DESIGN OF AN INTERNATIONAL, PHASE 3, RANDOMIZED, PLACEBO-CONTROLLED TRIAL WITH DAILY ORAL EDARAVONE (FNP122) IN ALS: THE ADORE STUDY

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Effective treatment of ALS continues to be a significant unmet need

Distinguishing pathogenic features of neurodegenerative diseases include high reactive oxygen species (ROS) levels and mitochondrial dysfunction.

Edaravone's potential in the treatment of ALS

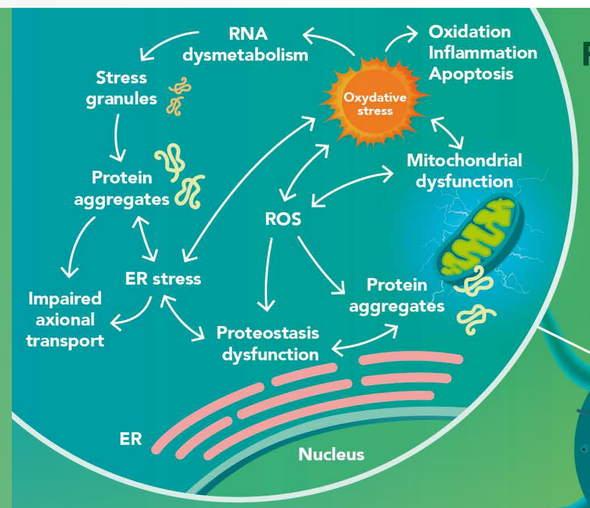
Supported by one randomized, double-blind, placebo-controlled Phase III study in Japanese patients with ALS after an intermitent use of intravenous 60 mg edaravone vs. placebo during 24 weeks.
This resulted in approval intermitent cycles use of intravenous edaravone for the inhibition of progression of functional disorder in ALS in some countries (US, JP, etc.), but not in EU.
Based on the initial results, **FNP122 is a newly developed oral liquid formulation of edaravone to be self-administered daily that is going to be assessed in a randomized double-blind placebo-controlled trial with efficacy and safety endpoints at 48 and 72 weeks.**

Edaravone plays an important role in ALS' pathogenesis and disease progression

- Antioxidant
- Anti-apoptosis
- Anti-inflammation

- Free radical scavenger
- Protects motor neurons from oxidative stress
- Reduces death of neuronal cells
- Modulates mitochondrial function

Proposed mechanism of action



Adapted from Carrì MT, et al. (2015) & Van Damme P, et al. (2017).

Objetive

The objective is to describe the design of a Phase 3 trial, assessing the safety and the efficacy on disease progression and survival of once-daily oral edaravone in patients with ALS

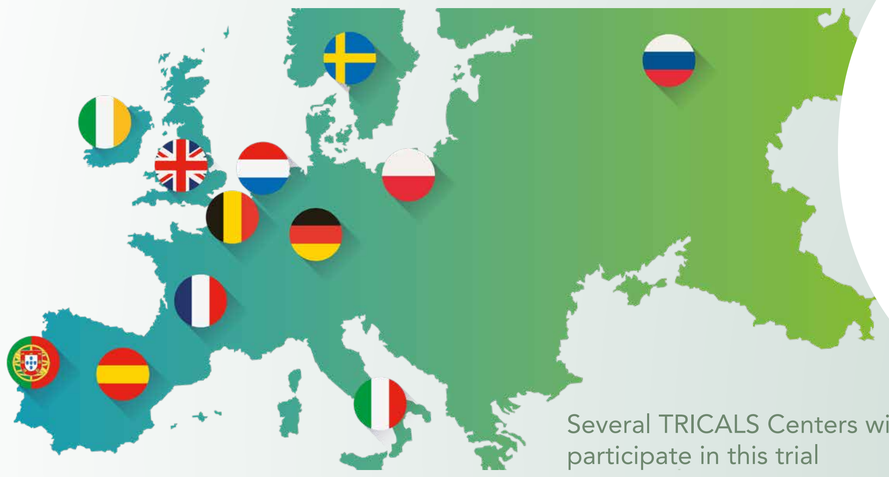
- Multicenter
- Multinational
- Double-blind
- Randomized
- Placebo-controlled

