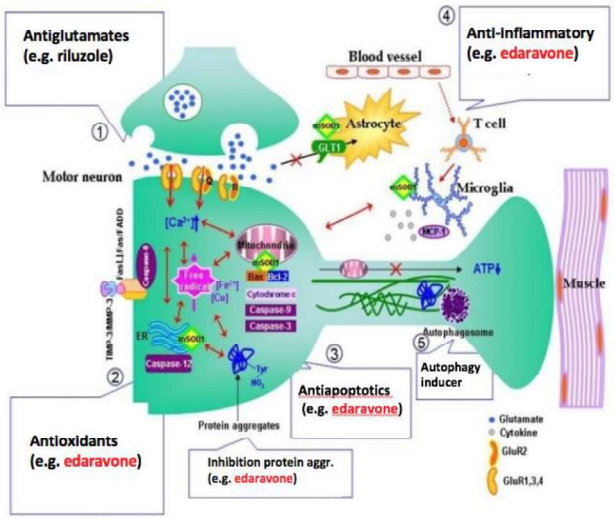
radical scavenger that has demonstrated cellular protective properties in animals and humans. Owing to its antioxidant activity, edaravone modulates oxidative damage in various diseases, especially neurodegenerative diseases (Hardiman, 2017b). It exerts anti-ischaemic actions and is capable of reducing oedema in the brain following ischaemia/reperfusion injury (Lapchak, 2010; Tabrizchi, 2000). In 2001, Mitsubishi Tanabe Pharma received a marketing approval in Japan for the intravenous (slow drip infusions) use of edaravone under the trade name Radicut® for improvement of neurological symptoms, disorder of activities of daily living, and functional disorder associated with acute ischaemic stroke (AIS) (Mitsubishi Tanabe Pharma Corporation, 2015). Edaravone's potential in the treatment of cerebrovascular ischaemia and cerebral oedema appears to be at least partly due to its action to reduce oxidative stress as a free radical scavenger and its capability to reduce the disintegration of the membrane lipid bilayer which is associated with neurodegeneration (Fujisawa and Yamamoto, 2016; Kamat et al., 2008; Kikuchi et al., 2013, 2012, 2011; Tabrizchi, 2000; Watanabe et al., 1997). In addition, edaravone was found to counteract oxidative neurotoxicity and neuronal cell death arising from activated microglia, as occurs in either inflammatory or neurodegenerative disorders of the central nervous system (CNS) (Banno et al., 2005). Therefore, edaravone was also considered to be a possible candidate drug for the treatment of ALS, since oxidative stress and inflammation-induced neuronal cell death are part of the underlying multifactorial pathogenic mechanisms of ALS (Franco et al., 2013; Rossi et al., 2013; Zoccolella, 2009).

To investigate edaravone's potential in the treatment of ALS, additional studies were performed by the Mitsubishi Tanabe Pharma, including an extensive pharmacology study in an ALS mouse model (Aoki et al., 2011; Ikeda and Iwasaki, 2015; Ito et al., 2008), an open label Phase II study (Yoshino and Kimura, 2006), two double-blind, placebo controlled Phase III studies in ALS patients (Abe et al., 2014; Takei et al., 2017; The Writing Group on behalf of the Edaravone (MCI-186) ALS 17 Study Group. 2017 a, 2017; The Writing Group on behalf of the Edaravone (MCI-186) ALS 19 Study Group. 2017 b, 2017; The Writing Group on behalf of the Edaravone (MCI-186) ALS 19 Study Group. 2017 c, 2017) and an explorative study in severe ALS patients (The Writing Group on behalf of the Edaravone (MCI-186) ALS 18 Study Group., 2017). This resulted in approval of edaravone for the inhibition of progression of functional disorder in ALS in Japan and South-Korea in June and December 2015 (Radicut®) (Mitsubishi Tanabe Pharma Corporation, 2015), respectively and later also for the treatment of ALS in the US (Radicava®) (Mitsubishi Tanabe Pharma Corporation, 2017) (April 2017), Canada (October 2018), Switzerland (January 2019) and China (August 2019). Radicava ORS™ as an oral formulation of edaravone, with the same intermittent posology of Radicava iv formulation and based on a bioavailability study, was approved by FDA in May 2022, for the treatment of ALS, as well (Radicava and Radicava ORS). Based on the initial results achieved with the intravenous edaravone formulation in ALS patients, Treeway initiated in Europe a phase I clinical development program with edaravone daily oral formulation (FAB122), in support of the orphan indication "treatment of ALS", that was followed by Ferrer phase III pivotal study, ADORE.

Multiple pathological mechanisms of neuronal death and associated clinical therapies involve:

1) Neuronal excitotoxicity
2) Oxidative stress*
3) Apoptosis *
   Protein aggregation*
4) Inflammation*
5) Autophagy

* Part of edaravone's proposed mechanism of action



Adapted from Shin & Lee, 2013

Figure 1: Possible mechanism of action of edaravone

(1) increased Ca 2^+ in the motor neuron: dysfunction or downregulation of glutamate transporters; (2) oxidative damage of the motor neuron; (3) apoptosis in the motor neuron: including alteration and aggregation of proteins via mitochondrial interaction with mSOD1; (4) inflammation: non-cell-autonomous motor neuron death (the disease progression is coordinated by mSOD1 expression in all neuronal and non-neuronal cells) and concurrent activation of the innate immune system and systemic inflammation; and (5) autophagy: increased auto-phagosome formation.

Please see FAB122 investigator's brochure (IB) for more details on intravenous edaravone and FAB122 (Nonclinical pharmacology; Toxicology and toxicokinetics; Pharmacokinetics and metabolism; Clinical data for edaravone administered via the intravenous route; and Phase 1 clinical data for FAB122 administered via the oral route).

Rationale for the Current Study

As ALS is a rapidly progressive and fatal disease, this study is designed as an open-label extension (OLE) study to provide longer term access to daily oral edaravone to patients who have demonstrated a good tolerance in the ADORE trial (either FAB122 or placebo arm) during 48 weeks and up to 72 weeks.

The good tolerance for each patient who could be included in the current OLE study will be evaluated by the investigator, according to the individual favourable benefit/risk ratio which will be based on the available data.

This OLE study will also assess longer term safety, survival and therapeutic potential of daily oral edaravone.

Rationale for Future Biomedical Research

This research may include genetic analyses (DNA and/or RNA) and/or the measurement of blood derived analytes. The objective of collecting specimens for Future Biomedical Research (FBR) is to explore and identify additional biomarkers which can improve our

current understanding of diseases and/or their therapeutic treatments. In particular, the information gathered may be used to aid diagnosis and/or prognosis of ALS, to develop safer, more effective drugs, and/or to ensure that subjects receive the correct dose of the correct drug at the correct time. Exploratory pharmacogenetic (PGt) studies may be performed if significant PK/PD relationships are observed or adverse events are identified. Genomic markers of disease may also be investigated. Such retrospective pharmacogenetic studies will be conducted with appropriate statistical design and analysis and compared to PK/PD results or clinical outcomes. Any significant PGt relationships to outcome would require validation in future clinical trials.

Collection of FBR samples is optional to the patient and blood samples for FBR can only be collected after the patient has reviewed and signed the FBR Informed Consent Form (ICF).

Biobank

Blood samples will be stored in a central biobank located in Barcelona, Biobanc IGTP-HUGTP. Institut de Recerca Germans Trias i Pujol (IGTP). Campus Can Ruti, for a maximum of 10 years.

Patients will have the right to withdraw their samples from storage at any time.

2.2. Risk-Benefit Assessment

ALS is a devastating neurological disease for which there is no cure and an urgent unmet need persists for effective therapies. The main aims in the care of these patients are to minimize morbidity and maximize quality of life. Riluzole and iv edaravone are the only current approved drugs for ALS.

In general, long-term treatment with intravenously administered edaravone showed clinical benefit and an acceptable safety profile in ALS patients. As well, single- and multiple dose of FAB122 was safe and well tolerated in ALS patients and healthy volunteers (FAB122 IB).

Overall, the safety and efficacy of edaravone administered by oral and intravenous routes have been demonstrated in many clinical trials in healthy volunteers and ALS patients. Also, a phase III clinical trial (ADORE) with daily oral edarovone is being conducted by Ferrer in 300 patients with ALS.

At the time of writing of this version of the protocol, all patients have been recruited in the main study ADORE and there are patients participating for up to 72 weeks. No safety concerns have been raised during the monthly safety data review by the Data Safety Monitoring Board (DSMB). The DSMB specially reviewed the data related to potential neurotoxicity and concluded that there is low incidence of neuropathies and abnormalities detected in NCS assessments.

Therefore, the expected clinical benefits from the participation in the current OLE study for selected patients overcome the potential risks.

3. OBJECTIVES AND OUTCOME MEASURES

3.1. Objectives

3.1.1. Primary Objective

To evaluate the long-term safety of FAB122 in patients with ALS.

3.1.2. Secondary Objectives

1. To evaluate the effect of treatment with FAB122 on overall survival;
2. To evaluate the effect of treatment with FAB122 on disease progression in patients with ALS;
3. To evaluate the effect of treatment with FAB122 on cognitive functioning;
4. To evaluate the effect of treatment with FAB122 on quality of life (QoL).

3.2. Endpoints

3.2.1. Primary Endpoint

Nature, frequency and severity of Treatment Emergent Adverse Events.

3.2.2. Secondary Endpoints

1. Mortality-adjusted change from baseline in ALSFRS-R total score until the end of the study;
2. Overall survival, defined as time to death from any cause or respiratory insufficiency (insufficiency defined as tracheostomy or the use of non-invasive ventilation for ≥20 h per day for ≥10 consecutive days);
3. Change from baseline in SVC until the end of the study;
4. Mean change in norm-standardized ECAS total score;
5. Change from baseline in the total score on the ALS Assessment Questionnaire-40-Item (ALSAQ-40) until the end of the study;
6. Change from baseline in EuroQoL – 5 Dimensions – 5 Levels (EQ-5D-5L) until the end of the study;
7. Change from baseline in Health related QoL Visual Analogue Scale (VAS) score until the end of the study;
8. Change from baseline in the prognostic ALS biomarker neurofilament light (NFL);
9. Change from baseline in the ALS biomarkers creatinine and creatinine kinase;

10. Change from baseline in the ALS biomarker Urinary extracellular domain of neurotrophin receptor p75 (Urinary P75ECD);

11. Change from baseline of oxidative stress biomarker 8-hydroxyguanosine (8-OHdG);

12. Cost-Utility analysis of treatment with FAB122.

3.2.3. Safety Endpoints

1. Parameters derived from vital signs and 12-lead electrocardiogram (ECG);

2. Parameters derived from laboratory tests (hematology, biochemistry, urinalysis);

3. Proportion of patients that drop out due to adverse events.

4. STUDY DESIGN

Multicenter, multinational, open-label Phase III extension study to investigate the long-term safety of 100 mg FAB122 once daily as oral formulation in ALS patients.

