CLINICAL STUDY PROTOCOL

Title

A multicenter, randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of FAB122 in patients with Amyotrophic Lateral Sclerosis

ADORE (ALS Daily ORal Edaravone) study

THE SPONSOR STUDY CODE: FAB 122-CT-2001

EudraCT NUMBER: **2020-003376-40**

Sponsor:	Ferrer Internacional, S.A. Barcelona, Spain
Study Drug Name:	FAB122
Development Phase:	PHASE III
Date of Protocol:	24/05/2023

DOCUMENT VERSION HISTORY

Date	Version	Reason for Revision
12/05/2021	1.0	Initial
18/10/2021	2.0	Correction of typos and inconsistencies. Inclusion of requirements received from RAs and ECs and incorporated in country specific versions: 1.1 BEL, 1.1 FRA, 1.2 FRA, 1.1 GBR, 1.1 IRL
30/08/2022	3.0	Update of study endpoints and statistical analysis section. Administrative updates.
24/05/2023	4.0	Non-Substantial Amendment Sub group analysis wording in statistical section (no change in primary or secondary endpoints), clarification if patients can not attend study visits or key safety assessments, clarification on IMP delivery. Minor administrative updates

PROTOCOL APPROVAL SIGNATURES

Sponsor Signatures

Declaration of Sponsor

Study title: A multicenter, randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of FAB122 in patients with Amyotrophic Lateral Sclerosis

Version number: 4.0

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

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Version number: 4.0

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
AESI	Adverse Event of Special Interest
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
CSF	Cerebrospinal Fluid
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
fALS	familial Amyotrophic Lateral Sclerosis
FDA	Food and Drug Administration
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
IE	Intercurrent Event
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
$P75^{ECD}$	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 Modeling
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
WBC	White blood cell
WFN	World Federation of Neurology
WHO	World Health Organisation

1. SYNOPSIS

TITLE:	A multicenter, randomized, double-blind, placebo-controlled study to investigate the efficacy and safety of FAB122 in patients with Amyotrophic Lateral Sclerosis
THE SPONSOR STUDY CODE:	FAB122-CT-2001
EudraCT NUMBER:	2020-003376-40
SPONSOR:	Ferrer Internacional, S.A. Barcelona, Spain
STUDY PHASE:	PHASE III
STUDY DESIGN:	Multicenter, multinational, double-blind, randomized (2:1), placebo-controlled Phase III study to investigate the efficacy and safety of 100 mg FAB122 (former TW001) once daily as oral formulation in ALS patients. Subjects will be screened to assess whether they comply with all enrolment criteria. Approximately 300 patients will be randomized to 100 mg FAB122 or matched placebo in a 2:1 ratio. Patients will be stratified by; 1)their ALS progression rate at the start of the study (the slope ALSFRS-R score from time of first symptoms till Screening <1.0 vs. ≥1.0), 2)additional co-medication for ALS (a. riluzole, b. no riluzole). Riluzole (100 mg/day or less) may be used as background (add-on) therapy. Patients on riluzole should be on stable doses at the start of the trial and for at least 30 days before the initiation of the study drug. It will not be allowed to initiate riluzole therapy during the trial. Additional supportive Standard Of Care (SOC) treatments will be allowed in all patients and will be standardized as much as possible. Subjects will receive double-blind treatment up to a maximum of 72 weeks. The study is planned to continue until the last randomized subject has reached 48 weeks of follow-up (or has reached an intercurrent event) AND the first one third of the subjects randomized (100) have reached 72 weeks of follow up (or has reached an intercurrent event). Subjects who discontinue treatment before week 72 will be followed as much as possible according to the planned visit schedule. Subjects will visit the clinic at Screening, Baseline, Week 4, Week 12, and every 12 weeks thereafter. Monthly telephone visits are performed in between the visits to the clinic until Week 48. Blood sampling for FAB122 plasma concentrations will be done in ~90 subjects treated with the study drug. After a subject completed the study (max at 72 weeks), he/she will be offered

	the possibility to roll over in an open label extension trial in which all subjects will be offered to receive FAB122.
STUDY PARTICIPANTS:	
Study Population	ALS patients
Inclusion Criteria	In order to be eligible for participation in this trial, a subject must meet all of the following criteria: 1. Age 18 – 80 years (both inclusive), male or female; 2. Diagnosis of definite, probable, probable laboratory supported or possible ALS as based on the El Escorial and the revised Airlie House diagnostic criteria for ALS; 3. Onset of first symptoms* no longer than 24 months prior to randomization; *Date of onset is the date the patient reported one or more of the following symptoms: ▪ Muscle weakness in limbs ▪ Speech/swallowing difficulties ▪ Respiratory symptoms: dyspnea was noticed 4. SVC equal to or more than 70% of the predicted normal value for gender, height and age at screening visit; 5. Change in ALSFRS-R score between 0.35 points and 1.5 points per month (both inclusive) in the period from onset of first symptoms to the Screening visit; 6. Patients on riluzole should be on stable doses ≥30 days prior to the baseline visit and this dose should be maintained during the entire trial. 7. A female subject should not be able to become pregnant 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 screening and at baseline and is non-lactating. A female subject who is of reproductive potential agrees 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. 8. A male patient must: • agree he will not donate sperm during the study and until 104 days after the last dose, AND • use a condom during sexual intercourse with pregnant or non-pregnant women of childbearing potential (WOCBP) partner even if he is vasectomized • 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 partners; 9. Capable of providing informed consent and complying with trial procedures.
Exclusion Criteria	A subject must not meet one or more of the following criteria: 1. Diagnosis of Primary Lateral Sclerosis; 2. Diagnosis of Frontotemporal Dementia; 3. Diagnosis of other neurodegenerative diseases (e.g. Parkinson disease, Alzheimer disease); 4. Diagnosis of polyneuropathy; 5. Other causes of neuromuscular weakness; 6. Have a significant pulmonary disorder not attributed to ALS and/or require treatment interfering with the evaluation of ALS on respiratory function; 7. Use of intravenous (IV) edaravone within 6 months of the screening visit; 8. Use of mechanical ventilation (invasive or non-invasive) at Screening; 9. Renal impairment as indicated by a creatinine clearance of less than 50 mL/min; 10. Subject has a history of clinically significant hepatic disease, hepatitis or biliary tract disease, ALT/AST levels ≥ 3xULN, bilirubin levels ≥2xULN or subject has a positive screening test for HIV, hepatitis B or C; 11. Presence of any of the following clinical conditions: a. Unstable cardiac, pulmonary, endocrine, hematologic or active infectious disease b. Severe active psychiatric illness e.g. psychosis, untreated major depression within 90 days of the screening visitSignificant cognitive impairment,

	clinical dementia or psychiatric illness c. Cancer that is currently under active treatment or is likely to require treatment during the trial that may alter the subject´s function and interfere with assessment of ALS disease progression. 12. Any comorbidity that may interfere with the functions as scored with the ALSFRS-R; 13. History of known sensitivity or intolerability to edaravone, to any related compound, or to any of the excipients; 14. Exposure to any investigational drug within 30 days of the screening visit or 5 half-lives, whichever is longer; 15. Current substance or alcohol dependence. 16. For patients undergoing optional CSF sampling: any condition that according to the investigator criteria is contraindicated for the procedure (e.g. space-occupying lesion with mass effect, increase of intracranial pressure due to increased CSF pressure; posterior fossa mass; Arnold-Chiari malformation; anticoagulant medication; coagulopathy; uncorrected bleeding diathesis; congenital spine abnormality; and skin infection at puncture site
SAMPLE SIZE:	Total of 300 ALS patients, randomized 2:1 to FAB122 100 mg and placebo, respectively
PLANNED STUDY PERIOD:	2 Years Double-blind treatment is planned to continue until the last randomized subject has reached 48 weeks of follow-up (or has reached an intercurrent event (IE)) AND the first one third of the subjects randomized (100) have reached 72 weeks of follow-up (or has reached an intercurrent event). The maximum treatment duration for a subject in this study is 72 weeks.
PLANNED RECRUITMENT PERIOD:	10 Months
STUDY SITES	Approximately 30 sites
OBJECTIVES AND OUTCOME MEASURES:	
PRIMARY OBJECTIVE:	To assess the effect of treatment with 100 mg of FAB122 on disease progression in patients with ALS
SECONDARY OBJECTIVES:	1. To evaluate the effect of treatment with FAB122 on survival 2. To evaluate the safety and tolerability of FAB122 3. To evaluate the effect of treatment with FAB122 on quality of life (QoL) 4. To evaluate the effect of treatment with FAB122 on cognitive functioning 5. To evaluate the pharmacokinetics (PK) of FAB122

EXPLORATORY OBJECTIVES	1. To evaluate the PK interaction of FAB122 and riluzole 2. To explore and identify biomarkers that inform the scientific understanding of ALS and/or their therapeutic treatments
PRIMARY ENDPOINT:	Change from baseline in Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS-R) score after 48 weeks
SECONDARY ENDPOINTS:	*Key secondary endpoints* 1. Combined assessment of function and survival (CAFS) at 48 and 72* weeks; 2. Survival time, i.e. time to death, tracheostomy or initiation of non-invasive ventilation for more than 20 hours a day for more than 10 consecutive days, over 72 weeks. *Efficacy* 1. Change from baseline in ALSFRS-R score after 24 and 72* weeks; 2. The slope of the decrease in ALSFRS-R score over time at 24, 48 and 72* weeks; 3. Change from baseline in ALSFRS-R score on Bulbar function (question 1-3 of the ALSFRS-R) after 24, 48 and 72* weeks; 4. Change from baseline in ALSFRS-R score on Fine motor function (question 4-6 of the ALSFRS-R) after 24, 48 and 72* weeks; 5. Change from baseline in ALSFRS-R score on Gross motor function (question 7-9 of the ALSFRS-R) after 24, 48 and 72* weeks; 6. Change from baseline in ALSFRS-R score on Respiratory function (question 10-12 of the ALSFRS-R) after 24, 48 and 72* weeks; 7. Time to a 3, 6, 9 and 12 points change or death from baseline in ALSFRS-R score, over 72* weeks; 8. Proportion of subjects with change from baseline in ALSFRS-R score at 24, 48 and 72* weeks in categories: categories will include change ≥0, change between <0 and ≥-1, change between <-1 and ≥-2 etc.; 9. Time to change in clinical staging or death (King's staging system and MiToS) over 72* weeks; 10. Overall survival: Proportion of subjects alive (survival rate) after 24, 48 and 72* weeks; 11. Proportion of subjects alive and no tracheostomy, or no initiation of non-invasive ventilation for more than 20 hours a day for more than 10 consecutive days after 24, 48 and 72* weeks; 12. Change from baseline in slow vital capacity (SVC, liters) at 24, 48 and 72* weeks; 13. Change from baseline in the overall mega score for the hand-held dynamometer (HHD) at 24, 48 and 72 weeks. *QoL* 1. Change from baseline in the total score on the ALS Assessment Questionnaire-40-Item (ALSAQ-40) Form at 24, 48 and 72* weeks;

	2. Change from baseline in EuroQoL – 5 Dimensions-5 Levels (EQ-5D-5L) questionnaire score and health related QoL at 24, 48 and 72* weeks. 3. Change from baseline in Visual Analogue Scale (VAS) score at 24, 48 and 72* weeks. *Cognition* 1. Proportion of subjects with a change of ≥8, ≥4, and ≥9 for ALS Specific, ALS Non-Specific, and ECAS (Edinburgh Cognitive and behavioural ALS Screen) total score; 2. Change from baseline for ALS Specific, ALS Non-Specific, and ECAS total score at 24, 48 and 72* weeks; 3. Time to a mean change of ≥8, ≥4, and ≥9 for ALS Specific, ALS Non-Specific, and ECAS total score. *Pharmacokinetics* (Population) PK parameters of FAB122 and riluzole *All secondary endpoints at 72 weeks will be analyzed for the subgroup of patients that reach 72 weeks (or IE).
EXPLORATORY ENDPOINTS:	*Pharmacokinetics* PK interaction between FAB122 and riluzole *Biomarkers* 1. Change from baseline in the prognostic ALS biomarker neurofilament light (NFL) 2. Change from baseline in the ALS biomarkers creatinine and creatinine kinase 3. Change from baseline in the ALS biomarker Urinary extracellular domain of neurotrophin receptor p75 (Urinary $P75^{ECD}$) 4. Change from baseline of oxidative stress biomarker 8-hydroxyguanosine (8-OHdG) *Health economics* Cost-Utility analysis of treatment with FAB122
SAFETY ENDPOINTS	1. Nature, frequency and severity of Treatment Emergent Adverse Events; 2. Parameters derived from in vital signs and 12-lead electrocardiogram (ECG); 3. Parameters derived from laboratory tests (hematology, biochemistry, urinalysis); 4. 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, or matched placebo in a 2:1 ratio, respectively.
nIMP(S):	**Riluzole:** The use of riluzole is allowed as add-on therapy on top of other supportive SOC treatments (such as symptomatic treatment of muscle spasms, pain, insomnia, dysphagia and emotional instability) during the study. Subjects taking riluzole must be on stable dosage ≥30 days prior to the baseline visit. The riluzole dose must not exceed the recommended dose of 100 mg/day. Riluzole will not be provided for the participating sites.
COMPARATOR:	Placebo
STATISTICAL METHODS:	The sample size estimation is based on the primary endpoint: the change from baseline in ALSFRS-R score after 48 weeks of follow up. A difference of 3.0 points between FAB122 treatment arm and placebo is assumed with a (pooled) standard deviation of 7.5 and an allocation ratio of 2:1 (FAB122: Placebo). With these assumptions, a total sample size of 300 (200 patients on FAB122 and 100 on placebo) is needed to achieve 90% power to detect the difference of 3.0 points between the two treatment groups at a 5% (2-sided) level of significance. The primary analysis will be performed on the modified intent-to-treat population (mITTs), i.e. all randomized patients who had at least one treatment intake. The analysis of the primary endpoint will be also assessed with the PP and ITT populations as per sensitivity analysis.

