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

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

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Neuromuscular disorders
Study type	Interventional

Summary

ID

NL-OMON54334

Source
ToetsingOnline

Brief title
ADORE

Condition

- Neuromuscular disorders

Synonym
Disease of nerve cells that control muscles, Neurodegenerative syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Ferrer Internacional, S.A.
Source(s) of monetary or material Support: Ferrer International

Intervention

Keyword: ALS (Amyotrophic Lateral Sclerosis), Deceleration, Edaravone, Oral

Outcome measures

Primary outcome

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

Secondary outcome

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 of treatment;

2. The slope of the decrease in ALSFRS-R score over time at 24, 48and 72 weeks of treatment;

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, 48and 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, 48and 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, 48and 72 weeks of treatment 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, 48and 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, 48and 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, 48and 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 of treatment.

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

Study description

Background summary

ALS is a very serious and fatal condition characterized by progressive degeneration of the upper and lower motor neurons.
Clinically ALS is characterized by muscle weakness and functional decline.
There are limited pharmacological options in the treatment of ALS, and they focus mainly on symptomatic treatment. The only existing authorized medicine for treating ALS in the European Union is Riluzole.

Results from previous phase II and Ill clinical studies in ALS patients administered IV FAB122 (edaravone) demonstrated the potential of edaravone for the treatment of ALS. The data from these studies led to the approval of IV-administered edaravone for the inhibition of ALS disease progression in Japan, the US, Canada and Switzerland. However, chronic IV administration has significant drawbacks, including the risk of both local and systemic side effects. The involvement of medical staff at home or the daily presence in the hospital for administration also complicates compliance with the medicine. In addition, during the necessary treatment holidays of 14 days per month, no exposure to the drug is obtained.

These drawbacks can be overcome by administration of the oral FAB 122 formulation as proposed in this study, and given the exposure-based efficacy of edaravone, a longer-term exposure profile may further enhance edaravone's efficacy in ALS. This can be achieved by once daily dosing of orally administered FAB122 without a drug break. This study is expected to benefit the ALS patient population, in general, as well as the patients participating in this study.

Study objective

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

Study design

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

Double-blind treatment is planned to continue for all subjects until the last randomized subject has reached at least 48 weeks of treatment AND at least one third of the subjects has reached 72 weeks of treatment. The maximum treatment duration for a subject in this study is 72 weeks

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.

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.

Intervention

Patients will take study medication daily for the entire duration of the study, from day 1 up to a maximum of 72 weeks. It concerns a
fasting daily dose of 100 mg of FAB 122 granules for oral solution in a few sachets, which must be dissolved in 100 ml of water
before administration, or matching placebo in a ratio of 2: 1, respectively.

Study burden and risks

Advantages
It is possible that the study drug will slow the development of ALS, but it is also possible that the development of ALS will continue despite use of this drug. It may be that participating in this study will not provide any benefit to your health. But with your participation, you will help researchers gain a better understanding of how to treat ALS.

Disadvantages
Disadvantages of participation in the study may be:
- possible side effects of the study drug.
- possible adverse effects/discomforts of the tests and procedures applied in the study.
- taking medication according to study procedures.

Participation in the study also means:
- That you have to invest time in participation in the study
- That you have to attend (additional) clinic visits, undergo testing, and be available for telephone calls.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion 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. Slow Vital Capacity (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 >=3months, 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. Capable of providing informed consent and complying with trial procedures.

Exclusion 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 visit
c. Significant cognitive impairment, clinical dementia or psychiatric illness
d. 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.

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	10-01-2022
Enrollment:	25
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	not applicable
Generic name:	Edaravone

Ethics review

Approved WMO Date:	27-10-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	15-12-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	18-08-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-10-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	12-12-2022
Application type:	Amendment
Review commission:	METC NedMec

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2020-003376-40-NL
CCMO	NL79225.041.21