All patients who participated in the ADORE study will be invited to roll over to FAB122 and to participate in ADOREXT study. Patients that discontinued treatment in the main ADORE study for other than safety reasons, will be also invited to re-start treatment with FAB122 in the OLE study. The duration of this open label extension (OLE) will be until the product is commercially available at each participant country, provided good tolerance and safety is proven. The sponsor could also make the decision to terminate the study at any time in case the objectives of the main study (ADORE) are not met.

Patients not willing to continue receiving active treatment in the extension study or that had already discontinued study treatment during the course of the main ADORE study for safety reasons, will be asked to be contacted by phone and followed up for vital status.

Double-blinding to original treatment assignment in the main ADORE study will be maintained.

Subjects rolling over active treatment will visit the clinic at Baseline (whenever possible, Visit 6 or 8 of the main study) and every 3 months thereafter.

End of study at each participant country is defined as the time when the product is commercially available; or prematurely in case the objectives of the main study are not met, at the time when the main study results show a negative benefit /risk ratio. Other reason for premature ending of the study would be in case that the product is not authorized by the local/regional authorities, at the time when the rejection is received.

5. STUDY POPULATION

5.1. Study Participants

ALS patients from main ADORE study.

5.2. Inclusion Criteria

All patients:

1. who completed the full study period in the main ADORE study (FAB122-CT-2001);

2. whom the investigator has no concern and judges tolerable receiving treatment with FAB122 from a risk and benefit point of view;

3. a female subject should not be able to become pregnant up to 30 days after the last dose of FAB122 and needs to meet at least one of the following criteria:

    - female subject who is not of reproductive potential is eligible without requiring the use of contraception. A woman is considered not having childbearing potential when becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.
    - female who is of reproductive potential and has a negative pregnancy test at baseline and is non-lactating. A female subject who is of reproductive potential agrees to use (or have their partner use) adequate birth control methods starting from the time of consent through 30 days after the last dose of study therapy. Longer periods of birth control may be required per local requirements. Acceptable methods of birth control include combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device in place for ≥3 months, intrauterine hormone-releasing system, bilateral tubal occlusion or vasectomised partner.

4. a male patient must:

    - agree he will not donate sperm during the period he will be using FAB122 AND use a condom during sexual intercourse with pregnant or non-pregnant women of childbearing potential (WOCBP) partner even if he is vasectomized until 104 days after the last dose.
    - in addition WOCBP partner of the male patient must use the following acceptable methods of birth control during the study and until 104 days after the last dose: combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), intrauterine device in

place for ≥3 months, intrauterine hormone-releasing system, bilateral tubal occlusion or vasectomised partner;

5. providing informed consent.

will be eligible and enrolled.

5.3. Exclusion Criteria

Patients who meet any of the following criteria, will not be eligible for the study:

1. Patient who has a medical condition (e.g. cardiac, pulmonary, gastrointestinal, musculoskeletal, or psychiatric illness) or personal circumstances which, in the opinion of the investigator, will make initiation or continuation of treatment with FAB122 not tolerable for them from a risk and benefit point of view.

2. Patient who discontinued study drug prematurely in the double-blind phase of the study (ADORE Study) for safety reasons.

3. Patient who has received any other investigational drug within the period between last visit of the main study and first visit of the extension study (i.e. another trial, managed access program, open label extension or early access program)

4. History of known hypersensitivity to edaravone or to any of the excipients.

For patients who do not take FAB122 but are only followed up by phone, only inclusion criteria #1 and #5 will apply.

6. STUDY PROCEDURES

All the study procedures are presented in the following table:

Table 1: Study Scheduled Visits

	Baseline[1]	
	V1 D1 W0	**V2-N End of Trial[4] Every 3 months (±1 week)**
Administrative procedures		
ICF	X	
ICF for FBR	X	
In/exclusion assessment	X	
Dispensing study medication	X	X
Clinical Procedures		
Physical examination	X	X[6]
Vital Signs	X	X
Weight	X	X
12-lead ECG	X	X[6]
Neurological examination	X	X[6]
(S)AE monitoring	X	X
Prior/Concomitant medication	X	X
Laboratory procedures		
Chemistry[2]/ Haematology[2]/Urinalysis[2]	X	X
Vitamin B6 monitoring[3]	X	X
Urine Pregnancy Test	X	X
Blood/urine sampling for biomarkers[7]	X	X[8]
Blood sampling for genotyping for FBR (if consented)	X	
ALS evaluation procedures		
ALSFRS-R	X	X
SVC	X	X
ALSAQ-40	X	X
EQ-5D-5L/VAS	X	X
ECAS	X	X[6]
King's staging system and MiToS	X	X
Cost questionnaire	X	X
Vital Status Follow Up[5]		X
Study Drug Administration	X	

V=visit

1. Baseline visit is V6 or V8 of the main study. In case the ADOREXT study is not fully set up at the time of subject's finalization in the main ADORE study, baseline visit could take place up to 6 weeks after finalization. For patients who do not take FAB122 but are only followed up by phone, only ICF will be obtained.

2. Hematology: hematocrit, hemoglobin, RBC (red blood cell count & parameters), WBC (white blood cell count inclusive differential count), platelet (thrombocytes). Biochemistry: total protein, alkaline phosphatase, AST (aspartate transaminase), ALT (alanine transaminase), GGT (Gamma-glutamyl transpeptidase), direct and total bilirubin, blood urea nitrogen (BUN), creatinine (serum), sodium, potassium, chloride, calcium, bicarbonate, LDH (lactate dehydrogenase), CK (creatinine kinase), eGFR (estimated glomerular filtration rate), uric acid and fasting glucose, activated partial thromboplastin time (aPTT), prothrombin time (PTT) and fibrinogen..
   Urinalysis or dipstick: Blood, Glucose, Protein, Specific gravity, Ketone, pH, Nitrite, Leukocytes, Bilirubin, Urobilinogen, Microscopic exam, if abnormal results are noted.
3. PLP levels will be monitored and, if necessary, supplementation of vitamin B6 (pyridoxine (100 mg/day)) will be prescribed.
4. When patient withdraws consent, is not able to attend the study visits any more or is discontinued.
5. Only for patients not taking IMP, phone conctact. For patients who do not take FAB122 but are only followed up by phone, only vital status will be collected. The rest of assessments will not be done.
6. Every 6 months.
7. Blood biomarkers: neurofilament light chain (NfL). Serum creatinine and serum creatine kinase will be measured in biochemistry lab testing. Urine biomarkers: 8-hydroxy-2 ′-deoxyguanosine (8-OhdG), extracellular domain of neurotrophin receptor p75 (p75ECD).
8. Every 12 months.

Follow up of patients unable to attend to one onsite study visit

In case that, on an ad hoc basis, due to ALS progression, the subject is not able to attend the clinic or perform specific testing such as SVC, at least ALSFRS-R score and adverse events will be collected (if necessary by telephone). Study medication will be provided to the patient as detailed in section 7.1.4. On site visit for key safety assessments needs to be performed as soon as possible (max. up to 6 months from last visit) to assess vital signs and perform physical exam, ECG and laboratory assessments.

Follow up of patients unable to attend to more than one onsite study visit

If, in the judgment of the site Investigator, the participant cannot reasonably be expected to travel to the clinic, the minimum data required to continue on study medication are laboratory tests (hematology, biochemistry and urinalysis or dipstick as per local lab standards), adverse event reporting and ALSFRS-R.

The monitoring of ALSFRS-R and AEs may continue by telephone according to the nominal visit schedule.

Laboratory samples for safety assessments may be obtained through a local laboratory, and results will be reviewed by the site investigator and the medical monitor. These data are to be obtained at least every 6 months until the patients withdraw, reaches the endpoint or the study completes, whichever occurs first.

In case the site has an established procedure in place to perform visits at the home of the participant, the sponsor will assess the adequacy of the procedure in order to be used in the ADOREXT study. If the procedure is deemed adequate to guarantee patient’s’ safety and the integrity of the data, home visits by the delegated site staff can be performed.

If the patient becomes unfit for travel, this information and the procedures to be followed to ensure the safety assessment of the patients must be documented in the source data. If no accommodations can be made for adequate safety monitoring, patients will be withdrawn from study medication.

The following sections provide details regarding the procedures to be performed at each study visit:

6.1. Eligibility Assessment

All subjects who completed the full study period in the main ADORE study, will sign the extension study-specific consent form. The procedures for Visit 6 or 8 of the main ADORE study will be considered for the baseline visit for the extension study. In case the ADOREXT study is not fully set up at the time of subject's finalization in the main ADORE study, baseline visit could take place up to 6 weeks after finalization. Study assessments performed at Visit 6 or 8 of the main study can be used as baseline assessments of the open label extension ADOREXT study within the allowed 6 weeks period.

A signed copy of the informed consent form (ICF) should be provided to each consenting subject and with the original to be retained in the subject's study records.

Baseline Assessments

6.2. Baseline (Visit 1)

The following procedures, performed at Visit 6 or 8 of the main study, will be considered as baseline procedures for the extension study:

- Review inclusion and exclusion criteria.
- Review ongoing concomitant medications.
- Complete physical examination.
- Neurological examination.
- Weight.
- Vital signs measured with the subject in a supine/semi-supine position (for at least 5 minutes prior), including blood pressure, pulse rate, respiratory rate, pulse oximetry and temperature.
- Standard 12-lead ECG (subject should be in a supine/semi-supine position for at least 5 minutes prior to assessment).
- Blood samples for routine clinical labs (clinical chemistry, haematology). See table 2 for lab assessments.
- Blood sampling for biomarkers: neurofilament light (NFL). Creatinine and creatine kinase will be measured in routine biochemistry lab testing.
- Urine collection for biomarkers: urinary extracellular domain of neurotrophin receptor p75 (Urinary $P75^{ECD}$) and oxidative stress biomarker 8-hydroxyguanosine (8-OHdG).
- Blood sampling for genotyping for Future Biomedical Research (FBR) (if consented).