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).
ALS is a rare disease with a relatively uniform estimated incidence and prevalence in Western countries of 1,89 per 100.000/year and 5,2 per 100.000, respectively (Wijesekera and Nigel Leigh, 2009; Worms, 2001). 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, over 20 genes have been identified, although the exact mechanism of the cause and the progression of ALS is unknown (Diamanti et al., 2013; Rossi et al., 2013).

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 behavorial 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)(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 2).

Pharmacological and non-pharmacological treatment options

There are limited pharmacological options in the treatment of ALS (an overview is provided in Annex 3); 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, anti-convulsants (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. 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. 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

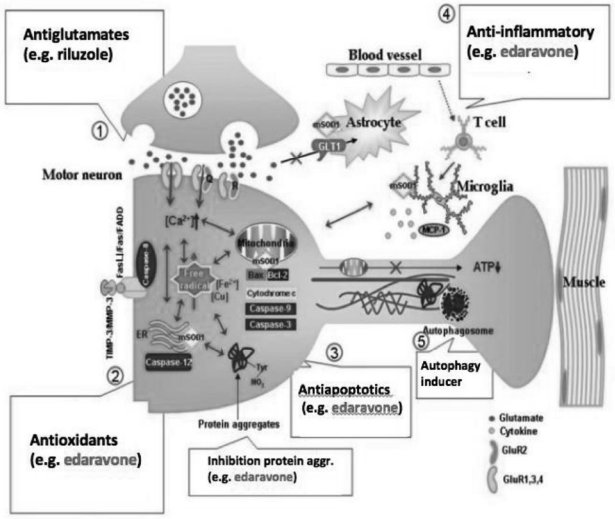
part of the underlying multifactorial pathogenic mechanisms of ALS (Franco et al., 2013; Rossi et al., 2013; Zoccolella, 2009).

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 more recently 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). Based on the initial results achieved with the intravenous edaravone formulation in ALS patients, Treeway started its own clinical development program in support of the orphan indication "treatment of ALS" with a newly developed oral edaravone formulation.

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: Posible 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

This is a multicenter, multinational, double-blind, randomized, placebo-controlled Phase III study to investigate the efficacy and safety of 100 mg FAB122 once daily as oral formulation in ALS patients.
Results from previous Phase II (Yoshino and Kimura, 2006) and III clinical trials (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 18 Study Group., 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) in ALS patients with IV administered edaravone showed the potential of edaravone for the treatment of ALS. The data from these trials led to the approval of IV administered edaravone (Radicut™ or Radicava™) for the inhibition of ALS disease progression in Japan, the USA, Canada and Switzerland. In these studies, edaravone was administered in repeated cycles of 28 days consisting of daily IV infusions of 60 mg edaravone for 60 minutes for 10 out of 14 days followed by 14 days without IV infusions of edaravone. Chronic IV administration has important drawbacks including the risk of both local and systemic side effects. Also, the involvement of medical personnel at home or daily attendance to the hospital for drug administration impedes compliance. In addition, no exposure to the drug is obtained during the treatment holidays of 14 days per month. These drawbacks could be overcome using administration of the oral FAB122 formulation as proposed in this trial and given the exposure-based efficacy of edaravone, a more sustained exposure profile may further increase the efficacy of edaravone in ALS. This may be achieved by once daily dosing of orally administered FAB122 (elimination half-life of FAB122 ~ 5 h) without drug holidays.

Rationale for dose

In a Phase III pivotal trial, a statistically significant reduction in ALSFRS-R decline was shown after 24 weeks of treatment with 60 mg edaravone administered as a 60-minute drip infusion as compared to placebo (The Writing Group on behalf of the Edaravone (MCI-186) ALS 19 Study Group. 2017 c, 2017). Therefore, the exposure and plasma levels associated with a 60 mg IV infusion of edaravone are correlated with efficacy in ALS patients. In three phase I studies, in both healthy volunteers and ALS patients, the exposure and plasma levels of oral intake FAB122 at different dose regimens were studied (Treeway, 2019, 2017a, 2017b). In addition, the bioavailability of oral intake of FAB122 was compared to 60 mg edaravone administered as a 60-minute drip infusion (Treeway, 2019), (Treeway, 2019). Recently, Ferrer has conducted two Phase I studies to confirm the selected dose for the current trial. The first study was a single center, randomized, double-blind, placebo-controlled study investigating the safety, tolerability, and pharmacokinetics of single ascending doses of 50, 100 and 200 mg FAB122 in healthy volunteers (Study EDV-PBA-01-FRI/20). The indirect comparative PK data with IV edaravone has demonstrated the selection of 100mg dose of FAB122 which has been confirmed by the second study, a single center, randomized, open label, two-treatment, three-period, crossover, single dose study to comparatively assess the bioavailability of 100 mg FAB122 administered under fasting and fed conditions versus Radicava 60 mg in healthy volunteers (Study EDV-BEFI-02-FRI/20).

Based on these data and literature data, a dose regimen of 100 mg FAB122 once daily has been chosen for this study according to the following considerations:

1. that all subjects treated with oral FAB122 should have an adequate AUC, that is at least equal to than the mean AUC of Radicava™. Oral dosing may have slightly higher variability than IV dosing. However, the differences in standard deviations between IV Radicava and oral FAB122 are small (23% for IV versus 28% for FAB122).
2. that FAB122 will be dosed continuously instead of intermittently. For this regimen a safety margin of 6.0 and 2.1 was established in rats and dogs respectively, in the chronic toxicity studies (FDA, 2017; Schoenmakers A., 2019; Stegeman H., 2020) and that – due to the continuous dosing – slight increases in variability, resulting in a slightly lower target exposure for subjects at the lower end of the distribution curve, will be largely compensated for as compared to the intermittent schedule for IV Radicava™.

The bioavailability of FAB122 after oral administration has been shown to decrease with ~40% when concomitantly given with food (Treeway, 2017a, EDV-BEFI-02-FRI/20). Therefore, FAB122 is to be administered under fasted conditions in this trial.

Rationale for dosing schedule

In the Phase III studies with IV edaravone, a dose of 60 mg was applied via IV infusion using 28-day treatment cycles (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 18 Study Group., 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). The first cycle of treatment consisted of a 2-week, once-daily treatment period, followed by a 2-week drug-free period. Subsequent cycles consisted of a 2-week treatment period during which a total of 10 doses of edaravone (5 doses/week) were administered, followed by a 2-week drug-free period. The once daily dosing and 14-day drug holiday were merely included to reduce the burden of the patient. Given the exposure-based efficacy of edaravone, a more sustained exposure profile may further increase the efficacy of edaravone in ALS. This may be achieved by once daily dosing of orally administered FAB122 (elimination half-life of FAB122 ~ 5 h) without drug holidays.

Rationale for trial duration

Double-blind treatment is planned to continue until the last enrolled subject reaches 48 weeks of participation (or has reached an intercurrent event) and the first one third of the subjects randomised (100) has reached 72 weeks of follow up (or has reached an intercurrent event). Thus, all patients will have at least a 48-week treatment duration which is considered to provide a reliable assessment of disease modifying effects in the ALS patients included in this study (EMA, 2015)(Continuation of the study for up to 72 weeks for the first one third of the subjects (100) allows collection of longer-term data on disease progression and survival.

Rationale for efficacy endpoints

Based on edaravone's mode of action and the results of the Phase II and III clinical trials on IV administered edaravone, FAB122 is expected to slow down disease progression in ALS patients. The most widely used instrument to measure the progressive decline in functional capabilities in ALS clinical trials is the ALSFRS-R score, which is a validated disease-specific questionnaire (Cedarbaum et al., 1999). The primary analysis is therefore based on the change from baseline in ALSFRS-R score after 48 weeks. The effect of FAB122 on survival will be assessed using the key secondary endpoints including the CAFS score and overall survival, defined as time to death from any cause or respiratory insufficiency (DRI; defined as tracheostomy or the use of non-invasive ventilation for more than 20 h per day for more than 10 consecutive days).
These primary and key secondary endpoints are in line with the EMA guideline on clinical investigation of medicinal products for the treatment of ALS (EMA, 2015). To support the outcomes of the primary and key secondary endpoints, additional measures of disease progression are included such as the assessment of muscle strength by hand-held dynamometer (HHD)(Shefner, 2017), respiratory function by SVC (Pinto and de Carvalho, 2019) as well as additional analysis on the (sub)scores of the ALSFRS-R questionnaire.
QoL will be measured both with an ALS-specific questionnaire, the ALSAQ-40 (Jenkinson et al., 1999), as well as with a more general QoL measure, the EQ-5D-5L questionnaire score and health-related QoL VAS score (Herdman et al., 2011). Potential cognitive effects will be measured by ECAS (Abrahams et al., 2014).

Rationale for vitamin B6 monitoring and Nerve Conduction Study
Axonal degeneration as observed in non-clinical studies (Schoenmakers A., 2019) are possibly related to reduced levels of pyridoxal 5'-phosphate (PLP) in plasma, the active form of vitamin B6 (CHMP EMA, 2019). In the clinic similar axonal damage has been associated with a decrease of vitamin B6. This was observed with tuberculosis therapy with the antibiotic isoniazid. Accordingly, supplementation with vitamin B6 is generally recommended during isoniazid therapy. The scientific rationale for reduction of vitamin B6 with edaravone treatment has been established (CHMP EMA, 2019), and therefore, during this study vitamin B6 levels will be monitored and, if necessary, supplementation of vitamin B6 with pyridoxine (maximal 100 mg/day) will be prescribed.

In addition, to allow early detection of neurotoxicity during treatment with FAB122, Nerve Conduction Study (NCS) will be performed at screening, week 4, week 12, and week 24, and DSMB interim assessment on vitamin B6, clinical signs, ALSFRS-R questions related to leg functioning (8. walking and 9. climbing stairs) and NCS data when 60 subjects (about 40 active and 20 placebo) have been treated for 24 weeks:

a. If no neurological concerns are observed, the study will continue with one additional NCS at week 48;

b. If NCS show signs of neurological damage, intensive NCS monitoring will continue every 12 weeks for all patients. All NCS measurements will be centrally analysed by an independent neurophysiologist from the Neuromuscular center, UMC Utrecht, The Netherlands.

Rationale for pharmacokinetic endpoints
FAB122 plasma concentrations will be used to further establish the concentration-time profiles. These and results of population PK analyses will be used to study the relation between PK and pharmacodynamics (PD) effects including retrospective assessment of possible dose/exposure-treatment response correlations.

Riluzole is allowed as add-on therapy in the present clinical trial. Riluzole and FAB122 have non-overlapping primary metabolic pathways i.e. phase 1 metabolism for riluzole by mainly CYP1A2 (CHMP EMA, 2005) and glucuronidation and sulfation for FAB122 (PMDA, 2015; Tabrizchi, 2000). Therefore, no relevant drug interaction between FAB122 and riluzole is anticipated within the proposed dose range. This was confirmed in the Phase II and Phase III studies with IV administered edaravone in which no interaction between FAB122 and riluzole was reported: most patients in studies MCI186-16 (n=182/205) and MCI186-19 (n=112/123) and the extension study MCI186-17 (n=161/180) received concomitantly riluzole (Abe et al., 2014; 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). Additional monitoring is included in the present trial in which the data obtained as part of the FAB122 PK analysis, as well as peak and trough levels from riluzole will be used to evaluate the PK interaction between riluzole and FAB122.

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). Samples will be stored in a biobank. The patients will have the right to always withdraw their samples from the biobank.

Rationale for biomarkers

NFL is a biomarker correlated with prognosis and remain relatively stable over time. A change in the expression of NFL may, therefore, be considered as a potential disease amelioration in ALS (Verber et al., 2019). Plasma creatinine is a surrogate ALS biomarker of muscle mass and is decreased in ALS patients. Serum creatine kinase (CK) is increased in ALS patients and correlates with survival in some studies. Both are considered muscle denervation biomarkers in ALS. Urinary $P75^{ECD}$ is a surrogate ALS biomarker and is elevated in ALS patients. The three biomarkers are associated with disease progression (Verber et al., 2019). To measure the pharmacological effect (target engagement) of edaravone, oxidative stress biomarkers, like 8-OHdG, will be measured (Verber et al., 2019).

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 (Europe and USA) and iv edaravone (USA) 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.

The animal toxicology studies revealed neurologic adverse findings (e.g. abnormal gait, decreased activity, prostration, reduced function of the hind limbs) with prolonged exposure to edaravone at relatively low safety margins compared to the anticipated human exposure levels. Analysis of the non-clinical data indicated that the neurotoxic effects seen after edaravone administration resulted from demyelination (primary effect) followed by axonal degeneration (secondary effect). Therefore, special monitoring of potential neurotoxicity will be performed by NCS during the conduct of the current study (For more details, see FAB122 IB).

In trial C1.02, an oral dose of 180 mg BID FAB122 was given to 12 healthy male volunteers for 9 days (Day 1 and 9 once daily dosing) and was shown safe and well tolerated. Eight (8) of the 12 subjects (66.7%) reported a total of 9 adverse events (AEs). All of the AEs were transient in nature and mild in intensity. Six (6) of the AEs were considered to be possibly drug related i.e. 4 events of headache, one event of oral herpes infection and one event of transiently increased aspartate aminotransferase (AST) levels at Day 5 (79 U/L; normal range 0-40 U/L). There were no discontinuations due to adverse events. No clinically significant abnormal values were observed for vital signs (blood pressure, heart rate, temperature) and 12-lead ECG. Also, no clinically significant abnormal values were observed in laboratory safety tests (haematology, biochemistry) except for the one case of transiently increased AST, nor were trends observed in mean safety analyses. In trial C1.04, a single oral dose of 140 mg FAB122 was administered to 36 healthy volunteers. The safety results showed that the oral administration was safe and well tolerated. In total 11 adverse events were reported of which headache (n=7) was most frequent. There were no discontinuations due to adverse events. No clinically significant abnormal values were observed for vital signs (blood pressure, heart rate, temperature) and 12-lead ECG. Also, no clinically significant abnormal values were observed in laboratory safety tests (hematology, biochemistry). In trial C1.01, 8 patients were dosed twice with a single dose of 90 mg FAB122, once under fed conditions and once under fasted conditions. Six (6) of the 8 patients (75%) reported a total of 21 AEs, all of mild intensity. None of them were deemed to be drug related by the investigator. No clinically significant abnormal values were observed in laboratory safety tests (haematology, biochemistry). No clinically significant abnormal values were observed for 12-lead ECG and vital signs (blood pressure, heart rate, temperature), except for one subject with high blood pressure starting pre-dose in the second dosing period. In the trial EDV-PBA-01-FRI/20 a single oral dose of 50mg, 100mg, and 200mg FAB122 (three cohorts ascending dose) was administered to 60 healthy volunteers. The safety results showed that the oral administration was safe and well tolerated. Only one AE “nausea” has been notified for cohort 1 (50mg), the AE was mild and transient in nature and was evaluated as related to

the study drug. No clinically significant abnormal values were observed for vital signs (blood pressure, heart rate, temperature) and 12-lead ECG. Also, no clinically significant abnormal values were observed in laboratory safety tests (hematology, biochemistry, urine analysis), except for one subject who has transient elevation of AST, ALT, and GGT in cohort 3 group (200mg FAB122). In the trial EDV-BEFI-02-FRI/20, two AEs of “headache” in two subjects have been notified, the AEs were mild and transient in nature and were evaluated as related to the study drug. No clinically significant abnormal values were observed for vital signs (blood pressure, heart rate, temperature) and 12-lead ECG. Also, no clinically significant abnormal values were observed in laboratory safety tests (hematology, biochemistry, urine analysis). (For more details, see FAB122 IB).