300 PATIENTS - 2:1

FNP122 (oral edaravone) : Placebo

Patients will receive double-blind treatment up to a maximum of 72 weeks

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



Several TRICALS Centers will participate in this trial

The ADORE study aims to randomize 300 ALS patients to 100 mg daily oral formulation of edaravone (granules for oral solution in sachet) or matched placebo in a 2:1 ratio

Patients will be stratified by:

- ALS progression rate at the start of the study (**slope ALSFRS-R score <1.0 vs. ≥1.0** from time of first symptoms till screening)
- Additional co-medication for ALS (**riluzole vs. no riluzole**)

OLE Study: ADOREXT

- All ADORE patients will be offered the possibility to roll over in an open label extension in which all patients will receive daily oral edaravone

Study visits • Enrolment started on October 2021

Main inclusion criteria

- Age 18 – 80 years (both inclusive), male or female
- **Onset of first symptoms ≤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
- Providing informed consent and complying with trial procedures
- **Definite, probable, probably laboratory supported or possible ALS** (based on the El Escorial and the revised Airlie House diagnostic criteria)
- **Slow Vital Capacity (SVC) ≥70%**, of the predicted normal value for gender, height and age at screening visit
- **Change in (ALSFRS-R) score between 0.35 and 1.5 points per month** (both inclusive) in the period between first symptoms and the screening visit

Main exclusion criteria

- Diagnosis of Primary Lateral Sclerosis
- Diagnosis of Frontotemporal Dementia
- Diagnosis of other neurodegenerative diseases (e.g. Parkinson disease, Alzheimer disease)
- Diagnosis of polyneuropathy
- Other causes of neuromuscular weakness
- Have a significant pulmonary disorder not attributed to ALS and/or require treatment interfering with the evaluation of ALS on respiratory function
- Depend on mechanical ventilation
- Renal impairment, clinically significant hepatic disease or other cliniclally significat disease

Enrolment Ongoing

This study is currently recruiting patients across Europe. Enrolment started in October 2021

Primary efficacy endpoint

- **Change from baseline in ALSFRS-R total score after 48 w**

Secondary efficacy endpoints

- Function and survival · CAFS at 48 and 72 w
- Survival time · Over 72 w
- Pulmonary function · Change from baseline in SVC
- Muscle strength · Change from baseline in HHD score
- QoL · Change from baseline in ALSAQ-40 and EQ-5D-5L scores
- Cognition · Change from baseline in ECAS score

Safety endpoints

- Treatment Emergent Adverse Events
- Parameters derived from vital signs and 12-lead electrocardiogram (ECG)
- Parameters derived from laboratory tests (hematology, biochemistry, urinalysis)

Exploratory endpoints

- ALS biomarkers

Conclusions

The ADORE trial is an ongoing phase 3 study designed to compare active treatment vs. placebo for a longer duration (up to 72 w of treatment) in patients with ALS.
The results will provide relevant safety and efficacy data on this new oral daily formulation of edaravone (FNP122)

- ✔ Robust trial design: In line with EMA's ALS guideline
- ✔ Large phase 3 study (300 patients)
- ✔ New daily oral formulation of edaravone (FNP122)
- ✔ Active treatment vs. placebo
- ✔ Low burden of study visit schedules
- ✔ Sensitive and reliable outcome measures
- ✔ Longer term efficacy & safety (up to 72 w of treatment vs. placebo)
- ✔ The sponsor is offering to all patients continuation of the FNP122 after the end of the study (ADOREXT)

TRICALS: Treatment Research Initiative to Cure ALS; CAFS: Combined assessment of function and survival; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; SVC: slow vital capacity; HHD: hand-held dynamometer