- Urine samples for urinalysis or dipstick testing
- Urine pregnancy test only in women of childbearing potential.
- Plasma pyridoxal 5'-phosphate (PLP) levels, and, if necessary, vitamin B6 supplements (pyridoxine (100 mg/day)) will be prescribed.
- ALS evaluation procedures: ALSFRS-R, Slow Vital Capacity (SVC), ALSAQ-40, EQ-ED-5L, VAS, King's staging system and, MiToS
- Cost questionnaire.
- Adverse Events monitoring.
- ECAS.
- Study drug administration
- Dispense study medication

6.3. Rest of visits

Every 3 months and up to the product is marketed, subjects will attend the study site and the following procedures will be performed:

- Review ongoing concomitant medications.
- Complete physical examination (every 6 months).
- Neurological examination (every 6 months).
- Weight.
- Vital signs measured with the subject in a supine/semi-supine position (for at least 5 minutes prior), including blood pressure, pulse rate, respiratory rate, pulse oximetry and temperature.
- Standard 12-lead ECG (subject should be in a supine/semi-supine position for at least 5 minutes prior to assessment) (every 6 months).
- Blood samples for routine clinical labs (clinical chemistry, haematology). See table 2 for lab assessments.
- Urine samples for urinalysis or dipstick testing.
- Blood sampling for biomarkers: neurofilament light (NFL) (every 12 months).
- Urine collection for biomarkers: urinary extracellular domain of neurotrophin receptor p75 (Urinary P75ECD) and oxidative stress biomarker 8-hydroxyguanosine (8-OHdG) (every 12 months).
- Urine pregnancy test only in women of childbearing potential.
- Plasma pyridoxal 5'-phosphate (PLP) levels, and, if necessary, vitamin B6 supplements (pyridoxine (100 mg/day)) will be prescribed.
- ALS evaluation procedures: ALSFRS-R, Slow Vital Capacity (SVC), ALSAQ-40, EQ-5D-5L, VAS, King's staging system and, MiToS.
- Adverse Events monitoring.
- ECAS (every 6 months).
- Vital status (tracheostomy or initiation of non-invasive ventilation for more than 20 hours a day for more than 10 consecutive days) / Date of death. Cost questionnaire
- Dispense study medication

6.4. Phone contacts

Patients not willing to receive or continue receiving active treatment in the extension study or that had already discontinued study treatment during the course of the main ADORE study for safety reasons, will be asked to be contacted by phone every three months and followed up for vital status. These patients will not undergo the baseline assessments or any other study procedures.

Table 2: Overview of laboratory assessments

Haematology	Chemistry	Urinalysis/Dipstick
Haematocrit	Bilirubin (direct) and Bilirubin (total)	Blood
Haemoglobin	Alkaline phosphatase	Glucose
RBC	Alanine aminotransferase (ALT)	Protein
Platelet count	Aspartate aminotransferase (AST)	Specific gravity
WBC	Bicarbonate	Microscopic exam, if abnormal results are noted
Differential count:	Calcium	Ketone
Basophils	Chloride	PH
Eosinophils	Creatinine	Nitrite
Lymphocytes	gammaGT (GGT)	Leukocytes
Monocytes	Glucose	Bilirubin
Neutrophils	Potassium	Urobilinogen
Large Unstained cells	Sodium	
	Uric Acid	
	Total protein	
	Urea (BUN)	
	eGFR	
	Activated partial thromboplastin time (aPTT)	
	Prothrombin Time (PTT)	
	Fibrinogen	
	Lactate dehydrogenase (LDH)	
	Creatinine kinase (CK)	
	Vitamin B6	

Blood and urine samples for routine clinical chemistry, haematology and urinalysis/dipstick will be analysed locally.

Vitamin B6 will be analysed by a central laboratory.

Instructions for handling, shipment and storing of blood and urine samples for Biomarkers testing will be described in a separate laboratory manual.

6.5. Early Discontinuation/Withdrawal of Participants

Subjects may withdraw consent at any time for any reason or be discontinued from the extension trial at the discretion of the investigator should any untoward effect occur. In addition, a subject may be withdrawn by the investigator or the Sponsor if enrolment into the trial is inappropriate, the trial plan is violated, or for administrative and/or safety reasons.

In this trial, a subject may discontinue from treatment but continue to participate in the regularly scheduled activities, as long as the subject does not withdraw consent.

A subject must be discontinued from the trial for any of the following reasons:

- The subject withdraws consent.
- The subject has a medical condition or personal circumstances which, in the opinion of the investigator and/or Sponsor, places the subject at unnecessary risk if participation in the trial is continued.

A subject must be discontinued from study treatment (but should continue to be monitored in the study) for any of the following reasons:

1) Key safety assessment cannot be performed.
2) The subject becomes pregnant during the study.
3) The subject's investigator considers it is in the best interest of the subject to discontinue.
4) Serious adverse event considered related to the IMP
5) Severe Neurotoxicity considered related to the IMP
6) Any other severe adverse event considered related to the IMP at the discretion of the investigator.
7) Acute renal failure (creatinine clearance of less than 30 mL/min)
8) Severe liver disorder defined as:
    a. ALT/AST ≥ 3xULN and bilirubin ≥2xULN (>35% direct bilirubin).
    b. ALT/AST ≥ 8xULN.
    c. ALT/AST ≥ 3xULN and with symptoms believed to be related to liver injury or hypersensitivity.
    d. ALT/AST ≥ 3x baseline ALT/AST and with symptoms believed to be related to liver injury or hypersensitivity.
    e. ALT/AST ≥ 5xULN and ALT/AST < 8xULN that persists more than two weeks.
9) Acute lung injury with pyrexia, cough, dyspnoea and chest X-ray abnormality.
10) Rhabdomyolysis.
11) Disseminated intravascular coagulation (DIC).
12) Hypersensitivity reaction
13) Anaphylactic reaction/shock
14) Thrombocytopenia
    a. Platelets <20 10^9/L or >100010^9/L
    b. Platelets between 20 and 50 10^9/L if in the investigator judgement the patient present risk of any kind of bleeding or haemorrhage.
15) Neutropenia of ≤ 0.5 10^9/L

The Sponsor reserves the right to terminate the extension study at any time if continuation of the protocol would present a potential safety risk to the subjects or in case that after the analysis of the main ADORE study it is concluded that there is no clinical benefit for the patients.

Patients who withdraw due to an Adverse Event (AE) or Serious Adverse Event (SAE) will be given appropriate care under medical supervision until the symptoms resolve or the patient's condition becomes stable.

7. STUDY INTERVENTIONS

7.1. Investigational Medicinal Product(s) (IMP) Description

Compound name: FAB122

INN/generic name: edaravone

Synonyms: norphenazone; methylphenylpyrazolone; norantipyrine

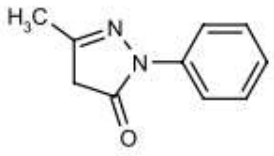
IUPAC name: 3-methyl-1-phenyl-4, 5-dihydro-1H-pyrazol-5-one

CAS name: 5-Methyl-2-phenyl-1, 2-dihydropyrazol-3-one (CAS Registry No. 89-25-8)

Molecular formula: $C_{10}H_{10}N_2O$

Chirality: FAB122 has no chiral centre

Structural formula:



Molecular weight: 174.20 g/mol

Appearance: off-white to white powder

Solubility: sparingly soluble in water, soluble in acetic acid and methanol, limited solubility in ethanol

Hygroscopicity: FAB122 is not hygroscopic

Each sachet of the active treatment contains the following composition given in the table 3:

Table 3: The theoretical quantitative composition of FAB122 granules for oral solution in sachet

Component	Amount/sachet
FAB122	100.0 mg
Spray dried mannitol 200	621.8 mg
Disodium hydrogen phosphate dihydrate	363.6 mg
Sodium Laurilsulfate (SLS)	5.5 mg
Total	1090.9 mg

The active ingredient and the investigational drug have been produced complying the Good Manufacturing Practices of the European Union for active pharmaceutical ingredients and ICH Q7A guidelines.

Study treatment is supplied as granules for oral solution, 100 mg FAB122 per sachet, to be dissolved in about 100 ml water approximately and stirred slightly by a teaspoonful. Study treatment must be administered immediately after its dissolution.

First dosing will be administered at the study site and patients will be instructed about study treatment administration.

Study treatment should be administered once a day at about the same time each day. Dosing needs to be done each morning under fasting conditions. This implies taking the dose: at least two (2) hours after a meal or snack and 30 min after a drink AND no eating or drinking for at least one-hour post dosing. If a subject misses a dose, the missed dose should be taken as soon as possible taking the fasted conditions into account if feasible. If the time period until the regular dosing time for the next dose is less than 4 hours, then the missed dose should be skipped, and the normal dosing schedule should be resumed. The next dose should not be doubled in order to make up for the missed dose.

The study medication is to be stored in the refrigerator at a temperature between 2 - 8 ˚C. Temperature excursions are permitted at 8-25ºC not exceeding 72 hours. Please contact the Sponsor in case the temperature excursion is on different conditions from the ones mentioned before.

Study treatment could be given via gastrostomy and feeding tube if applicable.

7.1.1. Packaging and Labelling

The label(s) for the investigational product will include all information according to GMP Annex 13. Additional information may be included on the label as applicable per local regulations.

7.1.2. Compliance with Trial Treatment

Patients will be instructed to return all used an unused medication at each study visit. The number of sachets dispensed and returned will be registered by the investigator at each visit to obtain information on patients' compliance. The patient will be considered compliant with treatment when > 80%-100% of the total scheduled doses since the last clinic visit are administered.

Investigational product used in this study will be monitored for compliant usage throughout the trial by the Sponsor or their designee.

7.1.3. Accountability of the Trial Treatment

Adequate supplies of the IMP will be provided to the site. Study drug should be stored in the original package under conditions as stated on the product label, in a secure, temperature-monitored, locked area, under the responsibility of the Investigator or other authorized individual until dispensed to the subjects.

The pharmacy of the site must maintain accurate records of the receipt of all study drug, including date received, lot number, expiration date if applicable, amount received, condition of the package, and the disposition of all study drug.