Overall, the preclinical toxicity profile as well as the clinical safety and efficacy profile of FAB122/edaravone administered by the oral and intravenous route support evaluation of FAB122 in an oral formulation in clinical trials in ALS patients and the expected clinical benefits overcome the potential risks.

3. OBJECTIVES AND OUTCOME MEASURES

3.1. Objectives

3.1.1. Primary Objective

To assess the effect of treatment with 100 mg of FAB122 on disease progression in patients with ALS

3.1.2. Secondary Objectives

1. To evaluate the effect of treatment with FAB122 on survival
2. To evaluate the safety and tolerability of FAB122
3. To evaluate the effect of treatment with FAB122 on quality of life (QoL)
4. To evaluate the effect of treatment with FAB122 on cognitive functioning
5. To evaluate the pharmacokinetics (PK) of FAB122

3.1.3. Exploratory Objectives

1. To evaluate the PK interaction of FAB122 and riluzole
2. To explore and identify biomarkers that inform the scientific understanding of ALS and/or their therapeutic treatments

3.2. Endpoints

3.2.1. Primary Endpoint

Change from baseline in Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS-R) score after 48 weeks.

3.2.2. Secondary Endpoints

<u>Key secondary endpoints</u>

1. Combined assessment of function and survival (CAFS) at 48 and 72* weeks;
2. Survival time, i.e. time to death, tracheostomy or initiation of non-invasive ventilation for more than 20 hours a day for more than 10 consecutive days, over 72 weeks.

<u>Efficacy</u>

1. Change from baseline in ALSFRS-R score after 24 and 72* weeks;

2. The slope of the decrease in ALSFRS-R score over time at 24, 48 and 72* weeks;
3. Change from baseline in ALSFRS-R score on Bulbar function (question 1-3 of the ALSFRS-R) after 24, 48 and 72* weeks;
4. Change from baseline in ALSFRS-R score on Fine motor function (question 4-6 of the ALSFRS-R) after, 24, 48 and 72* weeks;
5. Change from baseline in ALSFRS-R score on Gross motor function (question 7-9 of the ALSFRS-R) after, 24, 48 and 72* weeks;
6. Change from baseline in ALSFRS-R score on Respiratory function (question 10-12 of the ALSFRS-R) after 24, 48 and 72* weeks;
7. Time to a 3, 6, 9 and 12 points change or death from baseline in ALSFRS-R score over 72* weeks;
8. Proportion of subjects with change from baseline in ALSFRS-R score at 24, 48, and 72* weeks in categories: categories will include change ≥0, change between <0 and ≥-1, change between <-1 and ≥-2 etc.;
9. Time to change in clinical stage or death (King's staging system and MiToS) over 72* weeks;
10. Overall survival: Proportion of subjects alive (survival rate) after 24, 48 and 72* weeks;
11. Proportion of subjects alive and no tracheostomy, or no initiation of non-invasive ventilation for more than 20 hours a day for more than 10 consecutive days after 24, 48 and 72* weeks;
12. Change from baseline in slow vital capacity (SVC, liters) at 24, 48 and 72* weeks;
13. Change from baseline in the overall mega score for the hand-held dynamometer (HHD) at 24, 48 and 72* weeks.

<u>QoL</u>

1. Change from baseline in the total score on the ALS Assessment Questionnaire-40-Item (ALSAQ-40) Form at 24, 48 and 72* weeks;
2. Change from baseline in EuroQoL – 5 Dimensions-5 Levels (EQ-5D-5L) questionnaire score at 24, 48 and 72* weeks.
3. Change from baseline in Health related QoL Visual Analogue Scale (VAS) score at 24, 48 and 72 weeks.

<u>Cognition</u>

1. Proportion of subjects with a change of ≥8, ≥4, and ≥9 for ALS Specific, ALS Non-Specific, and ECAS (Edinburgh Cognitive and behavioural ALS Screen) total score;
2. Change from baseline for ALS Specific, ALS Non-Specific, and ECAS total score at 24, 48 and 72* weeks;

3. Time to a mean change of ≥8, ≥4, and ≥9 for ALS Specific, ALS Non-Specific, and ECAS total score.

Pharmacokinetics

(Population) PK parameters of FAB122 and riluzole

*All secondary endpoints at 72 weeks will be analyzed for the subgroup of patients that reach 72 weeks (or IE)

3.2.3. Safety Endpoints

1. Nature, frequency and severity of Treatment Emergent Adverse Events;
2. Parameters derived from in vital signs and 12-lead electrocardiogram (ECG);
3. Parameters derived from laboratory tests (hematology, biochemistry, urinalysis);
4. Proportion of patients that drop out due to adverse events.

3.2.4. Exploratory Endpoints

Pharmacokinetics

PK interaction between FAB122 and riluzole

Biomarkers

1. Change from baseline in the prognostic ALS biomarker neurofilament light (NFL)
2. Change from baseline in the ALS biomarkers creatinine and creatinine kinase
3. Change from baseline in the ALS biomarker Urinary extracellular domain of neurotrophin receptor p75 (Urinary P75ECD)
4. Change from baseline of oxidative stress biomarker 8-hydroxyguanosine (8-OHdG)

Health economics
Cost-Utility analysis of treatment with FAB122

4. STUDY DESIGN

Multicenter, multinational, double-blind, randomized (2:1), placebo-controlled Phase III study to investigate the efficacy and safety of 100 mg FAB122 (former TW001) once daily as oral formulation in ALS patients.

Subjects will be screened to assess whether they comply with all enrolment criteria. Approximately 300 patients will be randomized to 100 mg FAB122 or matched placebo in a 2:1 ratio. Patients will be stratified by;
1) their ALS progression rate at the start of the study (the slope ALSFRS-R score from time of first symptoms till Screening <1.0 vs. ≥1.0),
2) additional co-medication for ALS (a. riluzole, b. no riluzole).

Riluzole (100 mg/day or less) may be used as background (add-on) therapy. Patients on riluzole should be on stable doses at the start of the trial and for at least 30 days before the initiation of the study drug. It will not be allowed to initiate riluzole therapy during the trial. Additional supportive Standard Of Care (SOC) treatments will be allowed in all patients and will be standardized as much as possible.

Subjects will receive double-blind treatment up to a maximum of 72 weeks. The study is planned to continue until the last randomized subject has reached 48 weeks of follow up (or has reached an intercurrent event) AND the first one third of the subjects randomized (100) have reached 72 weeks of follow up (or has reached an intercurrent event). Subjects who discontinue treatment before week 72 will be followed as much as possible according to the planned visit schedule. In case of sanitary restrictions due to COVID-19 pandemic, home visits might be performed (for more details, see annex 4).

Subjects will visit the clinic at Screening, Baseline, Week 4, Week 12, and every 12 weeks thereafter. Monthly telephone visits are performed in between the visits to the clinic until Week 48.

Blood sampling for FAB122 plasma concentrations will be done in ~90 subjects treated with the study drug.

After a subject completed the study (max at 72 weeks), he/she will be offered the possibility to roll over in an open label extension trial in which all subjects will be offered to receive FAB122.

The end of the trial will correspond to the last subject last visit per the trial schedule.

The study flowchart is presented in the Figure 2.

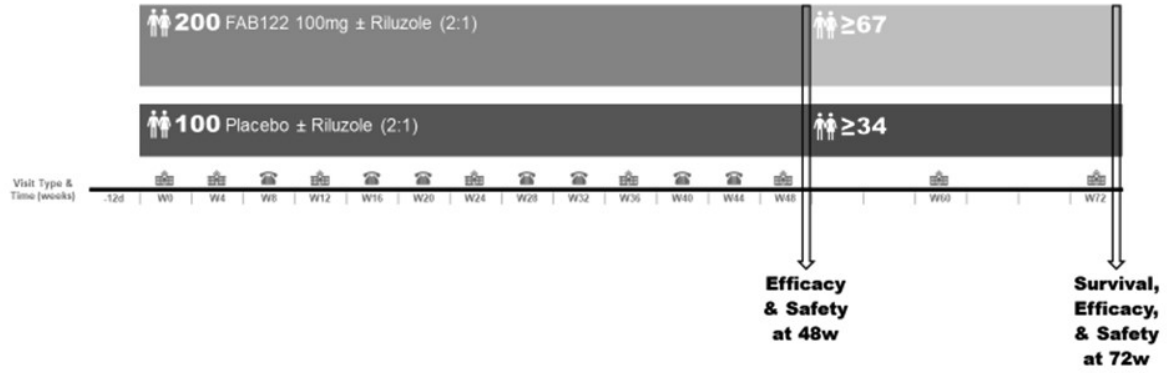


Figure 2: Study flowchart

5. STUDY POPULATION

5.1. Study Participants

ALS patients

5.2. Inclusion Criteria

In order to be eligible for participation in this trial, a subject must meet all of the following criteria:

1. Age 18 – 80 years (both inclusive), male or female;
2. Diagnosis of definite, probable, probable laboratory supported or possible ALS as based on the El Escorial and the revised Airlie House diagnostic criteria for ALS;
3. Onset of first symptoms* no longer than 24 months prior to randomization;
   *Date of onset is the date the patient reported one or more of the following symptoms:
   - Muscle weakness in limbs
   - Speech/swallowing difficulties
   - Respiratory symptoms: dyspnea was noticed
4. SVC equal to or more than 70% of the predicted normal value for gender, height and age at screening visit;
5. Change in ALSFRS-R score between 0.35 points and 1.5 points per month (both inclusive) in the period from onset of first symptoms to the Screening visit;
6. Patients on riluzole should be on stable doses ≥30 days prior to the baseline visit and this dose should be maintained during the entire trial.
7. A female subject should not be able to become pregnant 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 screening and 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.

8. A male patient must:
   - agree he will not donate sperm during the study and until 104 days after the last dose, AND
   - use a condom during sexual intercourse with pregnant or non-pregnant women of childbearing potential (WOCBP) partner even if he is vasectomized
   - 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;
9. providing informed consent and complying with trial procedures.

5.3. Exclusion Criteria

A subject must not meet one or more of the following criteria:

1. Diagnosis of Primary Lateral Sclerosis;
2. Diagnosis of Frontotemporal Dementia;
3. Diagnosis of other neurodegenerative diseases (e.g. Parkinson disease, Alzheimer disease);
4. Diagnosis of polyneuropathy;
5. Other causes of neuromuscular weakness;

6. Have a significant pulmonary disorder not attributed to ALS and/or require treatment interfering with the evaluation of ALS on respiratory function;
7. Use of intravenous (IV) edaravone within 6 months of the screening visit;
8. Use of mechanical ventilation (invasive or non-invasive) at Screening;
9. Renal impairement as indicated by a creatinine clearane of less than 50 mL/min
10. Subject has a history of clinically significant hepatic disease, hepatitis or biliary tract disease, ALT/AST levels ≥ 3xULN, bilirubin levels ≥2xULN or subject has a positive screening test for HIV, hepatitis B or C;
11. Presence of any of the following clinical conditions:
    - unstable cardiac, pulmonary, endocrine, hematologic or active infectious disease
    - Severe active psychiatric illness e.g. psychosis, untreated major depression within 90 days of the screening visit
    - significant cognitive impairment, clinical dementia or psychiatric illness
    - Cancer that is currently under active treatment or is likely to require treatment during the trial that may alter the subject´s function and interfere with assessment of ALS disease progression.
12. Any comorbidity that may interfere with the functions as scored with the ALSFRS-R;
13. History of known sensitivity or intolerability to edaravone, to any related compound, or to any of the excipients;
14. Exposure to any investigational drug within 30 days of the screening visit or 5 half-lives, whichever is longer;
15. Current substance or alcohol dependence.
16. For patients undergoing optional CSF sampling: any condition that according to the investigator criteria is contraindicated for the procedure (e.g. space-occupying lesion with mass effect, increase of intracranial pressure due to increased CSF pressure; posterior fossa mass; Arnold-Chiari malformation; anticoagulant medication; coagulopathy; uncorrected bleeding diathesis; congenital spine abnormality; and skin infection at puncture site.

This study permits the re-screening of a subject that has been deemed as ineligible (screen failure) during the Screening Period (ie, subject has not been randomized/has not been treated). Reasons that may qualify for a re-screening include medication stabilizing or ending, an acute event that has now resolved or any circumstance that is deemed appropriate by a medical monitor. If re-screened, the subject must be re-consented. Only one re-screening per subject is permitted.