REFERENCES: A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Investigate the Efficacy and Safety of FAB122 in Patients With Amyotrophic Lateral Sclerosis (ADORE). ClinicalTrials.gov [Internet]. January 5, 2022. Accessed April 07, 2022. https://clinicaltrials.gov/ct2/show/NCT05178810; Cha SJ, Kim K. Effects of the Edaravone, a Drug Approved for the Treatment of Amyotrophic Lateral Sclerosis, on Mitochondrial Function and Neuroprotection. Antioxidants (Basel). 2022;11(2):195; Cho H, Shukla S. Role of Edaravone as a Treatment Option for Patients with Amyotrophic Lateral Sclerosis. Pharmaceuticals (Basel). 2020;14(1):29; Jin Hee Shin and Jae Keun Lee (September 11th 2013). Multiple Routes of Motor Neuron Degeneration in ALS, Current Advances in Amyotrophic Lateral Sclerosis, Alvaro G. Estévez, IntechOpen, DOI: 10.5772/56625. Available from: https://www.intechopen.com/chapters/45122; EMA, 2015. Clinical investigation of medicinal products for the treatment amyotrophic lateral sclerosis [WWW Document]. Eur. Med. Agency. Accessed May 05, 2022. https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-treatment-amyotrophic-lateral-sclerosis; Carrì MT, Valle C, Bozzo F, Cozzolino M. Oxidative stress and mitochondrial damage: importance in non-SOD1 ALS. Front Cell Neurosci. 2015;9:41. Published 2015 Feb 17. doi:10.3389/fncel.2015.00041; Van Damme P, Robberecht W, Van Den Bosch L. Modelling amyotrophic lateral sclerosis: progress and possibilities. Dis Model Mech. 2017;10(5):537-549. doi:10.1242/dmm.029058.

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DESIGN OF AN INTERNATIONAL, PHASE 3, RANDOMIZED, PLACEBO-CONTROLLED TRIAL WITH DAILY ORAL EDARAVONE (FNP122) IN ALS: THE ADORE STUDY

Ruben Van Eijk (1), **Nuria Albareda** (2), **Ammar Al-Chalabi** (3), **Adriano Chio** (4), **Orla Hardiman** (5), **Chris McDermott** (6), **Mónica Povedano** (7), **Philip van Damme** (8), **Carla Varona** (9), **Cristina Tarragó** (10), **Mohammed Ezzeldin** (11), **Leonard van den Berg** (12)

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Objetive

To describe the design of a Phase 3 trial, assessing the safety and the efficacy on disease progression and survival of once-daily oral edaravone in people living with ALS (pALS).

Effective treatment of ALS continues to be a significant unmet need

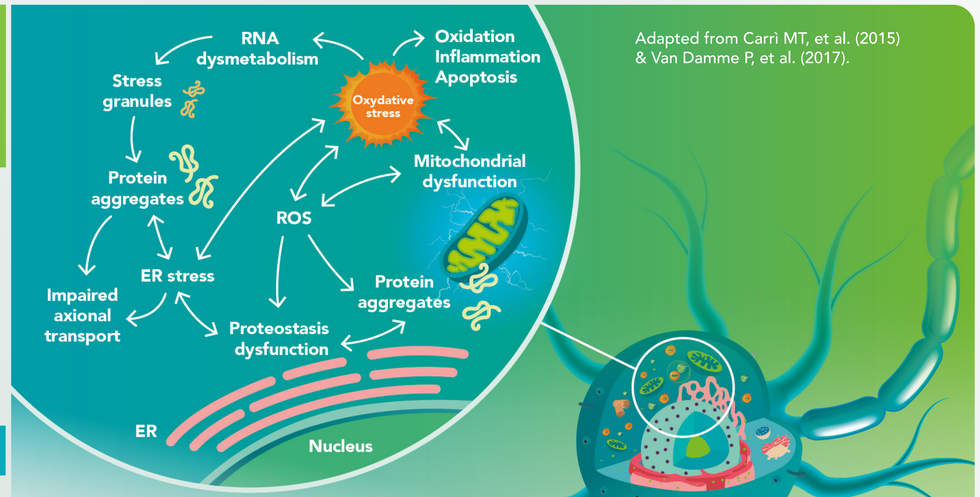
FNP122 is a newly developed oral formulation of edaravone to be administered daily in a liquid form.

Edaravone is a known free radical scavenger

Its mechanism of action in the treatment of ALS is thought to be multifactorial:

ANTIOXIDANT	ANTI-APOPTOSIS	ANTI-INFLAMMATION

- Protects motor neurons from oxidative stress
- Reduces death of neuronal cells

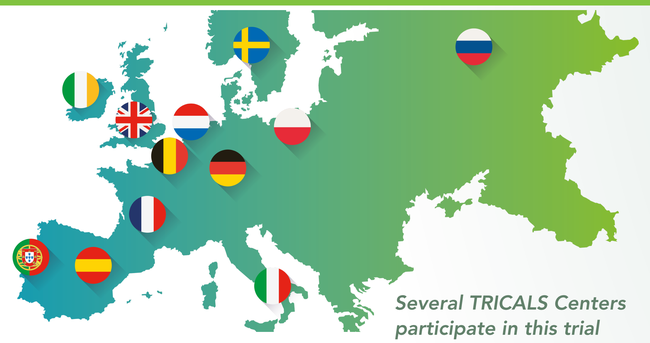


Adapted from Carrì MT, et al. (2015) & Van Damme P, et al. (2017).