Current dispensing records will also be maintained, including the date and amount of medication dispensed and the identity of the subject receiving the medication.

At the end of the study, it must be possible to reconcile delivery records with those of used, partially used and returned stocks.

All used and unused IMP must be returned to the storage/distribution facility after the study is completed.

In accordance with local regulations, in case it is necessary, and the site has not a specific procedure in place to deliver drugs directly to patients, IMP can be delivered directly to patient's home, through a validated direct to patient service provided by the Sponsor.

7.1.4. Concomitant Medication

Treatment of ALS impairments (nutrition, respiration, motricity, communication) will be done with a multidisciplinary approach and accordingly to European Federation of Neurological Societies (EFNS) Guidelines for ALS patients' management.

7.2. Other Treatments (non-IMPS)

Riluzole (100 mg/day or less) may be used as background (add-on) therapy.

8. PARAMETERS AND METHODS OF ASSESSMENT

8.1. Parameters

8.1.1. ALSFRS-R

The ALSFRS-R is a validated 12-item questionnaire designed to evaluate the functioning of respiratory, bulbar, fine and gross motor function in ALS patients. The total score ranges from 48 (no limitation in daily activities) to 0 (total inability). The patients will be asked to complete the ALSFRS-R questionnaire at each in-clinic visit. The total score of the ALSFRS-R and the score of each subdomain will be recorded in the eCRF by the investigator or designee.

8.1.2. Survival Time

If a patient dies over the study period, the date of death will be recorded in the eCRF. If a patient reaches the criteria for respiratory insufficiency (tracheostomy or the use of non-invasive ventilation for >20 hours per day for >10 consecutive days), the date this criterion was met will be recorded in the eCRF and the patient will no longer be part of the study.

8.1.3. Lung Function

Lung function is evaluated by using a non-invasive spirometer to determine the Slow Vital Capacity (SVC). During the test, the patient inspires fully and then slowly expires all the air in his/her lungs. The test will be done using a facemask. This procedure is repeated 3 times minimally until a steady recording is obtained; the highest score is recorded. A digital spirometer is used to determine SVC values. The SVC will be assessed at each in-clinic visit. The results of SVC in liters will be recorded in the eCRF by the investigator or designee.

8.1.4. Staging of Disease Progression

The King's staging system is a simple clinical staging system, which defines four stages of ALS. The first three stages are defined by functional involvement of a region: bulbar, upper limbs and lower limbs. The number of regions involved gives the stage. Stage 4 is reached if swallowing (4A) or respiratory (4B) difficulty is severe enough to require intervention. MiToS is a similar clinical staging system, in which the stages are defined as loss of independence on the four domains of the ALSFRS-R: swallowing, walking/self-care, communicating and breathing. The investigator will assess both staging systems for each patient and will record the results in the eCRF.

8.1.5. Health Status

ALSAQ40: The Amyotrophic Lateral Sclerosis Assessment Questionnaire is a patient reported outcome (PRO) designed to determine the patient's health status. The ALSAQ40 is specifically used to measure the subjective well-being of patients with ALS. There are 40 items/questions in the long form, the ALSAQ40, with 5 discrete scales: physical mobility (10 items), activities of daily living and independence (10 items), eating and drinking (3 items), communication (7 items), emotional reactions (10 items). During the study the

questionnaire will be provided in the local language of the patient. The ALSAQ40 questionnaire will be completed by the patient at each study visit via a study App or online questionnaire. In case of technical issues with the ePRO device these questionnaires can be completed on a paper version as a backup.

EQ-5D-5L is a is a patient reported outcome (PRO), simple, valid, standardized health state measure. It consists of five questions that relates to five dimensions of health: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. Each dimension/question can be scored on five levels of severity (1, no; 2, slight; 3, moderate; 4, severe; 5, extreme problems). In addition, responders will be asked to rate their current health related quality of life (HRQoL) on a visual analogue scale (VAS) ranging from 0 (bad) to 100 (very good). During the study the questionnaire will be provided in the local language of the patient. The EQ-5D-5L and VAS will be completed at each study visit via a study App or online questionnaire. In case of technical issues with the ePRO device these questionnaires can be completed on a paper version as a backup.

8.1.6. Cognition

The neuropsychological status of patients will be evaluated using the Edinburgh Cognitive and Behavioral ALS Screen (ECAS). The ECAS is independent of motor disability and evaluates five cognitive domains: language functions, executive functions, letter fluency, memory and visuospatial functioning. The ECAS is designed for ALS patients and answers can be given verbally, or by a combination of writing or pointing. It is suitable for patients who are anarthric or patients who have no hand motor function. The total score is 136 points and should take no longer than 15 minutes to administer. The ECAS will be completed by the investigator or designee at each study visit.

8.2. Safety Parameters

Occurrence of AEs, changes on physical examination (including body weight), vital signs, ECG parameters and laboratory examinations (biochemistry, haematology and urinalysis) will be registered throughout the entire study duration.

All AEs will be actively collected at each visit, from spontaneous declarations of the patient as well as from oral inquiry and clinical examination. All concomitant medications and/or therapies should be documented in the patient file and reported in the electronic Case Report Form (eCRF).

8.2.1. Physical and neurological examination

Physical examinations will be performed by qualified personnel according to the Schedule of Events. Symptom directed physical exams will be performed as applicable. Physical examination includes the following assessments: general appearance, head, eyes, ears/nose/throat, neck, lymph nodes, skin, lungs, heart, abdomen, musculoskeletal, and neurologic evaluations. Breast, rectal, and genitourinary/pelvic exams should be performed when clinically indicated. Weight (kilograms) will be measured as part of all physical examinations. Height (centimeters) will be measured only at the baseline visit. The BMI will be calculated.

Neurological examination will be performed by qualified personnel according to the Schedule of Events to asses possible peripheral nerve dysfunction (= sensory or motor symptoms), diminished or absent reflexes (compared with baseline examination), sensory abnormalities (e.g. numbness or tingling) or weakness. In case a subject experiences clinical signs or symptoms at home, subjects will be asked to contact the clinic. All abnormal findings will be documented in the database.

8.2.2. Laboratory Parameters

The results of all clinical laboratory tests conducted during the study must be assessed by the investigator to assess patients' safety.

Any significant abnormalities is to be documented and followed up as AEs and should be fully investigated. Whenever possible, the etiology of the abnormal findings will be documented in the database. Laboratory results with significantly abnormal values should be investigated as such and checked for verification. Additional tests and other evaluations required to establish the significance or etiology of an abnormal result or to monitor the course of an AE should be obtained when clinically indicated. In particular, if a clinically significant abnormal result is observed that is not resolved by the final study visit, repeat tests will be performed if possible and resolution or stability of the abnormality will be recorded in the source documentation.

Any significant laboratory abnormalities that are either serious or unexpected will be promptly reported to the Sponsor's Medical Monitor. Any additional relevant laboratory results obtained by the investigator during the course of this study will be reported to the Sponsor or its representative.

8.2.3. ECG

Twelve-lead ECGs will be performed according to the Schedule of Events. Subject should be resting supine/semi-supine for at least 5 minutes prior to all ECG measurements if possible.

8.2.4. Vital Signs

Vital signs, including blood pressure, heart rate, respiratory rate, pulse oximetry, and temperature, will be measured at study visits according to the Schedule of Events. Subject should be resting supine/semi-supine for at least 5 minutes prior to vital signs measurements.

9. SAFETY REPORTING

Adverse events will be recorded (using MEDRA version 23.0) beginning immediately after the ICF is signed. The investigator (and/or designee) must document all AEs reported by the subject from the signing of the ICF through completion of the final follow-up. Any subject who is withdrawn from the study due to an AE shall be followed until the outcome of the event is determined, and the investigator will document available follow-up information on the subject's database.

9.1. Definitions

9.1.1. Adverse Event

An AE is any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product. An AE is any symptom, sign, illness, or experience that develops or worsens in severity during the course of the study. Adverse events reported after consent but before the first dose of study drug are still to be documented by the investigator but will be considered non-treatment-emergent AEs.

Intercurrent illnesses or injuries should be regarded as AEs. Abnormal results of laboratory tests or diagnostic procedures are considered to be AEs if the abnormality:

- Is associated with clinical signs or symptoms.
- Is considered by the investigator to be of clinical significance.
- Results in study withdrawal.
- Fulfills any of the criteria for a SAE, as described in this section.
- Requires intervention or further evaluation to determine the etiology of the abnormality and/or assess the risk to the subject.
- Requires treatment.

Changes in ALS symptoms will not be documented as AEs unless they are extraordinary and/or unexpected.

A treatment-emergent adverse event (TEAE) is defined as an adverse event observed after the first dose of study drug. If a subject experiences an event both prior to and after starting study drug administration, the event will be considered a TEAE (of the treatment) only if it has worsened in severity (i.e., it is reported with a new start date) after study drug administration of the specific treatment, and prior to the start of another treatment, if any.

9.1.2. Adverse Reaction

All noxious and unintended responses to a medicinal product related to any dose should be considered an adverse drug reaction. "Responses" to a medicinal product means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility (e.g., the relationship cannot be ruled out).

9.1.3. Unexpected Adverse Reaction

An Unexpected Adverse Reaction is defined as an adverse reaction, the nature or severity of which is not consistent with the applicable product information. For FAB122, the reference safety information is included in the Investigator's Brochure. The reference safety information will be reviewed yearly, and the periodicity of the review will be harmonized with the reporting period of the Development Safety Update Report.

9.2. Severity Assessment

The severity of each AE will be graded by the investigator according to the following criteria:

- Mild: awareness of sign or symptom, but easily tolerated.
- Moderate: discomfort sufficient to cause interference with normal activities.
- Severe: incapacitating, with inability to perform normal activities.

9.3. Serious Adverse Event

A Serious Adverse Event (SAE) is any untoward medical occurrence at any dose that:

- Results in death.
- Is life threatening.
- Requires inpatient hospitalization or prolongation of existing hospitalization.
- Results in persistent or significant disability/incapacity.
- Is a congenital anomaly/birth defect.
- Is a medically important event that may jeopardize the subject or may require medical or surgical intervention to prevent one of the other outcomes listed above.

The term "life threatening" in the definition of "serious" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe. Death is an outcome of an event. The event that resulted in death should be recorded and reported on the SAE form and documented in the eCRF/study database.