6. STUDY PROCEDURES

All the study procedures are presented in the following table:

Table 1: Study Scheduled Visits

	Screening	Baseline	Treatment period													
	(-12/-2 days)	V1 D1 W0	V2 D28 W4 ±3D	T1 D56 W8 ±4D	V3 D84 W12 ±3D	T2 D112 W16 ±4D	T3 D140 W20 ±4D	V4 D168 W24 ±7D	T4 D196 W28 ±7D	T5 D224 W32 ±7D	V5 D252 W36 ±7D	T6 D280 W40 ±7D	T7 D308 W44 ± 7D	V6/EoT D336 W48 ±7D	V7 D420 W60 ±7D	V8[1] D504 W72 OR EoT[2]
Administrative procedures																
ICF	X															
ICF for PK	X															
In/exclusion criteria	X	X[3]														
Medical history	X															
Prior/Concomitant medication	x----------x															
Randomization		X														
Dispensing study medication/Compliance check		X*			X			X			X			X	X	
Clinical Procedures																
Physical examination	X	X						X						X		X
Weight	X	X						X						X		X
Height	X															
Vital Signs	X	X	X		X			X			X			X	X	X
12-lead ECG	X	X						X						X		X
Neurological examination[4]	X	X	X		X			X			X			X	X	X
NCS[5]	X*		X		X			X								
(S)AE monitoring	x----------x															
Laboratory procedures																

	Screening	Baseline	Treatment period													
	(-12/-2 days)	V1 D1 W0	V2 D28 W4 ±3D	T1 D56 W8 ±4D	V3 D84 W12 ±3D	T2 D112 W16 ±4D	T3 D140 W20 ±4D	V4 D168 W24 ±7D	T4 D196 W28 ±7D	T5 D224 W32 ±7D	V5 D252 W36 ±7D	T6 D280 W40 ±7D	T7 D308 W44 ± 7D	V6/EoT D336 W48 ±7D	V7 D420 W60 ±7D	V8[1] D504 W72 OR EoT[2]
Chemistry/ Haematology[6]	X	X[15]	X		X			X			X			X	X	X
Vitamin B6 monitoring[7]	X	X	X		X			X			X			X	X	X
Urinalysis[8]	X	X	X		X			X			X			X	X	X
β-hCG[3]	X															
Urine Pregnancy Test[3]	X	X	X		X			X			X			X	X	X
HIV/Hepatitis B,C	X															
ALS evaluation procedures																
ALSFRS-R	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
SVC	X	X			X			X			X			X	X	X
HHD		X			X			X			X			X	X	X
ALSAQ-40		X						X						X		X
ECAS		X						X						X		X
EQ-5D-5L		X			X			X			X			X	X	X
VAS		X			X			X			X			X	X	X
Cost questionnaire		X			X			X			X			X	X	X
King's staging system and MiToS		X			X			X			X			X	X	X
PK																
Blood sampling for FAB122[9]		X[9]	X[9]											X[9]		X[11]
Blood sampling for riluzole[10]		X	X													
ALS biomarkers																
Blood sampling for biomarkers[12]		X	X		X			X			X			X	X	X
Urine collection for biomarkers[13]		X	X		X			X			X			X	X	X
Future Biomedical Research																

	Screening	Baseline	Treatment period													
	(-12/-2 days)	V1 D1 W0	V2 D28 W4 ±3D	T1 D56 W8 ±4D	V3 D84 W12 ±3D	T2 D112 W16 ±4D	T3 D140 W20 ±4D	V4 D168 W24 ±7D	T4 D196 W28 ±7D	T5 D224 W32 ±7D	V5 D252 W36 ±7D	T6 D280 W40 ±7D	T7 D308 W44 ± 7D	V6/EoT D336 W48 ±7D	V7 D420 W60 ±7D	V8[1] D504 W72 OR EoT[2]
Blood sampling for genotyping for FBR (if consented)		X														
Blood sampling for RNA and serum collection for FBR (if consented)		X			X			X			X			X	X	X
CSF sampling for FBR (if consented)[14]		X			X			X								

V=visit; T= telephone call; EoT = End of Trial; W=Week, D=Day
*First dosing

1. If a patient is withdrawn from the study or discontinues study treatment, will be asked to return to the clinic and the procedures as depicted for the End-of-Trial visit will need to be done. The first 100 patients (1/3 of the total study population) will continue study participation until week 72 (Visit 8), or until reaching an intercurrent event. For all other patients (2/3 of the study population) the end of the study will be the week 48 (visit 6) of each patient (or an intercurrent event.
2. If a patient does not participate in the extended follow-up study the End of Trial (EoT) visit will take place between 1 and 14 days after treatment cessation. If a subject roll over to the extended treatment study, treatment is to be continued until the EoT visit. The EoT visit should also be performed 7-14 days after study termination in case of withdrawal or early termination of the study.
3. β-hCG in plasma and urine pregnancy test should only be performed in women of childbearing potential.
4. 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 on neurological examination) will be monitored during the study. In case a subject experiences clinical signs or symptoms at home, subjects will be asked to contact the clinic.
5. The DSMB will assess the results of the NCS for the first enrolled 60 patients (about 40 active and 20 placebo). The NCS will be conducted for the first enrolled 60 patients at screening , and on weeks 4, 12, and 24. Then according to the evaluation by the DSMB, one of the following options will be performed: 1) If no neurological concerns are observed, the study will continue with one additional NCS at week 48 for the first 60 patients. Then for the next enrolled patients, one NCS will be performed at Screening and another one at week 48. Additional NCS(s) could be performed between Screening and week 48 if any abnormality is detected by the neurological examination or any suggesting symptoms of neuropathy are reported by the patient. 2) If NCS show signs of neurological damage, intensive NCS monitoring will continue for all patients at Screening and on weeks 4, 12, 24, 36, 48, 60, and 72.
6. Hematology: hematocrit, hemoglobin, RBC (red blood cell count & parameters), WBC (white blood cell count inclusive differential count), platelet count. 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 glomular filtration rate), uric acid, aPTT, PTT, fibrinogen and fasting glucose. Cystacin C

7. Vitamin B6 levels will be monitored and, if necessary, supplementation of vitamin B6 (pyridoxine (100 mg/day)) will be prescribed.
8. Urinalysis: Blood, Glucose, Protein, Specific gravity, Ketone, pH, Nitrite, Leukocytes, Bilirubin, Urobilinogen, Microscopic exam, if abnormal results are noted.
9. Blood sampling for FAB122 PK analysis will be done in ~90 subjects in selected sites. Of those ~30 subjects will participate in a PK profiling sampling schedule and the additional ~60 subjects will participate in a population PK sampling schedule. Sampling schedule for PK profiling: pre-dose and 15 min, 30 min, 1, 1.,5, 2, 4 hrs., and 6hrs. after the FAB122 morning dose. The pre-dose sample may be collected within 30 minutes prior to dosing, the samples taken 15 and, 30 min post dosing samples should be taken within ±2 minutes of the scheduled time, the 1 hr. post dosing sample within ±5 minutes, the 2-hour sample within ±10 minutes and the 4 hr. and 6hr. sample within ±20 minutes of the scheduled time. The time of sampling will be accurately recorded. Sampling schedule for population PK: (1) pre-dose (within 1 hour prior to dosing), (2) within 5- and 30-minutes post dosing, (3) 1 hour and (4) 1.5 hour after the second PK sample was taken.
10. Blood sampling for the determination of riluzole concentration will be done in the subjects included in FAB122 population PK sampling in baseline and week 4 (~90 subjects) at (1) pre-dose (within 1 hour prior to dosing).(2) within 5- and 30-minutes post dosing, (3) 1 hour and (4) 1.5 hour after the second PK sample was taken. In case of discontinuation of a subject, due to safety reasons or early termination of the study, a PK sample for determination of the FAB122 concentration is to be taken in those sites where FAB122 sampling is operational. The clock time and time after last dosing is to be noted in the CRF.
11. Blood biomarkers: neurofilament light chain (NfL). Serum creatinine and serum creatine kinasa will be measured in biochemistry lab testing.
12. Urine biomarkers: 8-hydroxy-2 ′-deoxyguanosine (8-OhdG), extracellular domain of neurotrophin receptor p75 (p75ECD).
13. Optional CSF sampling will be performed (if consented) in about 30 patients at baseline, week 12, and week 24. Lumbar Puncture for CSF sampling is an aseptic procedure which needs standard bedside aseptic procedures with no-touch technique, sterile drapes and use of chlorhexidine or an equivalent antiseptic. Local anaesthesia with small amount of lidocaine can be infiltrated. A right-handed practitioner should position the patient in the left lateral decubitus position, with the vertebrae in line with the horizontal plane and the head in a neutral position and the knees flexed, also setting position could be applied if seemed by the practitioner. The bony landmark is the L4 spinous process and the L3/L4 interspace is recommended. Atraumatic 22-gauge needle could be used, however smallest diameter needle with which the practitioner can confidently perform the procedure avoiding an increased number of attempts should be chosen. 10 ml CSF sample will be drawn at each time point. After the procedure, a small sterile dressing is placed on the site and the patient can mobilise as soon as it is comfortable to do so. Regular analgesics such as paracetamol could be prescribed.
14. Only labs parameters that are abnormal in the screening visit will be re-evaluated in baseline visit.

* In case it's necessary, NCS assessment can be performed during the baseline visit, provided the approval from the central reader are available prior to randomization.

In case that, due to ALS progression, the subject is not able to attend the clinic or perform specific testing such as HHD or SVC, at least ALSFRS score, adverse events and concomitant medication use will be collected (if necessary by telephone). For safety assessments, the on-site visits are key for the study. In case a subject is not able to attend the site for two consecutive visits IMP must be discontinued at the second missed visit. The patient can continue its participation in the trial, via telephonic visits to collect ALSFRS-R, Adverse Events and Concomitant Medication, as long as the subject does not withdraw consent.

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

6.1. Screening and Eligibility Assessment

Subjects will report to the clinical site for a screening examination between Day -12 and Day -2.

Prior to performing any study-related activities or evaluations, the patient must be thoroughly informed about all aspects of the study, including scheduled visits and activities. Patients will sign the study-specific consent form prior to any screening procedure. 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. Depending on local regulations an independent ICF for Future Biomedical Research (FBR) should also be signed.

The following information and procedures will be performed and documented as part of the screening assessment:

- Assessment of eligibility according to inclusion/exclusion criteria
- Demographics, including sex, ethnic origin, date of birth
- Medical history including query for baseline signs/symptoms
- Review of prior and ongoing concomitant medications (taken in previous 30 days)
- Complete physical examination
- Neurological examination
- Height, weight and calculated BMI
- Vital signs measured with the subject in a supine/semi-supine position (for at least 5 minutes prior), including blood pressure, pulse 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)
- Nerve Conduction Study (NCS)
- Fasting blood samples for routine clinical labs (clinical chemistry, haematology). See table 2 for lab assessments.
- Blood samples for serology (HIV, and hepatitis B and C evaluations)
- Urine samples for urinalysis
- β-hCG in plasma and urine pregnancy test only in women of childbearing potential
- ALS evaluation procedures: ALSFRS-R and Slow Vital Capacity (SVC)
- Plasma vitamin B6 levels, and, if necessary, vitamin B6 supplements (pyridoxine (100 mg/day)) will be prescribed

Compliance with inclusion criteria and exclusion criteria will be verified against information collected and documented in the database.

Once all inclusion criteria are met, exclusion criteria ruled out, and safety* laboratory measurements obtained and reviewed, consenting subjects are eligible for randomization into the study.

*Vit B6 is not considered a safety assessment at screening

6.2. Baseline Assessments

Baseline (Visit 1) Week 0 (Day 1)

The following procedures will be performed:

- Assessment of eligibility according to inclusion/exclusion criteria
- Randomization

  Eligible patients will be randomized strictly sequentially, according to a randomization list prepared by the Biostatistician

  All patients will receive a unique patient identification number at screening visit when signing the informed consent and before any study procedures are performed. Three hundred patients will be randomized 2:1 in the following 2 groups:

1. 200 patients will receive FAB122 100mg/d + SOC

2. 100 patients will receive placebo + SOC

The investigators will randomize patients directly online. In case of discontinuation from the study, the randomization number will not be reused.

- Review of prior and 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, 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)
- Fasting blood samples for routine clinical labs (clinical chemistry, haematology). See table 2 for lab assessments.

* **Only labs parameters that are abnormal in the screening visit will be re-evaluated in baseline visit.**

- Urine samples for urinalysis
- Urine pregnancy test only in women of childbearing potential
- Plasma vitamin B6 levels, and, if necessary, vitamin B6 supplements (pyridoxine (100 mg/day)) will be prescribed.
- ALS evaluation procedures: ALSFRS-R, Slow Vital Capacity (SVC), Hand-Held Dynamometry, ALSAQ-40, Edinburgh Cognitive and Behavioural ALS Screen (ECAS), EQ-5D-5L, VAS, King's staging system and MiToS.
- Blood sampling for biomarker: 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)

- Blood sampling for RNA and serum collection for FBR (if consented)
- Cerebrospinal fluid (CSF) sampling for Future Biomedical Research (if consented)
- Dispensing study Medication: Instructions for dosing FAB122 and first dosing
- Blood sampling for FAB122, in selected sites if consented. Specific ICF will be provided.
- Blood sampling for riluzole, in selected sites if consented. Specific ICF will be provided.
- Adverse Events monitoring
- Cost questionnaire

6.3. Subsequent Visits

Visit 2 Week 4 (Day 28 ±3Days)

The following procedures will be performed:

- Review ongoing concomitant medications
- Neurological examination
- Vital signs measured with the subject in a supine/semi-supine position (for at least 5 minutes prior), including blood pressure, pulse rate, pulse oximetry and temperature
- Fasting blood samples for routine clinical labs (clinical chemistry, haematology). See table 2 for lab assessments
- Urine samples for urinalysis
- Plasma vitamin B6 levels, and, if necessary, vitamin B6 supplements (pyridoxine (100 mg/day)) will be prescribed.
- ALS evaluation procedures: ALSFRS-R
- Blood sampling for biomarker: 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 FAB122, in selected sites if consented
- Blood sampling for riluzole, in selected sites if consented
- Nerve Conduction Study (NCS)
- Adverse Events monitoring
- Compliance check

Visit 3 Week 12 (Day 84 ±3Days)

The following procedures will be performed:

- Review ongoing concomitant medications
- Neurological examination
- Vital signs measured with the subject in a supine/semi-supine position (for at least 5 minutes prior), including blood pressure, pulse rate, pulse oximetry and temperature
- Fasting blood samples for routine clinical labs (clinical chemistry, haematology). See table 2 for lab assessments
- Urine samples for urinalysis
- Urine pregnancy test only in women of childbearing potential
- Plasma vitamin B6 levels, and, if necessary, vitamin B6 supplements (pyridoxine (100 mg/day)) will be prescribed
- ALS evaluation procedures: ALSFRS-R, Slow Vital Capacity (SVC), Hand-Held Dynamometry, King's staging system and MiToS, EQ-5D-5L and VAS
- Blood sampling for RNA and serum collection for FBR (if consented)
- Blood sampling for biomarker: 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)
- Cerebrospinal fluid (CSF) sampling for Future Biomedical Research (if consented)
- Nerve Conduction Study (NCS)
- Adverse Events monitoring
- Cost questionnaire
- Dispensing study medication
- Compliance check

Visit 4 Week 24 (Day 168 ±7Days)

The following procedures will be performed:

- 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, 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)
- Fasting blood samples for routine clinical labs (clinical chemistry, haematology). See table 2 for lab assessments
- Urine samples for urinalysis
- Urine pregnancy test only in women of childbearing potential
- Plasma vitamin B6 levels, and, if necessary, vitamin B6 supplements (pyridoxine (100 mg/day)) will be prescribed

- ALS evaluation procedures: ALSFRS-R, Slow Vital Capacity (SVC), Hand-Held Dynamometry, ALSAQ-40, Edinburgh Cognitive and Behavioural ALS Screen (ECAS), EQ-5D-5L, VAS, King's staging system and MiToS
- Blood sampling for biomarker: 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 RNA and serum collection for FBR (if consented)
- Cerebrospinal fluid (CSF) sampling for Future Biomedical Research (if consented)
- Nerve Conduction Study (NCS)
- Adverse Events monitoring
- Cost questionnaire
- Dispensing study medication
- Compliance check

Visit 5 Week 36 (Day 252 ±7Days)

The following procedures will be performed:

- Review ongoing concomitant medications
- Neurological examination
- Vital signs measured with the subject in a supine/semi-supine position (for at least 5 minutes prior), including blood pressure, pulse rate, pulse oximetry and temperature
- Fasting blood samples for routine clinical labs (clinical chemistry, haematology). See table 2 for lab assessments
- Urine samples for urinalysis
- Urine pregnancy test only in women of childbearing potential

- Plasma vitamin B6 levels, and, if necessary, vitamin B6 supplements (pyridoxine (100 mg/day)) will be prescribed.
- ALS evaluation procedures: ALSFRS-R, Slow Vital Capacity (SVC), Hand-Held Dynamometry, King's staging system and MiToS, EQ-5D-5L and VAS.
- Blood sampling for biomarker: 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 RNA and serum collection for FBR (if consented)
- Nerve Conduction Study (NCS) (if required)
- Adverse Events monitoring
- Cost questionnaire
- Dispensing study medication
- Compliance check

Visit 6 Week 48 (Day 336 ±7Days)-End of Trial

The following procedures will be performed:

- 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, 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)
- Fasting blood samples for routine clinical labs (clinical chemistry, haematology). See table 2 for lab assessments
- Urine samples for urinalysis

- Urine pregnancy test only in women of childbearing potential
- Plasma vitamin B6 levels, and, if necessary, vitamin B6 supplements (pyridoxine (100 mg/day)) will be prescribed.
- ALS evaluation procedures: ALSFRS-R, Slow Vital Capacity (SVC), Hand-Held Dynamometry, ALSAQ-40, Edinburgh Cognitive and Behavioural ALS Screen (ECAS), EQ-5D-5L, VAS, King's staging system and MiToS
- Blood sampling for biomarker: 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 RNA and serum collection for FBR (if consented)
- Blood sampling for FAB122
- Nerve Conduction Study (NCS) (if required)
- Adverse Events monitoring
- Cost questionnaire
- Dispensing study medication
- Compliance check

Visit 7 Week 60 (Day 420 ±7Days)

The following procedures will be performed:

- Review ongoing concomitant medications
- Neurological examination
- Vital signs measured with the subject in a supine/semi-supine position (for at least 5 minutes prior), including blood pressure, pulse rate, pulse oximetry and temperature
- Fasting blood samples for routine clinical labs (clinical chemistry, haematology). See table 2 for lab assessments
- Urine samples for urinalysis

- Urine pregnancy test only in women of childbearing potential
- Plasma vitamin B6 levels, and, if necessary, vitamin B6 supplements (pyridoxine (100 mg/day)) will be prescribed
- ALS evaluation procedures: ALSFRS-R, Slow Vital Capacity (SVC), Hand-Held Dynamometry, King's staging system and MiToS, EQ-5D-5L and VAS
- Blood sampling for biomarker: 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 RNA and serum collection for FBR (if consented)
- Nerve Conduction Study (NCS) (if required)
- Adverse Events monitoring
- Cost questionnaire
- Dispensing study medication
- Compliance check

Visit 8 Week 72 (Day 504 ±7Days)-End of Trial visit (first 100 patients enrolled)

The following procedures will be performed:

- 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, 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)

- Fasting blood samples for routine clinical labs (clinical chemistry, haematology). See table 2 for lab assessments
- Urine samples for urinalysis
- Urine pregnancy test only in women of childbearing potential
- Plasma vitamin B6 levels, and, if necessary, vitamin B6 supplements (pyridoxine (100 mg/day)) will be prescribed
- ALS evaluation procedures: ALSFRS-R, Slow Vital Capacity (SVC), Hand-Held Dynamometry, ALSAQ-40, Edinburgh Cognitive and Behavioural ALS Screen (ECAS), EQ-5D-5L, VAS, and King's staging system and MiToS
- Blood sampling for biomarker: 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 RNA and serum collection for FBR (if consented)
- Blood sampling for FAB122 (if early withdrawal)
- Nerve Conduction Study (NCS) (if required)
- Adverse Events monitoring
- Cost questionnaire
- Compliance check

Table 2: Overview of laboratory assessments

Haematology	Biochemistry	Urinalysis	Other	Biomarkers
Haematocrit	Bilirubin (direct) and Bilirubin (total)	Blood	Serum β-human chorionic gonadotropin (β-hCG)	Urinary $P75^{ECD}$
Haemoglobin	Alkaline phosphatase	Glucose	Hepatitis B surface antigen (HBsAg)	Urinary 8-OHdG
RBC	Alanine aminotransferase (ALT)	Protein	Hepatitis C virus antibody (HCV-Ab)	Blood neurofilament light (NFL)
Platelet count	Aspartate aminotransferase (AST)	Specific gravity	HIV antibody (HIV-Ab)	

Haematology	Biochemistry	Urinalysis	Other	Biomarkers
WBC	Bicarbonate	Microscopic exam, if abnormal results are noted	Plasma vitamin B6 levels	
Differential count:	Calcium	Ketone	Cystatin C	
Basophils	Chloride	PH		
Eosinophils	Creatinine	Nitrite		
Lymphocytes	gammaGT (GGT)	Leukocytes		
Monocytes	Fasting Glucose	Bilirubin		
Neutrophils	Potassium	Urobilinogen		
	Sodium			
	Uric Acid			
	Total protein			
	Urea (BUN)			
	eGFR			
	Activated partial thromboplastin time (aPTT)			
	Protrombin Time (PTT)			
	Fibrinogen			
	Lactate dehyrdognease (LDH)			
	Creatinine kinase (CK)			

6.4. Telephonic visits

Seven telephone calls will be performed throughout the study by the study team. These calls will be done in the following time points: Week 8, 16, 20, 28, 32, 40, and 44. The following activities will be performed in each call:

- ALSFRS-R questionnaire
- Adverse Events monitoring
- Review prior and ongoing concomitant medications

6.5. Early Discontinuation/Withdrawal of Participants

Subjects may withdraw consent at any time for any reason or be dropped from the 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. Once a subject has discontinued treatment, he/she may be allowed to start treatment again after consultation with the investigator, if discontinuation of treatment is ≤ 2 weeks.

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.
- The subject reaches the criteria for respiratory insufficiency (tracheostomy or the use of non-invasive ventilation for >20 hours per day for >10 consecutive days),

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

1-The subject becomes pregnant during the study.
2-The subject's investigator considers it is in the best interest of the subject to discontinue including worsening or disease progression if the investigator considers that it is in the patient's best interest the initiation of any standard of care treatment prohibited in the study
3-Serious adverse event considered related to the IMP
4-Severe Neurotoxicity considered related to the IMP
5-Any other severe adverse event considered related to the IMP at the discretion of the investigator.
6-Acute renal failure (creatinine clearance of less than 30 mL/min as calculated by the Cockcroft Gault equation)
7-Severe liver disorder defined as:

- ALT/AST ≥ 3xULN and bilirubin ≥2xULN (>35% direct bilirubin)
- ALT/AST ≥ 8xULN
- ALT/AST ≥ 3xULN and with symptoms believed to be related to liver injury or hypersensitivity.
- ALT/AST ≥ 3x baseline ALT/AST and with symptoms believed to be related to liver injury or hypersensitivity.
- ALT/AST ≥ 5xULN and ALT/AST < 8xULN that persists more than two weeks

8-Acute lung injury with pyrexia, cough, dyspnoea and chest X-ray abnormality
9-Rhabdomyolysis
10-Disseminated intravascular coagulation (DIC)
11-Hypersensitivity reaction
12- Anaphylactic reaction/shock
13- Thrombocytopenia
14- Neutropenia
15-Introduction of riluzole
16-The subject cannot attend two consecutive study visits and key safety assessment cannot be performed

If a subject discontinues the trial for safety reasons, a PK sample is to be taken (with the time of sampling after last dosing clearly documented) in those sites participating in the PK sub study.
In case a subject withdraws FBR consent, the blood samples taken for FBR will be destroyed (when not analysed yet).
The sponsor reserves the right to terminate the study at any time if continuation of the protocol would present a potential safety risk to the subjects.
Every effort will be made to ensure that patients who do not complete all study requirements return to the site for the End-of-Trial Visit. 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. The End-of-Trial Visit will be performed 7-14 days after withdrawal and the same procedures as Visit 8 will be performed.

6.6. Sample Handling

To minimise variability between centres in this multicentre study all clinical laboratory assays will be performed by a central laboratory (see details on Study Contacts Section). Blood samples are to be handled, shipped and stored according to the instructions provided by the laboratory. Laboratory kits, shipment material and a comprehensive laboratory manual will be provided to all sites.

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

Samples for future Biomedical Research of those patients providing consent, will be appropriately stored in the central laboratory facilities. Details will be included in the laboratory manual.

6.7. PK Samples

Blood Sampling FAB122

Blood sampling for FAB122 PK analysis will be done in ~90 subjects in selected sites. Of those ~30 subjects will participate in a PK profiling sampling schedule and the additional ~60 subjects will participate in a population PK sampling schedule, both at baseline, week 4 and week 48 (or Early Termination).

Sampling schedule for PK profiling: pre-dose and 15 min, 30 min, 1, 1.5, 2, 4 hrs., and 6hrs. after the FAB122 morning dose. The pre-dose sample may be collected within 30 minutes prior to dosing. 15 and 30 min post dosing samples should be taken within ±2 minutes of the scheduled time, the 1 hr. post dosing sample within ±5 minutes, the 1.5 and 2-hour sample within ±10 minutes and the 4 hr. and 6hr. sample within ±20 minutes of the scheduled time. The time of sampling will be accurately recorded.

Sampling schedule for population PK: (1) pre-dose (within 1 hour prior to dosing), (2) within 5- and 30-minutes post dosing, (3) 1 hour and (4) 1.5 hour after the second PK sample was taken. The time of sampling will be accurately recorded.

Patient should come fasted and will take the IMP dose in the clinic.

Patients participating in the PK profiling will not be allowed to eat until 4 hours post dose.

Blood Sampling Riluzole

Blood sampling for the determination of riluzole concentration will be done in the subjects included in FAB122 PK sampling in baseline and week 4 (~90 subjects) at (1) pre-dose (within 1 hour prior to dosing).(2) within 5- and 30-minutes post dosing, (3) 1 hour and (4) 1.5 hour after the second PK sample was taken. The time of sampling will be accurately recorded.

Patient should come fasted and will take the riluzole dose in the clinic, at the same time that the IMP dose.

Table 3: Overview of PK sampling

Baseline (V1)	Week 4 (V2)	Week 48 (V6)*	Early Termination**
30 subjects FAB122 PK profiling Riluzole PK*** pre-dose and 0.25, 0.5, 1, 1.5, 2, 4 hrs., and 6hrs after FAB122/riluzole morning dose	30 subjects FAB122 PK profiling Riluzole PK*** pre-dose and 0.25, 0.5, 1, 1.5, 2, 4 hrs., and 6hrs after FAB122/riluzole morning dose	30 subjects FAB122 PK profiling pre-dose and 0.25, 0.5, 1, 1.5, 2, 4 hrs., and 6hrs after FAB122 morning dose	30 subjects FAB122 PK profiling pre-dose and 0.25, 0.5, 1, 1.5, 2, 4 hrs., and 6hrs after FAB122 morning dose
60 subjects FAB122 PK population Riluzole PK pre-dose (within 1 hour prior to dosing), (2) within 5- and 30-minutes post dosing, and (3) 1 hour and (4) 1.5 hour after the second PK sample was taken	60 subjects FAB122 PK population Riluzole PK pre-dose (within 1 hour prior to dosing), (2) within 5- and 30-minutes post dosing, and (3) 1 hour and (4) 1.5 hour after the second PK sample was taken	60 subjects FAB122 PK population pre-dose (within 1 hour prior to dosing), (2) within 5- and 30-minutes post dosing, and (3) 1 hour and (4) 1.5h after the second PK sample was taken	60 subjects FAB122 PK population pre-dose (within 1 hour prior to dosing), (2) within 5- and 30-minutes post dosing, and (3) 1 hour and (4) 1.5h after the second PK sample was taken

*If feasible (if patients continue up to week 48)
**Only for patients included in the FAB122 profiling PK and FAB122 population PK and who discontinue treatment before week 48
***Riluzole will only be analyzed in pre-dose, 0.5, 1.5 and 2h samples.