Any hospital admission with at least 1 overnight stay will be considered an inpatient hospitalization. An emergency room or urgent care visit without hospital admission will not be recorded as an SAE under this criterion, nor will hospitalization for a procedure scheduled or planned before signing of informed consent, or elective treatment of a preexisting condition that did not worsen from baseline. However, unexpected complications and/or prolongation of hospitalization that occur during elective surgery should be recorded as adverse events and assessed for seriousness. Admission to the hospital for social or situational reasons (i.e., no place to stay, live too far away to come for hospital visits, respite care) will not be considered inpatient hospitalizations.

9.4. Assessment of Causality

The Investigator must determine the relationship between the administration of Investigational product and the occurrence of an AE/SAE as Unrelated, Unlikely related, Possibly related or Probably related as defined below:

Unrelated or Unlikely related:	Means a causal relationship of the adverse event to investigational product administration is **unlikely or remote**, or other medications, therapeutic interventions, or underlying conditions provide a sufficient explanation for the observed event. Event can be readily explained by other factors such as the subject's underlying medical conditions, concomitant therapy, or accident; or there is no temporal relationship between study drug or procedure and the event. A reasonable possibility or clinical evidence that the study drug or procedure caused the event is lacking.
Possibly or Probably related:	Means there is a **reasonable possibility** that the administration of investigational product caused the adverse event. 'Reasonable possibility' means there is evidence to suggest a causal relationship between the investigational product and the adverse event. The AE follows a reasonable temporal sequence from administration of the study drug or procedure and at least one of the following instances of clinical evidence: • Follows a known or suspected response pattern to the study drug or procedure. • Is confirmed by improvement upon stopping the study drug, i.e., after single dose (dechallenge). There is a reasonable possibility that the study drug or procedure caused the event i.e., there is evidence to suggest a causal relationship. In such case, the AE is considered an *adverse reaction* (AR). A *suspected* AR has a lesser degree of certainty about causality than an AR.

Causality should be assessed and provided for every AE/SAE based on currently available information. Causality is to be reassessed and provided as additional information becomes available.

9.5. Reporting Adverse Events

All AEs (regardless of seriousness or relationship to study drug) including those from the time of signing of the ICF through to the follow-up/early withdrawal visit are to be recorded in the subject's source documents and on the corresponding page(s) in the database. Whenever possible, symptoms, signs, and laboratory abnormalities should be grouped as a single syndrome or diagnosis. The investigator should specify the date of onset, severity, action taken with respect to study drug, corrective treatment/therapy given, outcome and

his/her opinion as to whether there is a reasonable possibility that the AE was caused by the study drug, according to the definitions noted above. All medications administered to treat an AE must be recorded in the subject's source documentation and documented in the database.

9.6. Reporting Serious Adverse Events

Reporting of SAEs will be conducted in accordance with the appropriate regulatory guidelines. All SAEs that occur from the time of signing the ICF to the follow-up/early withdrawal visit must be reported, whether or not the event is considered associated with the study drug. SAEs must be reported, via eCRF, within 24 hours of site awareness. For Germany, SAEs must be reported immediately (without undue delay) after site awareness, as per German ordinance (§ 12 (4) GCP-V). Safety reporting information and contact numbers will be provided to the clinical site.

The investigator must complete the SAE Reporting Form in English and submit it via eCRF, with other relevant source documentation, to the medical monitor (clinicalsafety@ferrer.com) and the Sponsor's Pharmacovigilance (PV) representative within 24 hours of awareness of the event to:

Miriam Abril (Head of PV team, Pharmalex)
Tel: +34 976 20 44 00 / Fax: +34 976 20 44 02
Email: clinical.trial@pharmalex.com

The investigator must also provide with urgent priority (upon receipt of a request) other relevant documentation (e.g., copies of diagnostic test results, hospital discharge summary, and/or autopsy report) and send this information to the Sponsor 's medical monitor.

All SAEs and medications administered in association with SAEs must be recorded in the study database. The investigator must also promptly notify the Independent Ethics Committee (IEC) of SAEs, including any follow-up information, in accordance with local institutional policy and applicable regulatory requirements.

The responsible medical monitor at the Sponsor will evaluate causality and expectedness of SAEs and in case of a suspected unexpected serious adverse reaction (SUSAR), such information will be sent to the Sponsor 's PV representative for review.

9.6.1. Adverse Event Follow-up

The investigator should take all appropriate measures to ensure the safety of the subjects, including referral to a specialist if indicated. The investigator should follow up on the outcome of any AE until the return to normal or stabilization of the subject's condition.

In case of an SAE, the subject must be followed up until clinical recovery is complete and laboratory results have returned to normal, or until the condition becomes chronic in nature, stabilizes (in the case of persistent impairment), or the patient dies. This implies that follow-up may continue after the subject discontinues from the study and that additional information may be requested.

Any SAE brought to the attention of the investigator any time after cessation of study drug and considered by him/her to be caused by the study drug with a reasonable possibility, should be reported through the SAE reporting process.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form and submit it by email or fax with other relevant source documentation to the Sponsor's Pharmacovigilance (PV) representative.

9.7. Expedited Reporting

Competent authorities will be notified of any AE associated with the use of the study drug that is both serious and unexpected, in accordance with the appropriate local regulatory guidelines.

The Sponsor's PV representative will report all relevant information about SUSARs that are fatal or life-threatening as soon as possible to the applicable competent authorities in all the countries concerned, and to the Central Ethics Committee concerned (if applicable), in any case no later than 7 days after first knowledge by the Sponsor/designee of such a case, followed by a period of maximum of 8 days to complete the initial preliminary report. All other SUSARs will be reported within a period of maximum 15 days after the Sponsor/designee has first knowledge of the SAE.

The Sponsor/designee will also report any additional expedited safety reports required in accordance with the timelines outlined in country-specific legislation.

The Sponsor/designee will also inform all Investigators as required per local regulation.

Events associated with placebo will usually not satisfy the criteria for a SUSAR and therefore for expedited reporting.

9.8. Pregnancy

According to the recommendations on the CTFG contraception guidance, highly effective contraception measures are required for this study. All females patients who are of reproductive potential will be requested to use (or have their partner use) or practicing adequate birth control methods starting from the time of consent through 30 days after the last dose of study therapy. Longer periods of birth control may be required per local requirements. Acceptable methods of birth control include combined (estrogen and progestogen containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal), progestogen-only hormonal contraception associated with inhibition of ovulation (oral, injectable, implantable), , intrauterine device in place for ≥3 months, intrauterine hormone-releasing system, bilateral tubal occlusion or vasectomised partner.

If a patient becomes pregnant during the study or within the safety follow-up period defined in the protocol, the Investigator is to stop dosing with study drug(s) immediately.

A pregnancy as such is not an AE, however, it must be reported to the Sponsor within 24 hours of knowledge of the event completing a Pregnancy Reporting Form.

Female patients will be instructed to notify the investigator immediately if they become pregnant during the study. Male patients will be instructed to notify the investigator immediately if their partner becomes pregnant. Pregnant patients will be withdrawn from further study treatment. The patients will also be instructed to report pregnancies discovered after the last visit, if they believe that conception occurred during their participation in the study.

The pregnant patient or partner will be followed until the end of the pregnancy. Any complication during the pregnancy should preferably be reported as an AE. The outcome of the pregnancy must be reported on the Pregnancy Reporting Form. Any spontaneous abortion, stillbirth, birth defect/congenital anomaly, death, or other serious infant condition must be reported and followed up as an SAE. If the pregnancy outcome meets seriousness criteria the both the SAE form and pregnancy form should be forwarded.

10. HEALTH ECONOMICS

ALS is a devastating neurological disease for which there is no cure. The disease results in a progressive impairment in activities of daily living, including walking, eating and speaking. As a result, there is a significant negative impact on the quality of life of both patients and their families with associated considerable economic burden.

Expenses associated with the disease can be divided into direct and indirect costs. Direct costs are those expenses requiring payment, whether by the patient, government or a third-party payer (i.e., health insurance and non-profit-organizations), such as those associated with formal health care, medications, equipment, home or vehicle adaptations, medical devices, mobility aids and services. Direct costs can be further divided into healthcare costs and non-healthcare costs. Indirect costs represent opportunity loss, most notably lost income due to a patient's illness related absence from work or the voluntary caregiver duties taken on by family or friends. Both direct and indirect costs can overwhelm the financial resources of patients and their families and should be considered when evaluating the overall economic burden of ALS.

In this study, an exploratory cost-utility analysis for treatment with FAB122 will be conducted using the following data:

- Cost questionnaire: Data provided by a specific questionnaire for the direct and indirect costs associated with the disease (see annex 2). The consented patients will complete the questionnaire at baseline and every 3 months thereafter. up to the end of the study.
- eCRF: Some data will be gathered form the patient's dataset such as hospitalizations, concomitant medications, and occurrence of AEs.

The following cost parameters will be considered for the cost-utility analysis:

1. Number of visits classified per specialist and type of visit (scheduled vs not scheduled).
2. Number of hospitalizations related to ALS classified per unit of stay and length of stay.
3. Medication and administration cost (inpatient vs outpatient).
4. Specialized equipment / Devices cost (i.e. mechanical ventilation-invasive or not, artificial nutrition – percutaneous endoscopic gastrostomy).
5. Number of new orthopaedic devices (i.e. wheelchair).
6. Paramedical treatment visits (i.e. physical therapy, rehabilitation, occupational therapist, speech and language therapist, or otherwise specified by the patient).
7. Formal care (i.e. health professional) and informal care (i.e. familiar/friend).
8. Employment situation.
9. Occurrence of AEs.

An ad-hoc cost questionnaire will be completed at Baseline and every 3 months thereafter.

After the end of the study, analysis of each category will be done, then costs will be calculated by category and for all categories per patient. Costs would be calculated

according to local tariffs and according to guidelines for cost analysis in healthcare research. All costs will be presented in euros.

11. STATISTICS

11.1. Statistical Analysis Plan (SAP)

The statistical analysis will be carried out in accordance with the principles specified in the International Conference on Harmonization (ICH) Topic E9. A detailed Statistical Analysis Plan (SAP) will be made available before the un-blinding of the data base.

11.2. Sample Size Determination

No formal size calculation has been done for the extension study.

The main study plans to include approximately 300 patients. It is anticipated that 200-225 patients might be included in this extension study.

All subjects who completed the full study period in the main ADORE study and providing informed consent to comply with extension trial procedures are eligible to participate in this extension study.

11.3. Description of Statistical Methods

11.3.1. Analysis Populations

Safety Analysis Set: The safety analysis set will consist of all subjects who receive at least 1 dose of IMP in the extension study.

11.3.2. Demographics, baseline characteristics

Demographics and medical history will be retrieved from the main ADORE study.

11.3.3. Subject Disposition

Subject disposition (analysis population allocation, entered, discontinued, along with primary reason for discontinuation) will be summarized using frequency and percent.

11.3.4. Efficacy Analysis

Descriptive statistics (median, and the 25^{th} and 75^{th} percentiles with 95% confidence intervals) and Kaplan-Meier curves will be provided for patients participating in the extension study and patients that consented to only follow their vital status.

The primary aim of the analysis is to evaluate the difference between patients originally randomized to FAB122 versus those originally randomized to placebo using the extended follow-up data from the open-label phase. The difference in overall survival between patients originally randomized to FAB122 versus those originally randomized to placebo will be evaluated using a log-rank test, stratified for randomization factors. The effect of treatment will be expressed as hazard ratio. In case of non-proportional hazards, we will estimate the difference in restricted mean survival time (RMST).

In addition, we will explore the effect of treatment switching in the placebo arm using a rank preserving structural failure time model (RPSFTM) and inverse probability of censoring weights (IPCW). Details of the analyses will be provided in the SAP.

Changes in the in ALSFRS-R score, SVC, ALSAQ-40, EQ-5D-5L, and VAS score over time will be presented descriptively.

11.3.5. Safety Analysis

Safety evaluations will be based on the incidence, severity, and type of AEs and clinically significant changes in the subject's physical examination findings, vital signs, and clinical laboratory results. Safety variables will be tabulated and presented for all subjects in the Safety Population. Data will be summarized by treatment and time. Exposure to study drug and reasons for discontinuation of study drug will be tabulated.

11.3.5.1. Physical Examination

All abnormalities reported by the physical examinations will be listed and tabulated by treatment arm. Weight (kilograms), Height, and BMI (calculated) will be summarized by treatment and time.

11.3.5.2. Adverse Events

All treatment emergent AEs (TEAE) will be coded using the Medical Dictionary for Regulatory Activities (MedDRA version 23.0) coding dictionary. And all preferred terms (PT) will be tabulated by System organ Class (SOC) and additional tabulations will be made by severity and drug relatedness. A separate table (or listing will be created for serious TEAEs (SAE).

11.3.5.3. Concomitant Medication

All concomitant medications will be summarized by medication class or ATC classification.

11.3.5.4. Laboratory Parameters

Clinical laboratory tests (including re-check values if present) will be listed chronologically. 'H' and 'L', denoting values above or below the investigator reference range (when present), will flag out-of-range results. At each time point, absolute values and change from baseline of the hematology and chemistry variables will be summarized by treatment and time with n, mean, SD, SEM, median, Min, and Max values. The categorical data of the urinalysis will be summarized by treatment and time in frequency tables by variable.

11.3.5.5. ECG

From the 12-lead ECG data, HR, PR, RR, QRS, QT, and QTcF will be reported for each time-point and summarized using descriptive statistics. Mean (SD) temporal profiles for 12-lead ECG (QT, QTcF) will be presented graphically. The frequency (number) of clinically significant findings may be reported and summarized.

11.3.5.6. Vital Signs

Vital signs, including blood pressure, pulse rate, respiratory rate, pulse oximetry and temperature will be summarized at each time point, using descriptive statistics and will be presented graphically.

12. DATA MANAGEMENT

12.1. Case Report Form

The investigator or designee will record all data collected in the eCRF provided for that purpose. The site will be suitably trained on the use of the eCRF and appropriate site personnel will be provided electronic signatures.

Completed eCRFs will be submitted according to the instructions of the CRO and reviewed by the CRO to determine their acceptability. If necessary, data correction requests will be generated for resolution by the study site. The investigator or designee will make necessary eCRF corrections.

All site entries will be made in a secured web site and the Principal Investigator (PI) will review the record for completeness. Upon completion of the review, including review of any corrections, the PI will sign electronically in the signature page of the eCRF.

12.2. Source Data

Patient confidentiality is strictly held in trust by the participating investigators, research staff, and the Sponsoring institution and their agents. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to patients. Authorized representatives of the Sponsoring institution, Ethics Committee and Regulatory Authorities may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic or hospital) and pharmacy records for the patients in this study. The clinical study site will permit access to such records. Any data, specimens, forms, reports, and other records that leave the site will be identified only by a patient identification number to maintain confidentiality.

The investigator must maintain adequate and accurate records to enable the conduct of the study to be fully documented and the study data to be subsequently verified. These documents include Investigators' Study Files and original patient clinical source documents generated at the study site. The term "original" means the first recording of the data.

The investigator will ensure the site master files are maintained, including the study protocol and its amendments, IRB/IEC and regulatory approvals with associated correspondence, informed consents, study drug records, staff curriculum vitae, all correspondence, and other appropriate documents.

Patient clinical source documents may include, but are not limited to, patient hospital/clinic records, physicians' and nurses' notes, appointment books, laboratory reports, ECGs, radiographs, pathology and special assessment reports, and consultant letters. The investigator must assure that all original source documents are available to support monitoring activities.

12.3. Data Processing

Julius Clinical will be responsible for data management. A Data Management Plan (DMP) will be prepared in order to define all activities in the data collection, validation and cleaning process. The detailed DMP will be based on the protocol, work scope, contract, analysis plans, data-flows, database, data cleaning procedures, other supporting documents, and data management standards and practices.

Programmed data validations will be run to check for database completeness and consistency, and queries will be generated upon data entry or via review by a Clinical Data Manager after entry. The sites will respond to the data queries in a timely manner.

At the end of the study, database will be locked and an expert Statistician will check the database and extract all data for statistical analyses.

12.4. Central Data Monitoring

Central monitoring of data will be conducted in order to review data for completeness, systemic and/or significant errors, query resolution and protocol deviations, to identify outliers and review for plausibility and completeness, to analyse site characteristics and performance metrics and to identify high-risk sites for targeted on-site monitoring.

13. QUALITY ASSURANCE PROCEDURES

The CRO and the Sponsor has implemented a quality assurance system to ensure that the study is performed and the data are generated, documented (recorded), and reported in compliance with GCP as defined in ICH E6 (R2) guidelines and the applicable regulatory requirement(s).

The Sponsor and the CRO SOPs have been created to ensure that clinical studies are conducted in compliance with regulatory requirements and GCP. Quality control will be applied to each stage of data handling to ensure that data are accurate, reliable and processed correctly.

Authorised representatives of CRO, the Sponsor and/or a Competent Authority and/or the EC may visit the centre to perform audits/inspections, including source data verification.

13.1. Monitoring

The monitor will visit the study site on a regular basis to ensure that the study is conducted and documented in accordance with this protocol, applicable SOPs, ICH GCP guidelines, regulatory requirements and any study specific document.

Monitoring visits will be conducted to confirm, but not limited to, that:

- The investigational team is adhering to this study protocol.
- Informed consent has been obtained for all participants.
- AEs have been collected and reported.
- Data are being accurately recorded in the eCRFs.
- Investigational products have been stored correctly and that drug accountability has been performed.
- Facilities are and remain acceptable.
- The Investigator and the site receive sufficient information and support.

Moreover, during monitoring visits the data recorded in the eCRFs, source documents and other study-related records will be compared against each other in order to ensure accurate data that reflects the actual existence of the patient in the study i.e. source data verification.

When a protocol deviation is detected, the investigator will contact the Sponsor to discuss the measures to be adopted, and if required, the expedited notification to the IEC and CAs.

14. ETHICS AND REGULATORY CONSIDERATIONS

14.1. Approvals

This protocol and any amendments will be submitted to and approved in writing by a properly constituted EC and by the Competent Authorities, in accordance with the International Conference on Harmonization (ICH) guidelines and local legal requirements, for formal approval of the study.

14.2. Ethical Conduct of the Study

The study will be conducted in compliance with the protocol, regulatory requirements, data protection laws, good clinical practice (GCP) and the ethical principles of the Declaration of Helsinki as adopted by the World Medical Assembly, 1964 (and subsequent revisions).

Before the first subject is enrolled in the study, all ethical, regulatory, and legal requirements must be met.

An investigator participating in this study is required to maintain complete and accurate study documentation in compliance with current GCP standards and all applicable local regulations related to the conduct of a clinical study.

14.3. Participant Information and Confidentiality

All subjects will receive written and verbal information regarding the study prior to any study related procedures. This information will emphasise that participation in the study is voluntary and that the subject may withdraw from the study at any time and for any reason. All subjects will be given the opportunity to ask questions about the study and will be given sufficient time to decide whether to participate in the study.

Before any study-related procedures, the informed consent will be signed and dated by the subject (or their legally acceptable representative and/or witness, as applicable) and by the Investigator who gave each subject the verbal and written information.

The patient information leaflet consent includes information that data will be recorded, collected processed and may be transferred (to EU and non-EU countries). In case data will be transferred outside of the EU the sponsor safeguards for an adequate level of protection of the data. The data will not identify any persons taking part in the study, in accordance with the applicable legislation.

A copy of the subject information including the signed consent form must be provided to the subject.

The patient can take any time needed to decide whether to participate in the study. If the patient requires more time to decide, the investigator may schedule a date with the patient to re-discuss.

15. FUNDING AND INSURANCE

Each subject is insured against study-related injuries in accordance with applicable laws and regulations and the ICH E6 (R2) GCP guideline.

According to the ICH Good Clinical Practice guidelines, the Sponsor has contracted an insurance policy which covers the liabilities of the Sponsor/principal investigator, the research staff and the sites where the clinical trial is conducted, in the event of any damage or injury to the health of the patient resulting from this research, conducted strictly in accordance with both the scientific protocol and applicable law and professional standards, during the conduct of the study and for one year following termination of the study treatment, unless otherwise proven.

Ferrer Internacional, S.A. is the Sponsor of the study and is funding the study.

The patient will be reimbursed for travel expenses for visits to the study site and back, as well as drinks and meals for the patient and accompanying person during the respective study visits in the clinic. Reimbursement will be made against receipt or mileage allowance.