PK Samples Handling

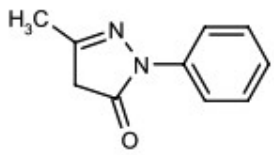
Plasma will be prepared from the blood samples and split into two aliquots (one for backup) for analysis of plasma concentrations of FAB122 and riluzole using a validated LC/MS/MS assay method. Instructions for handling, shipment and storing of the PK samples will be described in a separate study PK laboratory manual. Plasma concentrations will be measured using validated bioanalytical methods and according to the bioanalytical laboratory's Standard Operating Procedures (SOP). Qualitative/comparative assessments of metabolite profiles will be performed.

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 4:

Table 4: 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 or placebo 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 gastric gavage and feeding tube if applicable.

7.1.1. Packaging and Labelling

The label(s) for the investigational product and placebo 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. Blinding of IMP

Verum and placebo are identical and unrecognizable sachets by form size, weight, and colour, and will be indistinguishable to patients and investigators.

7.1.3. 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 complaint with treatment when 80%-120% of the total scheduled doses since the last clinic visit are administered.
All investigational products used in this study will be monitored for compliant usage throughout the trial by the sponsor or their designee.

7.1.4. 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 case of sanitary restrictions or if a patient cannot attend one study visit, following local regulation, IMP can be delivered directly to patient’s home, as per site internal procedure or through a validated direct to patient service provided by the sponsor. For more details, please refer to the IP Manual.

7.1.5. Concomitant Medication

The permitted concomitant medication for ALS patients' management (such as symptomatic treatment of muscle spasms, pain, insomnia, dysphagia and emotional instability) are listed in the Annex 3.

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.

7.1.6. Post-trial Treatment

Once patients have completed the study (max week 72) and if potential clinical benefit is achieved, patients could be enrolled in an open-label one group extension study and FAB122 will be given for all included patients.

7.2. Other Treatments (non-IMPS)

Riluzole (100 mg/day or less) may be used as background (add-on) therapy. Patients on riluzole should be on stable doses ≥30 days prior to the baseline visit and this dose should be maintained during the entire trial. It will not be allowed to initiate riluzole therapy during the trial.

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 on Screening, Baseline, and weeks 4, 12, 24, 36, 48, 60, and 72, as well on each phone call on weeks 8, 16, 20, 28, 32, 40, and 44. 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 during the 72 weeks of participation, 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 Screening, Baseline, and weeks, 12, 24, 36, 48, 60, and 72. 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. The assessments will be performed at Baseline and weeks 12, 24, 36, 48, 60, and 72.

8.1.5. Strength Test

Handheld dynamometry (HHD) is a procedure for quantitative strength testing. This testing will be conducted by the Investigator or any designee who has been properly trained for the quantitative muscle strength evaluation. When possible, it is highly recommended that

all assessments be performed by the same assessor. Muscle strength testing will be performed on prespecified muscles in the upper and lower extremities bilaterally and the force measurement recorded. HHD will be assessed at Baseline and weeks 12, 24, 36, 48, 60, and 72. The results of the HHD will be recorded in the eCRF by the investigator or designee.

8.1.6. 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 Baseline and weeks 24, 48, and 72 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 three 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 Baseline and weeks 12, 24,36, 48, 60 and 72 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.

8.1.7. 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 Baseline and weeks 24, 48, and 72. The total score of the questionnaire will be recorded in the eCRF.

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 screening visit. The BMI will be calculated.

Neurological examination will be performed by qualified personnel according to the Schedule of Events to assess 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 clinical laboratory tests conducted at the screening visit must be assessed by the investigator to determine each subject's eligibility for participation in the study. 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.

8.2.5. Nerve Conduction Study

The NCS protocol evaluates the sensory nerve action potential (SNAP) amplitudes using standard ring-electrodes and predefined sites for both stimulus (antidromic) and recording sites, including standardized distances that also apply for the inter-electrode distances. Hence, routine signal averaging for the recorded SNAP's will be performed after supramaximal stimulation. These measures will eliminate any unwanted variation due to instrumentational differences. For these recordings, limb temperature should be at 31^0C, otherwise warming may be considered or alternatively accepted correction factor for decreased temperature could be done. Sensory latencies and velocities are less robust parameters that may also depend on filter settings between different machines and, therefore, will not be used. NCS criteria for neuropathy are decreased sural nerve SNAP amplitudes or decreased sural/radial nerve amplitude ratio (SRAR).

NCS will include sensory recordings from sural nerves (unilateral) and sensory recordings from median, ulnar, radial nerves (unilateral) with standardized distances between recording and stimulation sites of 12cm. NCS data will be evaluated by neurophysiologists at the participating centres and also reviewed independently at the UMC Utrecht, taking into account reference values provided by participating sites, and using age adjusted reference values. Additional testing may be requested if required.
Instructions on operational aspects of the NCS are described in a separate NCS manual.

The main aim of NCS is to identify subclinical damage of sensory function before the potential development of a clinically significant neuropathy. The relevant expected clinical presentation of neuropathy is predominantly sensory and includes relative symmetric paraesthesia and/or numbness mainly in feet.

The DSMB will assess the results of the NCS, simultaneously with the assessment on vitamin B6, clinical signs, ALSFRS-R questions related to leg functioning (8. walking and 9. climbing stairs) for the first enrolled 60 patients (about 40 active and 20 placebo).
The NCS will be conducted for the first enrolled 60 patients at screening, and on weeks 4, 12, and 24. Then according to the evaluation by the DSMB, one of the following options will be performed:

- If no neurological concerns are observed, the study will continue with one additional NCS at week 48 for the first 60 patients. Then for the next enrolled patients, one NCS will be performed at screening and another one at week 48. Additional NCS(s) could be performed between screening and week 48 if any abnormality is detected by the neurological examination or any suggesting symptoms of neuropathy are reported by the patient.
- If NCS show signs of neurological damage, intensive NCS monitoring will continue for all patients at screening and on weeks 4, 12, 24, 36, 48, 60, and 72.

All NCS values will be recorded by the investigator in the eCRF at the corresponding time points.

8.3. Pharmacokinetic Assessments

Details of analyses methods of the pharmacokinetic, population PK, pharmacokinetic-pharmacodynamic modelling and pharmacokinetic interaction between FAB122 and riluzole as well as the software packages used will be described in a separate PK analysis plan that will be finalized before the database closure and the formal treatment code breaking.
The plasma concentration for FAB122 and riluzole will summarized over time. The primary pharmacokinetics parameters of interest derived of the plasma concentration of FAB12 and riluzole are: C_{max}, T_{max}, $t_{1/2}$, and AUC.

Pharmacokinetic parameters may include, but not be limited to (see table 5):

Table 5: Pharmacokinetic parameters of FAB122 and riluzole

Parameter	Definition
AUC_{last}	Area under the concentration-time curve from time 0 (time of drug administration) to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule
C_{max}	Maximum plasma concentration
T_{max}	Time of the maximum plasma concentration
C_{last}	Last quantifiable concentration
T_{last}	Time of the last quantifiable concentration
$T_{1/2}$	Time taken for C_{max} to drop in half
AUC_{inf}	Area under the concentration-time curve from time 0 to infinite

The pre-dose concentration may be extrapolated to the 24-hour time point to estimate AUCtau, Vss/F and CL/F.

8.3.1. Population and profiling PK Analysis

FAB122 plasma concentration-time data will be subjected to a population PK analysis using nonlinear mixed-effects modelling. Blood sampling for FAB122 PK analysis will be done in ~90 subjects. Of those ~30 subjects will participate in a PK profiling sampling schedule at baseline, week 4 and week 48 and a population PK sampling schedule at baseline, ~60 subjects participate in the population PK sampling schedule at baseline, week 4 and week 48. Plasma concentrations of all these PK samples may be included in the population PK analysis. For this analysis, the data may be combined with results of other studies. The aim of the population PK analysis is to develop a compartmental model of the FAB122 concentration vs. time profiles, which will provide a good understanding of the inter-subject and intra-subject (if possible) variability in the exposure. Available subject characteristics (such as demographics, laboratory variables and co-medication) will be tested as potential covariates affecting PK parameters.

It is estimated that about 90% of the patients included in this study will concomitantly receive riluzole treatment. Results from pharmacokinetic profiling and population PK analysis will therefore also be used to study the effect of riluzole on FAB122 concentrations and vice versa. Therefore, mean plasma PK parameters of subjects who received FAB122 and riluzole will be compared to those of subjects who received riluzole and placebo.

In addition, blood sampling for the determination of riluzole concentrations will be done in the subjects included in FAB122 PK sampling in baseline and week 4 (~60 subjects). Mean plasma Ctrough and Cmax levels of subjects who received riluzole and FAB122 at

baseline visit and after 4 weeks of treatment with FAB122, as well as changes in these metrics between baseline and week 4 will be compared to those of subjects who received riluzole and placebo. If needed and feasible, modelling will be applied to support statistical analysis methods.

8.3.2. Concentration-Response Relationship Analysis

The data may be subjected to PK-PD modelling including retrospective assessment of dose- and exposure-response correlations. An additional advantage of this approach is that it allows the data to be included in further modelling and simulation analyses characterizing the effects of FAB122 on disease progression and enabling the development of a predictive model framework to support dose justification (including in special subpopulations) and aid in the optimization of the design of future clinical studies.

In case PK-PD modelling will be performed, the details of the PK-PD modelling will be described in a separate PK analysis plan.

9. SAFETY REPORTING

Adverse events will be recorded (using MEDRA version 24.0) 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.

In this study, an external Data Safety Monitoring Board (DSMB) will be appointed to review all safety data generated during the study. For more details see section 13.2.1

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. In the same way planned hospitalizations for procedures which are related to the patient's disease, and are expected within the evolution of the ALS symptoms (i.e. PEG procedure; Mechanical ventilation set up) will not be considered as SAEs unless they are extraordinary and/or unexpected and/or of they meet other seriousness criteria.

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.

9.1.4. Adverse Event of Special Interest

AESI (serious or non-serious) is one of scientific and medical concern specific to the sponsor's product or program, for which ongoing monitoring and rapid communication by the investigator to the sponsor can be appropriate. Such an event might warrant further investigation in order to characterize and understand it. Depending on the nature of the event, rapid communication by the sponsor to other parties (e.g., regulators) might also be warranted.

For this study, any significant abnormalities detected in the NCS or any AE which might suggest neuropathy (e.g., numbness) should be considered an AESI and must be communicated appropriately to the sponsor and DSMB.

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 (ie, 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. 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. Unblinding

This study will be performed in a double-blind fashion. The randomization list will not be available to the investigator, study staff, subjects, sponsor, or monitor. The investigational drug and its matching placebo are indistinguishable and will be packaged in the same way. Treatment emergency codes should not be broken except in emergency situations i.e., in case of a medical emergency or in the case a SUSAR occurs, the investigator or the sponsor's Unblinding Manager, will break the patient's code, through interactive web response system (IWRS), and if possible, the sponsor should be contacted before the emergency code is opened.

The investigator should only unblind the treatment allocation in the course of a clinical trial if this is relevant to the safety of the subject.

As regards the sponsor, when an event may be a SUSAR the blind should be broken by the sponsor only for that specific subject. The blind should be maintained for persons responsible for the ongoing conduct of the study (such as the management, monitors, investigators) and those responsible for data analysis and interpretation of results at the conclusion of the study, such as biometrics personnel. Unblinded information should only be accessible to those who need to be involved in the safety reporting to national competent authorities, Ethics Committees and Data Safety Monitoring Boards (DSMB), or persons performing ongoing safety evaluations during the trial.

It should be noted that unblinding is not necessarily a reason for patient's discontinuation and the patient could continue the study treatment and procedures after unblinding. Furthermore, patient's death will not be considered a systematic reason for unblinding and will only be performed if deemed necessary or requested by the IEC and/or CA.

The Unblinding Manager contact details are:
Miriam Abril (Head of PV department, Pharmalex)
Tel:0034976204400
Email: clinical.trial@pharmalex.com

9.9. Pregnancy

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 and the patient should be withdrawn from the study. Early termination procedures should be implemented at that time.

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 5). The consented patients will complete the questionnaire at baseline and every 12 weeks 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 among study groups:

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 in each group.

An ad-hoc cost questionnaire will be completed at Baseline and weeks 12, 24,36, 48, 60 and 72 via a study App or online questionnaire.

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.

The plan for the pharmacokinetic analysis will be fully detailed in the pharmacokinetic analysis Plan (PAP) that will be finalized before data base closure.

All statistical analyses will be performed using SAS Version 9.4 or higher (SAS Institute, Cary, NC 27513).

11.2. Sample Size Determination

The sample size estimation is based on the primary endpoint: the change from baseline in ALSFRS-R score after 48 weeks. A difference of 3.0 points between FAB122 treatment arm and placebo is assumed with a (pooled) standard deviation of 7.5 and an allocation ratio of 2:1 (FAB122:Placebo). With these assumptions, a total sample size of 300 (200 patients on FAB122 and 100 on placebo) is needed to achieve 90% power to detect the difference of 3.0 points between the two treatment groups at a 5% (2-sided) level of significance.

The standard deviation of 7.5 is based on recent study results with edaravone using a similar trial population as applied in this trial, where standard deviations varied between 3.4 and 6.9 (The Writing Group on behalf of the Edaravone (MCI-186) ALS 19 Study Group. 2017 b, 2017;). The variability in this study can be expected to be somewhat higher due to the change of formulation and due to the fact that in this study patient can use riluzole as background therapy.

The hypothesis in this study includes detection of a difference of 3 points in ALSFRS-R at week 48 between the two treatment arms. The patients in the placebo group in ALS studies typically deteriorate by 1 point per month, so 12 points in 12 months. A difference of 3 points therefore corresponds to a 25% difference in deterioration, which is considered clinically significant.

11.3. Description of Statistical Methods

11.3.1. Analysis Populations

- Intent-to-treat (ITT) Analysis Set: The ITT analysis set will consist of all randomized subjects.

- Modified Intent-to-treat (mITT) Analysis Set: The mITT analysis set will consist of randomized subjects who receive at least 1 dose of investigational product (IP) regardless of any protocol deviation. The treatment arm will be the arm to which they were randomized, regardless of what treatment they received.