16. PUBLICATION POLICY

All publications and presentations must be based upon the clinical study protocol and report.

All information supplied by the Sponsor in connection with this study will remain the sole property of the Sponsor and is to be considered confidential information. No confidential information will be disclosed to others without obtaining prior written consent from the Sponsor and will not be used except in the performance of this study.

The Sponsor will be the owner of all eCRFs, data analysis and reports derived from this study. All the information obtained as a result of the study will be considered confidential until its analysis and review by the Sponsor and Researchers has been completed.

The Sponsor undertakes to make the results of the study public. The Sponsor may choose to publish or present data from this study.

The researchers will agree that the first publication on the results should be a joint publication that includes all the centers participating in the study. However, if a joint manuscript has not been submitted for publication before 12 months after the end of the study in all participating centers, the investigator is free to publish separately, subject to the other requirements listed in this section.

If an Investigator wishes to publish results from this clinical study, written permission to publish must be obtained from the Sponsor in advance. As some of the information regarding the investigational product and development activities at the Sponsor may be of a strictly confidential nature, the Sponsor must first review any publication manuscript prior to their submission to journals, meetings or conferences. The researcher will provide manuscripts, abstracts or the full text of any other planned disclosure (poster presentation, guest speaker reading or guest speaker written presentation, etc.) to the Sponsor at least 30 days before they are submitted for publication or disclosed by another way. If any overt action is required to protect intellectual property rights, the investigator will delay the disclosure for a period not exceeding 60 additional days. The investigator will remove, upon request, any previously undisclosed confidential information (other than the study results itself) prior to disclosure.

If an Investigator is offered first authorship, he/she will be asked to comment and approve the publication. The Sponsor has the right to use the results for registration and internal presentation and for promotion.

For all publications related to the study, the institution will comply with all recognized ethical standards related to the publications and their authorship, including Section II - «Ethical Considerations in the Conduct and Reporting of Research » of the Uniform Requirements for Manuscripts Submitted to Biomedical Journals, http://www.icmje.org/index. html # authorship, established by the International Committee of Medical Journal Editors.

17. ARCHIVING

Clinical Study Documentation including but not limited to all study related correspondence, patient's notes, consent forms, Data Protection Consent Forms, drug accountability documentation, need to be retained by the Investigator at each site for the period of time according to applicable regulatory requirements (25 years, as per CTR: article 58 of the EU- ordinance 536/2014). Clinical Study Documentation is to be retained in a secure place and treated as confidential material.

Clinical Study Documentation has to be retained according to International Conference on Harmonization (ICH) guidelines.

Investigator shall inform the Sponsor about the allocation of the Clinical Study Documentation and in case of having any problem with regard to retention of the Clinical Study Documentation. The Documentation may not be destructed by the Investigator until receipt of the Sponsor's approval in writing.

All data will be stored in a purpose-built data base for the study.

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19. ANNEXES

Annex 1, ALS Functional Rating Scale – revised (ALSFRS-R)

Bulbar function	**Gross Motor Function**
1. Speech 4 Normal speech processes 3 Detectable speech disturbance 2 Intelligible with repeating 1Speech combined with non-vocal communication 0 Loss of useful speech	**7. Turning in bed and adjusting bed clothes** 4 Normal function 3 Somewhat slow and clumsy, but no help needed 2 Can turn alone or adjust sheets, but with great difficulty 1 Can initiate, but not turn or adjust sheets alone 0 Helpless
2. Salivation 4 Normal 3 Slight but definite excess of saliva in mouth; may have night time drooling 2 Moderately excessive saliva; may have minimal drooling 1 Marked excess of saliva with some drooling 0 Marked drooling	**8. Walking** 4 Normal 3 Early ambulation difficulties 2 Walks with assistance 1 Non-ambulatory functional movement only 0 No purposeful leg movement
3. Swallowing 4 Normal eating habits 3 Early eating problems-occasional choking 2 Dietary consistency changes 1 Needs supplemental tube feeding 0 NPO	**9. Climbing stairs** 4 Normal 3 Slow 2 Mild unsteadiness or fatigue 1 Needs assistance 0 Cannot do
Fine Motor Function	**Respiratory Function**
4. Handwriting 4 Normal 3 Slow or sloppy; all words are legible 2 Not all words are legible 1 No words are legible, but can still grip a pen 0 Unable to grip pen	**10. Dyspnea** 4 None 3 Occurs when walking 2 Occurs with one or more of the following: eating, bathing, dressing 1 Occurs at rest:difficulty breathing when either sitting or lying 0 Significant difficulty, considering using mechanical respiratory support
5a. Cutting Food and handling utensils (without gastrostomy) 4 Normal 3 Somewhat slow and clumsy, but no help needed 2 Can cut most foods (>50%), although slow and clumsy; some help needed 1 Food must be cut by someone, but can still feed slowly 0 Needs to be fed	**11. Orthopnea** 4 None 3 Some difficulty sleeping at night due to shortness of breath, does not routinely use more than two pillows 2 Needs extra pillow in order to sleep (more than two) 1 Can only sleep sitting up 0 Unable to sleep without mechanical assistance
5b. Cutting Food and handling utensils (with gastrostomy) 4 Normal 3 Clumsy but able to perform all manipulations independently 2 Some help needed with closures and fasteners	**12. Respiratory insufficiency** 4 None 3 Intermittent use of BiPAP 2 Continuous use of BiPAP 1 Continuous use of BiPAP during day and night

1 Provides minimal assistance to caregiver 0 Unable to perform any aspect of task	0 Invasive mechanical ventilation by intubation or tracheostomy
6. Dressing and hygiene 4 Normal function 3 Independent; can complete self-care with effort or decreased efficiency 2 Intermittent assistance or substitute methods 1 Needs attendant for self-care 0 Total dependence	

Annex 2: Cost Questionnaire

Disclaimer (original English version): The following cost questionnaire is the original version which was included in the clinical trial protocol for FAB-122. The sections included in the questionnaire are the following:

- Clinical visits & hospitalisations
- Paramedical treatment visits
- Specialized equipment & devices
- Formal care
- Informal care

Disclaimer (translated versions from English): The following cost questionnaire is a straightforward translation of the original English version. The authors want to note that the translational process did not use forward and backward translation techniques as this was not the main goal of the protocol and beyond the scope of the study. The English version should therefore be taken as a useful starting point for a more in-depth adaptation. This should also take then into count the peculiarities of the service provision in the country in which the questionnaire is to be used.

Presentation

We would like to find out what extra money you and your family had to spend due to your disease. Your answers are important because they will give professionals who make decisions about patient treatment within the National Health Service an idea of how much it costs you to use health services.
We hope you will be able to find the time to complete this questionnaire. It would be very helpful if you could reply at the visit every 3 months. If you have difficulty with answering any of the questions, please give the best answer you can.
The information that you provide will be completely confidential. Your answers will be combined with the answers of other patients involved in the study and reported in such a way that it will not identify you or influence your pattern of treatment.

If you would like any further information about this study, please contact (name) at (location) on (telephone number). (**Investigator`s contact details**)

Instructions for filling out the cost diary

Please fill out this diary before visits every 3 months.

While filling out, please keep in mind that for this study, only expenditures and benefits related to your disease (ALS, motor neurone disease) are of importance. Should you, for example, have visited a doctor due influenza and would have been prescribed medication, please do not enter this into the cost book.

Please go over the following pages step-by-step, unhurriedly. Even if our cost diary may seem bulky to you on a first glance, you will not need much time for answering the questions. It is very unlikely, that you will be able to answer all questions.

Please, answer each question. If "No" applies, you may directly move on to the next question. If "Yes" applies, please also fill out the associated table.

There you may put several statements one below the other, e.g. if you took several types of drugs.

Sometimes you will be asked for multiple statements about an issue. For example, if you accepted help from relatives, please enter the accrued time. Should there have also been expenses, please enter that into the table as well.

Example:

Help (Kind of help)	Overall expenditure of time and costs per week
Help from relatives, friends or acquaintances	Hours: 4
	€: 20

In this way, please go through every question, one after the other. Keep in mind, that sometimes instead of number of contacts or costs, you will be asked for different statements.

You will find several answers to questions which may arise while filling out the cost diary.

Once you complete the diary, data will be sent to the study database for further analysis.

We assure you, that we will handle your data confidentially.

Please note:

• Please only make statements which are related to your disease (ALS, motor neurone disease).

• Please answer every question. If you are not sure or cannot remember the exact details, please give the best answer you can. If you have a problem in answering any question, please write that problem beside the question.

• Please note that the following questions apply to the period of the last 3 months.

12 weeks ago	8 weeks ago	Last 4 weeks
Day 1.	Day 1.	Day 1.

Day 2.	Day 2.	Day 2.
Day 3.	Day 3.	Day 3.
…	…	…
Day 29.	Day 29.	Day 29.
Day 30.	Day 30.	Day 30.
Day 31.	Day 31.	Day 31.

Your participation by periodically responding to this Questionnaire will be of invaluable help to better understand the reality of patients affected by ALS and thus help making better decisions regarding your treatment and care.

We deeply appreciate your collaboration and support.

Sincerely,
ADOREXT Trial Group

Quarterly questionnaire (From ____.____.____ to ____.____.____) (DD-MM-YYYY)

CLINICAL VISITS & HOSPITALISATIONS		
1. During the last 3 months, due to your disease, have you had to see a doctor (e.g. general practitioner, neurologist, etc)? (also telephone calls, apart from the ones for the clinical study) or to make an appointment for a home visit?	Yes…… 1 No…… 2 If you have checked "Yes" please complete the subsequent table A. If you have checked "No" please move on to question number 2.	

Table A. If "Yes", which type of treatments did you receive? (e.g. lab test, filled prescription)

GP and specialist visits (specialization)	Number of contacts during the last 3 months	What was done?	How often?
General practitioner	_____	□ Blood test □ Prescription filled □ Telephone call □ Computer tomography □ Magnetic resonance imaging □ _____	_____ _____ _____ _____
Nurse	_____	□ Blood test □ Prescription filled □ Telephone call □ Computer tomography □ Magnetic resonance imaging □ _____	_____ _____ _____ _____
Neurologist	_____	□ Blood test □ Prescription filled □ Telephone call □ Computer tomography □ Magnetic resonance imaging □ _____	_____ _____ _____ _____
Psychologist	_____	□ Counselling □ Prescription filled □ Telephone call □ Computer	_____ _____ _____ _____

		tomography □ Magnetic resonance imaging □ _____	
Ambulatory care in hospital	_____	□ Blood test □ Prescription filled □ Telephone call □ Computer tomography □ Magnetic resonance imaging □ _____	_____ _____ _____ _____
Emergency department	_____	□ Blood test □ Prescription filled □ Telephone call □ Computer tomography □ Magnetic resonance imaging □ _____	_____ _____ _____ _____
Other (please specify) _____	_____	□ Blood test □ Prescription filled □ Telephone call □ Computer tomography □ Magnetic resonance imaging □ _____	_____ _____ _____ _____
Other (please specify) _____	_____	□ Blood test □ Prescription filled □ Telephone call □ Computer tomography □ Magnetic resonance imaging □ _____	_____ _____ _____ _____

2. During the last 3 months, due to your disease, were you in hospital or a rehabilitation clinic?	Yes…… No…… If you have checked "Yes" please complete the subsequent table B. If you have checked "No" please move on to question	1 2

	number 3.	

Table B. Please enter the number of activities.

Hospital/ Rehabilitation spells	Date from – until (DD-MM-YY)	Date from – until (DD-MM-YY)	Date from – until (DD-MM-YY)
Hospital spells	From ___.___.___ Until ___.___.___	From ___.___.___ Until ___.___.___	From ___.___.___ Until ___.___.___
Centre (& Town)			
Reason for admittance	□ Surgery □ Other _____ _	□ Surgery □ Other _____ _	□ Surgery □ Other _____ _
Unit of hospital stay (e.g. neurology, intensive care unit)			
Procedure (e.g. percutaneous endoscopic gastrostomy)			
Rehabilitation stays	From ___.___.___ Until ___.___.___	From ___.___.___ Until ___.___.___	From ___.___.___ Until ___.___.___

PARAMEDICAL TREATMENT VISITS

3. During the last 3 months, due to your disease, have you regularly been active for prevention or relief of your disease, e.g. by going to rehabilitation groups, alternative practitioner or going to physical therapy? If so, which type of treatments did you make use of? (e.g. exercise therapy).	Yes…… …… No…… …… If you have checked "Yes" please complete the subsequent table C. If you have checked "No" please move on to question number 4.	1 2

Table C. Please enter the number of activities.

Activities	Treatments (please give a short description)	Number of treatments	Cost of all visits (in €)
Physical therapy	1. _____ 2. _____	_____	_____
Rehabilitation	1.		

Occupational therapist	2. _____		
Speech and language therapist	1. _____ 2. _____	_____	_____
Gym	1. _____ 2. _____	_____	_____
Alternative practitioner	1. _____ 2. _____	_____	_____
Social worker	1. _____ 2. _____	_____	_____
Homeopath/ Naturopath	1. _____ 2. _____	_____	_____
Acupuncturist	1. _____ 2. _____	_____	_____
Other (please specify) _____	1. _____ 2. _____	_____	_____

4. During the last 3 months, did you attend events/courses, which were directly related to your disease or your emotional situation e.g., information evenings, adult evening classes or similar?	Yes…… …… No…….…… …… If you have checked "Yes" please complete the subsequent table D. If you have checked "No" please move on to question number 5.	1 2

Table D. Please enter the number of activities.

Event/Course	Cost/period (DD-MM-YY)
	_____ € From ___.___.___ Until ___.___.___
	_____ €

	From ___.___.___ Until ___.___.___
	_____ € From ___.___.___ Until ___.___.___
	_____ € From ___.___.___ Until ___.___.___

SPECIALIZED EQUIPMENT & DEVICES

5. During the last 3 months, did you, e.g. in connection with your disease buy yourself medical aids, e.g. wheelchair? Did you even have done modification measures (e.g. build in a stairlift)? Or did you have further expenditures?	Yes…… …… No…… …… If you have checked "Yes" please complete the subsequent table E. If you have checked "No" please move on to question number 6.	1 2

Table E. Please enter the names and description.
If you used any equipment but did not pay for it please specify who arranged this for you (e.g. hospital, social services, voluntary sector etc.) at the column "Provided by".
If you had any adaptations done to your home but did not pay for it please specify who provided this for you at the column "Provided by".

Medical Aids (examples)	Dida you have to pay anything?	Provided by	Costs in €
□ Wheelchair	□ Yes □ No □ N/A	_____	_____
□ Special bedding	□ Yes □ No □ N/A	_____	_____
□ Special mattresses	□ Yes □ No □ N/A	_____	_____
□ Dehumidifier	□ Yes □ No □ N/A	_____	_____
□ Medical lift	□ Yes □ No □ N/A	_____	_____
□ Other	□ Yes □ No □ N/A	_____	_____
_____	□ Yes □ No □ N/A	_____	_____
□ Other _____	□ Yes □ No □ N/A	_____	_____
□ Books	□ Yes □ No □ N/A	_____	_____
□ Videos	□ Yes □ No □ N/A	_____	_____
□ Other _____	□ Yes □ No □ N/A	_____	_____

□ Private medical care	□ Yes □ No □ N/A	N/A	_____
□ Stairlift □ Ramp □ Changes to the bathroom/shower □ Car modifications □ Other home modifications _____ _ □ Other car modifications _____ _ □ Other modifications _____ _ □ Change residence (own) □ Change residence (new house) □ Change residence (relative's house)	□ Yes □ No □ N/A □ Yes □ No □ N/A □ Yes □ No □ N/A □ Yes □ No □ N/A □ Yes □ No □ N/A □ Yes □ No □ N/A □ Yes □ No □ N/A □ Yes □ No □ N/A □ Yes □ No □ N/A □ Yes □ No □ N/A	_____ _____ _____ _____ _____ _____ _____ N/A N/A N/A	_____ _____ _____ _____ _____ _____ _____ N/A N/A _____ N/A

6. In the following table you may enter all expenses, which you had due to your disease, which have not been accounted for so far.

Further expenses, which have not been accounted for so far (name)	Costs in €
_____ _	_____ _
_____ _	_____ _
_____ _	_____ _
_____ _	_____ _

FORMAL CARE

7. During the last 3 months, due to your disease, did you have to hire professional services for homecare?	Yes…… …… No……..…… …… If you have checked "Yes" please complete the subsequent table F. If you have	1 2

	checked “No” please move on to question number 8.	

Table F. Please enter the names and description.

Kind of service	Number of days per week	Number of hours per day	Wage per hour
Day homecare			
Night homecare			
Full time homecare			
Housekeeping			

INFORMAL CARE

8. During the last 3 months, due to your disease, did you have to accept help from relatives, friends or from professional services for work, which you usually carry out by yourself? For example; for housekeeping or for shopping.	Yes…… 1 No…… 2 If you have checked “Yes” please complete the subsequent table G. If you have checked “No” please move on to question number 9.	

Table G. Please insert here the average time in hours of help and the average cost of help per week. In case you do not know the cost please insert a question mark.

Kind of help	Average duration per week	Average cost per week
Help from relatives, friends or acquaintances	_____ h	_____ €
Home help	_____ h	_____ €
Professional aids (e.g. Red cross)	_____ h	_____ €
	_____ h	_____ €
	_____ h	_____ €
	_____ h	_____ €

EMPLOYMENT SITUATION

9. Are you currently employed?	Yes…… 1 No…… 2	

	If you have checked "Yes" please move on to question number 10. If you have checked "No" please move on to question number 13.	
10. If you returned to work in the last 3 months, is it the same employment that you had before your illness?	Yes…… No……	1 2
11. During the last 3 months, have you been on sick leave due to your disease (at home or in hospital)?	Yes…… No…… If you have checked "Yes" please complete the subsequent table H. If you have checked "No" please move to question number 12.	1 2

Table H. Please complete the information.

Time you were on sick leave	Date from – until (DD-MM-YY)	Date from – until (DD-MM-YY)	Date from – until (DD-MM-YY)
Medically certified absence from work	From ___.___.___ Until ___.___.___	From ___.___.___ Until ___.___.___	From ___.___.___ Until ___.___.___
Reduced hours of work for gradual reintegration	From ___.___.___ Until ___.___.___	From ___.___.___ Until ___.___.___	From ___.___.___ Until ___.___.___

12. During the last 3 months, have you seen a doctor or therapist during your working hours?	Yes…… No…… If you have checked "Yes" please complete the subsequent table I. If you have checked "No" please move on to question number 14.	1 2

Table I. Please complete the information.

Number of working hours, which	Overall loss of working time

you spent to see a doctor or therapist	
General practitioner	_____ h
Nurse	_____ h
Neurologist	_____ h
Psychologist	_____ h
Ambulatory care in hospital	_____ h
Emergency department	_____ h
Other (please specify) _____	_____ h
Other (please specify) _____	_____ h

13. Which category describes best your status?	Retired…… Retired on medical grounds…… Unemployed…… Student……	1 2 3 4
14. During last 3 months have you suffered from income loss due to your illness?	Yes…… No……	1 2
15. Do you have any health-related insurance policy/plan?	Yes…… No…… If you have checked "Yes" please complete question 16. If you have checked "No" you have finished the questionnaire.	1 2
16. Is your health-related insurance policy/plan public or private?	Public…… Private……	1 2
17. Please tell us what it covers by ticking one or more of the	Health care costs (i.e.	1

following options:	medical, visits) Medication Income protection Any other (please specify) _____ _____	 2 3 4

Frequently asked questions

I have had the flu and have therefore visited my doctor, who certified me unfit for work. Do I have to enter the drugs, the doctor visit, the time of sick leave and the time in which I was not able to carry out my housework?

No, please only enter things, which are directly related to your disease. We do not want to include all treatments and expenses, you had due to other diseases.

I cannot remember the exact information on the package of my drug. What should I enter?

Please try to answer as exactly as possible. If you do not have the package of the drug for copying the name from it anymore, please enter the type of drug, e.g. beta blocker.

I have not received the bill for my alternative practitioner visit yet. What should I do now?

Please enter a question mark. Unless, from experience, you are quite sure how much the bill will be. In that case, please enter your estimate.

Due to my ALS disease, I have had expenses, which I do not know where to put, because none of the tables seems to really apply to them. Where should I enter these expenses?

Please enter all expenses, treatments and applications which you cannot clearly assign to any question, into the questionnaire. Please do not leave out anything that is related to your disease.