- Safety Analysis Set: The safety analysis set will consist of randomized subjects and who receive at least 1 dose of IP. Subjects will be analysed according to treatment received. This population will be used for baseline characteristics and for safety data summaries

- Per-protocol (PP) Analysis Set: The PP analysis set will consist of all mITT subjects who do not have major protocol deviations that may affect the primary efficacy endpoint. These deviations will be determined before the study database will be closed.

- The PK Population will consist of all subjects who received study drug and provided evaluable PK data.

Subjects who prematurely discontinue from the study will be included in the safety population but may be excluded from the PK analysis population unless sufficient data is provided for PK evaluation. Subjects who are included in the PK population but have missing data for a particular endpoint will not be included in the analysis for that endpoint. Unused data, measurements from excluded subjects, unscheduled collections, or extra measurements, will not be included in the summaries, but will be presented in the subject listings.

The primary analysis will be performed on the modified intent-to-treat population (mITTs), i.e. all randomized patients who had at least one treatment intake. The analysis of the primary endpoint will be also assessed with the PP and ITT populations as per sensitivity analysis.

11.3.2. Demographics, baseline characteristics

Demographics and medical history will be collected during Screening and summary of data will include date subject signed the informed consent. The subjects' age, height, weight, and baseline characteristics will be summarized by treatment using descriptive statistics, while gender, race and other categorical variables will be provided using frequency tabulations. Medical history data will be listed. Medical history data will include any prior reaction to drugs, use of alcohol and tobacco, history and treatment (if any) of cardiovascular, pulmonary, gastrointestinal, hepatic, renal, immunologic, neurologic, or psychiatric diseases, and confirmation of relevant inclusion criteria.

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 for

both treatment and follow-up phase. A summary of subjects screened and enrolled will be provided.

A subject is considered to complete the study if he/she completed the 72 week period OR if she/he completed at least 48 week at study completion (i.e. after the last subjects have completed the study up to at least 48 week). Withdrawal from treatment or protocol deviations will not necessarily preclude from recording the respective follow-up information. Efforts will be made to follow all subjects up to 72 or 48 weeks after start of treatment (or to study end if that occurs earlier) and collect data as planned.

11.3.4. Efficacy Analysis

11.3.4.1. Hierarchical multiple testing

A hierarchical multiple testing procedure will be used to evaluate superiority of the primary endpoint, followed by the evaluation of superiority of the key secondary endpoints. A fixed sequence stepwise multiple testing procedure at the 0.05 level will be performed in the following pre-specified hierarchical order:

I. Primary endpoint: change from baseline ALSFRS-R score after 48 weeks.

II. Key secondary endpoint: CAFS at 48 weeks

III. Key secondary endpoint: Survival time (death, tracheostomy or initiation of non-invasive ventilation for more than 20 hours a day for more than 10 consecutive days) over 72 weeks

Each step will be considered confirmatory if all previous steps were successful (i.e. if superiority was achieved). If any of the previous steps were unsuccessful, the subsequent steps are regarded as exploratory.

11.3.4.2. Primary Efficacy Endpoint

The primary endpoint is defined as the change from baseline in ALSFRS-R score after 48 weeks (primary time point).
For the primary analyses placebo (reference) multiple imputation will applied to impute missing data for any subjects (i.e. from both treatment arms) who discontinue treatment early, irrespective the reason for drop-out, and for which no data was collected after treatment discontinuation. A total of 20 imputed data sets will be created.
Linear mixed modelling for repeated measures will be applied on each of the imputed data set to estimate the average (lsmeans) treatment effects and the treatment difference (estimand) of the change from baseline of ALSFRS-S score at week 48.
The model will include factors for treatment, time, treatment-by-time interaction, and concomitant use of riluzole (yes/no) as fixed effects and baseline ALSFRS-R score and slope of disease progression (based on change in ALSFRS-R score) as (random) covariates.
The results of the 20 imputed data sets will be combined to obtain the final estimate of the treatment difference with 95% confidence interval an p-value.

The primary analysis will be performed on the modified intent-to-treat population (mITTs), i.e. all randomized patients who had at least one treatment intake

11.3.4.3. Secondary Efficacy Endpoints

Key secondary endpoints

- Combined assessment of function and survival (CAFS) at 48 and 72 weeks
- Survival time, i.e. time to death, tracheostomy or initiation of non-invasive ventilation for more than 20 hours a day for more than 10 consecutive days, over 72 weeks

The CAFS will be used as key secondary endpoint as it combines information on survival and ALSFRS-R scores. For this endpoint, each patient's outcome will be ranked: the worst patient outcomes will receive the lowest rank numbers such that a higher CAFS score indicates a better outcome. The deceased cases will receive the lowest rank numbers followed by the level of decreases in ALSFRS-R scores. Descriptive statistics for this endpoint will be made but are difficult to interpret as mean values depend on the size of the study. In this study, with 300 patients the CAFS scores range from 1 to 300 with a total sum of 28,920 and an overall mean value of 120.5. The difference between treatments will be assessed using an ANCOVA model with the same covariates as the primary efficacy analysis. A rank-ANOVA will be used as a sensitivity analysis. Subsequent component analyses of function and survival will be used to determine which parameter(s) drive the overall effect on the CAFS results. The direction and magnitude of the function and survival components of the CAFS will inform the interpretation of the results.

'Survival', i.e. time to death, tracheostomy or initiation of non-invasive ventilation for more than 20 hours a day for more than 10 consecutive days, over 72 weeks Descriptive statistics (median and 25% and 75% quartiles with 95% confidence intervals) and Kaplan-Meier curves will be provided. The difference between oral FAB122 and placebo will be assessed using restricted mean survival time (RMST) analysis up to week 48 (and week 72), controlling for the stratification variables. In addition, also a Cox regression model and a stratified log-rank test will also be applied as sensitivity analysis, including factors for treatment and stratification variables.

Other secondary endpoints

The following exploratory secondary endpoints will also be summarized, as applicable: Continuous endpoints will be summarized by descriptive statistics (mean, median, standard deviation, minimum and maximum), but can also be summarized with frequency count and percentage for appropriated categories. These will be defined in the SAP. Binary or categorical endpoints will be summarized with frequency counts and percentages. Time to event endpoints will be summarized by median values with 95% confidence intervals. The statistical method that will be applied for each endpoint will be detailed in the SAP.

- Change from baseline in ALSFRS-R score after 24 and 72* weeks;
- The slope of the decrease in ALSFRS-R score over time at 24, 48 and 72* weeks;

- Change from baseline in ALSFRS-R score on Bulbar function (question 1-3 of the ALSFRS-R) after 24, 48 and 72* weeks;
- Change from baseline in ALSFRS-R score on Fine motor function (question 4-6 of the ALSFRS-R) after 24, 48 and 72* weeks;
- Change from baseline in ALSFRS-R score on Gross motor function (question 7-9 of the ALSFRS-R) after 24, 48 and 72* weeks;
- Change from baseline in ALSFRS-R score on Respiratory function (question 10-12 of the ALSFRS-R) after 24, 48 and 72* weeks;
- Time to a 3, 6, 9 and 12 points change or death from baseline in ALSFRS-R score over 72* weeks;
- Proportion of subjects with change from baseline in ALSFRS-R score at 24, 48 and 72* weeks in categories: categories will include change ≥0, change between <0 and ≥-1, change between <-1 and ≥-2 etc.;
- Time to change in clinical staging or death (King's staging system and MiToS) over 72* weeks;
- Overall survival: Proportion of subjects alive (survival rate) after 24, 48 and 72* weeks;
- Proportion of subjects alive and no tracheostomy, or no initiation of non-invasive ventilation for more than 20 hours a day for more than 10 consecutive days after 24, 48 and 72* weeks;
- Change from baseline in slow vital capacity (SVC, liters) at 24, 48 and 72* weeks;
- Change from baseline in the overall mega score for the hand-held dynamometer (HHD) at 24, 48 and 72* weeks.

QoL

- Change from baseline in the total score on the ALS Assessment Questionnaire-40-Item (ALSAQ-40) Form at 24, 48 and 72* weeks;
- Change from baseline in EuroQoL – 5 Dimensions-5 Levels (EQ-5D-5L) questionnaire score 24, 48 and 72* weeks.
- Change from baseline in Health related QoL Visual Analogue Scale (VAS) score at 24, 48 and 72* weeks.

Cognition

- Proportion of subjects with a change of ≥8, ≥4, and ≥9 for ALS Specific, ALS Non-Specific, and ECAS (Edinburgh Cognitive and behavioural ALS Screen) total score;
- Change form baseline for ALS specific and ALS non specific, and ECAS total score at 24, 48 and 72* weeks.
- Time to a mean change of ≥8, ≥4, and ≥9 for ALS Specific, ALS Non-Specific, and ECAS total score.

*All secondary endpoints at 72 weeks will be analyzed for the subgroup of patients that reach 72 weeks (or IE).

11.3.4.4. Additional analysis

As an additional analysis, the joint assessment of change in functional decline and overall mortality using a joint modelling (i.e. shared-parameter) framework over 72 weeks will be determined. The statistical model will combine ALSFRS-R score and survival, using a linear mixed model and a Cox model as sub models combined into a non-linear mixed model using the SAS procedure PROC NLMIXED.

11.3.5. PK Analysis

Refer to the PAP for full analysis details. Differences between scheduled and actual PK sampling times will be listed for all subjects. All statistical summaries and displays will be based on scheduled sampling times unless there are significant deviations of actual sampling times from scheduled sampling times.

Concentration-time data and PK parameters will be summarized by treatment group with summary statistics at each scheduled time point, where applicable. Summary statistics will include: Number (N), mean, standard deviation (SD), coefficient of variation (%CV), median, minimum (min), maximum (max). In addition, geometric mean and CV% geometric mean will be presented for C_{max} and AUC_{last}.

Each subject's exposure to study drug will be summarized using descriptive statistics, as described in detail in the PAP.

11.3.6. 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.

11.3.6.1. 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.

11.3.6.2. 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).

11.3.6.3. Concomitant Medication

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

11.3.6.4. 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.

11.3.6.5. ECG

From the 12-lead ECG data, HR, PR, 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.

11.3.6.6. Vital Signs

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

11.4. Study Estimand and Handling of Missing Data

To be noted that in this study all efforts will be made to ensure collection of data up to week 48 for all randomized subjects and at least for 100 subjects up to week 72 regardless of treatment withdrawal or protocol deviations.

As per the ICH E9(R1) (*draft addendum on estimands and sensitivity analysis in clinical trials*), the plan for the assessment of the Primary endpoint (PEP) is described here after using the 4 attributes of the estimand:

1. Population: ALS patients fulfilling the selection criteria, as described in section 5 of this protocol

2. Primary endpoint (PEP): Change from baseline in Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised (ALSFRS-R) score after 48 weeks (see sections 3.2.1 and 11.3.4.1)

3. Intercurrent events (IE): The assumptions and expectations on the relevant intercurrent for this study have been based on the publication of a similar trial (Cudkowicz et al., 2013)

4. Accordingly, the following situations have been identified:

    a. No treatment initiation with the IMP: exclusion from the main analysis with the mFAS population.
    b. Treatment discontinuation because of adverse events: expected rates ≈3 (control arm) - 7% (experimental arm).
    c. Treatment discontinuation because of lack of efficacy: expected rates ≈5 (control arm) 10% (experimental arm).
    d. Other treatment related reasons (i.e. due to efficacy or safety issues). To this category will apply other treatment related reasons that those specified in “b” and “c”, even that, *a priori*, no potential scenarios are foreseen at the moment of the planning.
    e. Rescue medication. No clear prevalence rates can be ascertained, but differential higher rates are expected in placebo. This situation is likely to be closely related to IE #c.
    f. Non treatment-related reasons, others than specified in this list of IE: very low expected rates (i.e. ≤1%). This will also situations like patients moving (not because bad prognosis) to another location or death for completely treatment-unrelated reasons.
    g. Related death (or death with unknown reasons): it is expected that the rate of death at 52 weeks will be lower than the observed in that trial (<17%). A non-substantial but lower rate is expected in the experimental arm.

The primary strategy for handling the IE will consist of the “Treatment Policy” strategy applied for all these intercurrent events, i.e., the efficacy observed assessment will be used regardless of the intercurrent event. Therefore, overall the amount of missing data generated will be a very small. For these cases a placebo (copy from reference) multiple imputation will applied. A total of 20 imputed data sets will be created.

However, it is noted that the “Treatment Policy” strategy will not be applicable for terminal intercurrent events such as death (IE #g) or when there are real lost to follow-up cases after doing all efforts to retrieve the data (some cases in IE #f). For cases with missing data in IE #f, the same general approach as described above will be implemented. For related death (IE #g) it is proposed to use a “Composite strategy” and thus a conservative scenario using a 95th worst percentile combined with multiple to avoid variance artefactual shrinking.

h. Population-level summary: the change from baseline in ALSFRS-R score after 48 weeks (primary time point), using a linear mixed modelling for repeated measures. The model will include factors for treatment, time, treatment-by-time interaction, and concomitant use of riluzole (yes/no) as fixed effects and baseline ALSFRS-R score and slope of disease progression (based on change in ALSFRS-R score) as (random) covariates (see section 11.3.4.1)).

To evaluate the impact of missing data and of the handling methods, a number of sensitivity analyses will be performed for the primary endpoint:

- **As treatment multiple imputation**: For any subject with missing values, the estimates for the missing assessments will be based on the actual treatment group of that subject. One hundred imputations will be performed.
- **Tipping-poin**t analysis: The tipping point is defined as the difference in the change from baseline in ALSFRS-R score at week 48 between FAB122 and placebo at which the study conclusion (i.e. the statistical significance) changes. To find this tipping point a systematic shift will be applied to the (as-treated) imputed values (i.e. a MNAR adjustments in the multiple imputation process) in the FAB122 treatment arm. These shifts will cover a large enough range, in steps of 0.2 to find the value for which the analyses shows a change of in significance of the primary hypothesis test, the tipping point. For each shift the primary analysis method will be repeated on the 20 multiple imputed data sets. In case such a tipping point has an unrealistic value, this will increase the confidence of the primary analysis.
- **Hybrid approach**: With the hybrid approach the missing weeks for subjects who discontinued due to AE or lack of efficacy will be imputed using placebo-based pattern imputation under the MNAR assumption. . All other discontinuation/missing will be imputed using multiple imputation by treatment group using a multivariate step-wise approach using a fully conditional specification (FCS) regression method (Rubin, 1987). Missing baseline values if any, will be imputed using age and time since diagnose. Subsequent visits will be imputed using data of all previous weeks in a stepwise fashion. One hundred imputations will be performed.
- **Completer analysis**: This analysis includes only subjects who have completed the study up to week 48.
- **Per Protocol and ITT Analysis:** This analysis will include subjects from the PP and the ITT analysis sets.

11.5. Health Economics Analysis

Descriptive statistical methods will be used to evaluate health economics parameters. A more detailed approach will be described in the SAP.

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 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.

12.2.1. Remote Source Data Verification

Remote source data verification (SDV) may be applied during the public health crisis related to COVID-19, following the recommendation on “Guidance on the Management of clinical trials during the Covid-19 Pandemic”. Remote SDV will focus on the quality control of critical data such as primary efficacy data and important safety data. Important secondary efficacy data may be monitored simultaneously if these are captured on the same documents. The data to be checked via remote SDV will be documented in the monitoring plan.

When the situation allows and the COVID-19 outbreak has passed, full (re-)monitoring will be performed on-site.

Remote SDV will be performed through:

• Sharing pseudonymised copies of trial related source documents with the monitor;

• Video review of medical records with clinical site team support, without sending any copy to the monitor and without the monitor recording images during the review;

• Direct, suitably controlled remote access to the subjects’ electronic medical records.

During remote SDV adequate data protection will be ensured, including data security and protection of personal data even if pseudonymised. The principal investigator (PI)/PI’s institution and the sponsor will be jointly responsible as controllers for ensuring information is safeguarded. The following controls will be implemented:

• Site staff will inform each subject and ensure that they do not object to the remote review of their records for trial purposes. This process will be documented in the subject’s medical records.

• Remote SDV of subjects’ medical records will take place from a (remote) monitoring location within the European Union (EU)/European Economic Area (EEA). In case the data are processed outside the European Union (EU)/European Economic Area (EEA), it will be contractually ensured that a level of data protection will be applied that is essentially equivalent to EU data protection legislation.

• Performance of remote SDV will only occur in locations that prevent viewing by any unauthorised person, through a secure internet connection and on a computer appropriately protected against unauthorised access to the data.

• Monitors will sign a written confidentiality agreement committing to securely destroy any copy of redacted documents, whether paper or electronic, as soon as they have been used for SDV and committing not to make any copy (or recording in the case of video access) of any non-pseudonymised document.

If the agreed remote SDV process involves redaction by the site staff (pseudonymisation) of source records:

- The monitor will provide a written request to the site for the subject's specific trial records required for SDV;

- Site staff will create copies of the requested subject's records, redact the copies (i.e., pseudonymise and mask any unnecessary private information unrelated to the trial), identify them with the subject identification code, have a second person perform and document a quality control to ensure that all identifying information has been redacted and is no longer readable, and make the pseudonymised copies available to the monitor using a secure mechanism. The redacted copies will be kept in the investigator's site master file with records of their communication to the monitor;

- The monitor will access the records securely, complete the monitoring task, securely destroy any copy made locally.

- Once on-site monitoring visits are again feasible, the monitor will verify that the provided pseudonymised (coded) data are indeed data related to the subject with the provided code.

If the agreed remote SDV process involves a video review of records:

- It will be assured that the quality of the video adequately enables reading;

- No videoconferencing solutions will be used where data may be captured on third country servers;

- The transmission of the data will be adequately protected against unauthorised third party access.

If the agreed remote SDV process involves the site providing the monitor remote access to the site electronic medical record (EMR) system:

- The monitor will be provided with a secure, read-only access to the EMR system, including all modules relevant for review. This access will be restricted to the records of only those patients who participate in the trial and who did not object against remote access to their medical records. Access rights will be revoked once remote SDV tasks have been completed;

- A list of the monitors to whom remote access has been granted will be maintained;

- The EMR system will have an audit trail and be able to log information on who accessed data and when;

- Remote access to the EMR will only be possible using a two-factor authentication.

Measures will be taken to prohibit making local copies of subjects' health records. Any automatically created temporary files on the monitor's computer when reviewing subject data, will be securely deleted immediately after each SDV session.

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 CRFs
- 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 CRFs, 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.

13.2. Study committees

13.2.1. Data Safety Monitoring Committee

An independent data safety monitoring board (DSMB) will oversee the safety aspects of this study. The DSMB will include a neurologist with expertise in ALS, neurophysiologist with expertise in ALS, and a biostatistician. The DSMB will periodically examine the safety data emerging from the study and provide its recommendations to the sponsor who will then pass these to IEC and CA, if applicable. The roles and responsibilities of the DSMB, their operational procedures, and method of communication with the sponsor will be described in a separate DSMB charter. Members of DSMB will not be investigators in the study nor will they have any conflict of interest with the study's investigators.

The study may be prematurely suspended or terminated if, in the opinion of the DSMB, there is reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party. The pertinent regulatory authorities will be informed according to the national regulations.

Circumstances that may warrant termination include:

- Determination of unexpected, significant, or unacceptable risk to patients.
- Insufficient adherence to protocol requirement
- Data that are not sufficiently complete and/or evaluable.
- Plans to modify, suspend, or discontinue the development of the FAB122.

If the study is prematurely terminated or suspended, the CRO will promptly inform the site-specific PIs, their institutions, IEC, and the regulatory authority of the termination or suspension and the reason(s) for the termination or suspension.

The schedule of the DSMB meetings and the safety aspects which will be analised will be detailed in the DSMB charter.

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 consent includes information that data will be recorded, collected processed and may be transferred (to EU and non-EU countries). 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.

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

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 CRFs, 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. 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, El Escorial Criteria

Categories of clinical diagnostic certainty on clinical criteria alone

Definite ALS

UMN signs and LMN signs in 3 body regions

Probable ALS

UMN signs and LMN signs in 2 regions with at least some UMN signs rostral to LMN signs

Probable ALS – Laboratory supported

UMN signs in 1 or more regions and LMN signs defined by EMG in at least 2 regions

Possible ALS

UMN signs and LMN signs in 1 region (together), or

UMN signs in 2 or more regions

UMN and LMN signs in 2 regions with no UMN signs rostral to LMN signs

UMN signs: clonus, Babinski sign, absent abdominal skin reflexes, hypertonia, loss of dexterity.
LMN signs: atrophy, weakness. If only fasciculation: search with EMG for active denervation.
Regions reflect neuronal pools: bulbar, cervical, thoracic and lumbosacral.

Principles (from the Airlie House criteria)
The diagnosis of amyotrophic lateral sclerosis [ALS] requires
the presence of

- evidence of *lower motor neuron (LMN) degeneration* by clinical, electrophysiological or neuropathological examination
- evidence of *upper motor neuron (UMN) degeneration* by clinical examination; *and*
- *progressive spread of symptoms or signs* within a region or to other regions, as determined by history, physical examination, or electrophysiological tests

the absence of

- *electrophysiological or pathological evidence of other disease processes* that might explain the signs of LMN and/or UMN degeneration, and
- *neuroimaging evidence of other disease processes* that might explain the observed clinical and electrophysiological signs

Diagnostic categories *Clinically definite ALS* is defined by *clinical or electrophysiological* evidence by the presence of LMN as well as UMN signs in the bulbar region and at least two spinal regions or the presence of LMN and UMN signs in three spinal regions *Clinically probable ALS* is defined on *clinical or electrophysiological* evidence by LMN and UMN signs in at least two regions with some UMN signs necessarily rostral to (above) the LMN signs *Clinically possible ALS* is defined when *clinical or electrophysiological* signs of UMN and LMN dysfunction are found in only one region; or UMN signs are found alone in two or more regions; or LMN signs are found rostral to UMN signs. Neuroimaging and clinical laboratory studies will have been performed and other diagnoses must have been excluded.

Annex 2, 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 1 Provides minimal assistance to caregiver 0 Unable to perform any aspect of task	**12. Respiratory insufficiency** 4 None 3 Intermittent use of BiPAP 2 Continuous use of BiPAP 1 Continuous use of BiPAP during day and night 0 Invasive mechanical ventilation by intubation or tracheostomy
6. Dressing and hygiene 4 Normal function 3 Independent; cancomplete self-care with effort or decreased efficiency	

2 Intermittent assistance or substitute methods 1 Needs attendant for self-care 0 Total dependence

Annex 3, Treatment options for ALS

Treatment	Administration	Indication
Riluzole	50 mg BID	ALS
Multidisciplinary care	Every three monthly visits	All symptoms of ALS
Non-invasive ventilation	Night time and during symptoms as needed	Respiratory insufficiency
Gastrostomy	Daily calorie supplements	Dyshagia and malnutrition
Dextromethorphan/quinidine	20 mg/10 mg BID	Pseudobulbar affect
Amitriptyline	12.5 - 125 mg OD	
SSRI antidepressants	10 - 100 mg OD	
Mirtazapine	15 - 30 mg OD	Anxiety
Buspirone	10 mg TID	
Diazepam	2 - 10 mg TID	
Lorazepam	0.5 -2 mg TID	
Diazepam	2 - 10 mg tid	
Phenytoin	100 - 300 mg OD	Cramps
Vitamin E	400 IU TID	
Mirtazapine	15 - 30 mg OD	
SSRI antidepressants	20 - 100 mg OD	Depression
Tricyclic antidepressants	12.5 - 150 mg OD	
Venlafaxine	37.5 - 75 mg OD	
Amantadine	100 mg BID	
Buproprion SR	150 - 450 mg OD	
Fluoxetine	20 - 80 mg OD	Fatigue
Pemoline	18.75 - 93.75 mg OD	
Pyridostigmine	60 mg TID	
Venlafaxine	75 - 225 mg OD	
Amitriptyline	12,5-125 mg qhs	
Atropine sulphate	0.4 mg q4-6h 1-2 / Ophthalmic drops SL q4-6h	
Diphenhydramine	25 -50 mg TID	Sialorrhea
Hyoscyamine sulphate	0.125 - 0.25 mg q4h	
Scopolamine transdermal patch	0.5 mg q72h	
Baclofen	10 - 60 mg TID	
Benzodiazepines	2 -10 mg TID	Spasticity
Dantrolene	25 - 100 mg TID	
Tizanidine	2 -8 mg TID	

Annex 4, COVID-19 impact mitigation Plan

The details of potential COVID-19 impact on the study's procedures and activities will be provided in the Risk Management Plan of the study and other applicable study plans (i.e: monitoring plan).

Screening and Baseline assessment will always be done in clinic by the study physician and nurse. Every effort should be made to perform these visits, depending on local regulations. The contingency would only be applicable for the randomized/ongoing subjects.

In case of sanitary restrictions, the following assessment might be performed at patient's home by the site study team personnel or by a validated Home Nursing services provider, provided by the sponsor.

	COVID-19 situation							
	Assessment to be performed by nurse at patient's home	**V2 D28 W4 ±3D**	**V3 D84 W12 ±3D**	**V4 D182 W24 ±7D**	**V5 D252 W36 ±7D**	**V6 D336 W48 ±7D**	**V7 D420 W60 ±7D**	**V8 D504 W72 OR EoT**
Weight	**YES**			X		X		X
Height	**YES**							
Vital Signs	**YES**	X	X	X	X	X	X	X
12-lead ECG	**YES (optional)**			X		X		X
(S)AE monitoring	**YES**	X	X	X	X	X	X	X
Laboratory procedures								
Chemistry/ Haematology	**YES**	X	X	X	X	X	X	X
Vitamin B6 monitoring	**YES**	X	X	X	X	X	X	X
Urinalysis	**YES**	X	X	X	X	X	X	X
β-hCG	**YES**							
Urine Pregnancy Test	**YES**		X	X	X	X	X	X
ALS evaluation procedures								
SVC	**YES (reduced)**			X		X		X
ALSAQ-40	**YES**			X		X		X
EQ-5D-5L	**YES**		X	X	X	X	X	X

The following assessments will be done by phone by the site study team personnel:

	COVID-19 situation							
		V2 D28 W4 ±3D	**V3 D84 W12 ±3D**	**V4 D182 W24 ±7D**	**V5 D252 W36 ±7D**	**V6 D336 W48 ±7D**	**V7 D420 W60 ±7D**	**V8 D504 W72 OR EoT**
ALS evaluation procedures								
ALSFRS-R	**YES**	X	X	X	X	X	X	X
ECAS	**YES**			X		X		X

For safety reasons, every effort should be made in order to perform NCS assessment in clinic, depending on local regulations. The sponsor will provide all the necessary measures, according to local regulations, to facilitate the performance of this testing.

Annex 5: 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 every 12 weeks. 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 1, 3, 4, 5, 6, 7 and 8 (every 12 weeks).

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 12 weeks.

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,
ADORE Trial Group

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

CLINICAL VISITS & HOSPITALISATIONS		
1. During the last 12 weeks, 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 …… 2 No…… …… 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 12 weeks	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 12 weeks, 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 12 weeks, 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 12 weeks, 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…… 1 No…… 2 If you have checked "Yes" please complete the subsequent table D. If you have checked "No" please move on to question number 5.	

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 12 weeks, 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 □ Special bedding □ Special mattresses □ Dehumidifier □ Medical lift □ Other _____ □ Other _____	□ 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	_____ _____ _____ _____ _____ _____ _____ _____	_____ _____ _____ _____ _____ _____ _____ _____
□ Books □ Videos □ Other _____	□ Yes □ No □ N/A □ Yes □ No □ N/A □ 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 _____ 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 12 weeks, 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 12 weeks, 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…… No…… If you have checked “Yes” please complete the subsequent table G. If you have checked “No” please move on to question number 9.	1 2

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…… No……	1 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 12 weeks, is it the same employment that you had before your illness?	Yes…… No……	1 2
11. During the last 12 weeks, 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 12 weeks, 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 12 weeks 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.