Study design

300 pALS

FNP122 (daily oral edaravone) *vs.* Placebo
2:1 ratio to reduce placebo burden



Several TRICALS Centers participate in this trial

- Multicenter
- Multinational
- Double-blind
- Randomized
- Placebo-controlled

This study is ongoing across Europe. Enrolment started in October 2021.

pALS will receive double-blind treatment* up to a maximum of 72 weeks

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

Main inclusion criteria

- **Definite, probable, probably laboratory-supported or possible ALS** (based on the El Escorial and the revised Airlie House diagnostic criteria)
- **Slow Vital Capacity (SVC) ≥70%**
- **Onset of first symptoms ≤24 months** prior to randomization
- **Change in ALSFRS-R score between 0.35 and 1.5 points per month** (both inclusive) in the period between first symptoms and the screening visit

Primary efficacy endpoint

- **Change from baseline in ALSFRS-R total score after 48 weeks**

Secondary efficacy endpoints

- Function and survival · *CAFS at 48 and 72 w*
- Survival time · *72 w*
- Pulmonary function · *Change from baseline in SVC*
- Muscle strength · *Change from baseline in HHD score*
- QoL · *Change from baseline in ALSAQ-40 and EQ-5D-5L scores*
- Cognition · *Change from baseline in ECAS score*

Exploratory endpoints

- Plasma and urine ALS biomarkers

Conclusions

The ADORE trial is an ongoing phase 3 study designed to compare active treatment vs. placebo for a longer duration (up to 72w of treatment) in people living with ALS.

The results will provide relevant safety and efficacy data on this new oral daily formulation of edaravone (FNP122).

* Dosing needs to be done each morning under fasting conditions. This implies taking the dose: at least two hours after a meal or snack and 30 min after a drink AND no eating or drinking for at least one hour post dosing.

TRICALS: Treatment Research Initiative to Cure ALS; CAFS: Combined assessment of function and survival; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; SVC: slow vital capacity; HHD: hand-held dynamometer; pALS: people living with ALS; cALS: caregivers for people with ALS

REFERENCES: A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Investigate the Efficacy and Safety of FAB122 in Patients With Amyotrophic Lateral Sclerosis (ADORE). ClinicalTrials.gov [Internet]. January 5, 2022. Accessed September, 2022. https://clinicaltrials.gov/ct2/show/NCT05178810; Cha SJ, Kim K. Effects of the Edaravone, a Drug Approved for the Treatment of Amyotrophic Lateral Sclerosis, on Mitochondrial Function and Neuroprotection. Antioxidants (Basel). 2022;11(2):195; Cho H, Shukla S. Role of Edaravone as a Treatment Option for Patients with Amyotrophic Lateral Sclerosis. Pharmaceuticals (Basel). 2020;14(1):29; Jin Hee Shin and Jae Keun Lee (September 11th 2013). Multiple Routes of Motor Neuron Degeneration in ALS, Current Advances in Amyotrophic Lateral Sclerosis, Alvaro G. Estévez, IntechOpen, DOI: 10.5772/56625. Available from: https://www.intechopen.com/chapters/45122; EMA, 2015. Clinical investigation of medicinal products for the treatment amyotrophic lateral sclerosis [WWW Document]. Eur. Med. Agency. Accessed September, 2022. https://www.ema.europa.eu/en/clinical-investigation-medicinal-products-treatment-amyotrophic-lateral-sclerosis; Carri MT, Valle C, Bozzo F, Cozzolino M. Oxidative stress and mitochondrial damage: importance in non-SOD1 ALS. Front Cell Neurosci. 2015;9:41. Published 2015 Feb 17. doi:10.3389/fncel.2015.00041; Van Damme P, Robberecht W, Van Den Bosch L. Modelling amyotrophic lateral sclerosis: progress and possibilities. Dis Model Mech. 2017;10(5):537-549. doi:10.1242/dmm.029058.

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ADOREXT study

ALS TRIAL WITH DAILY ORAL EDARAVONE EXTENSION

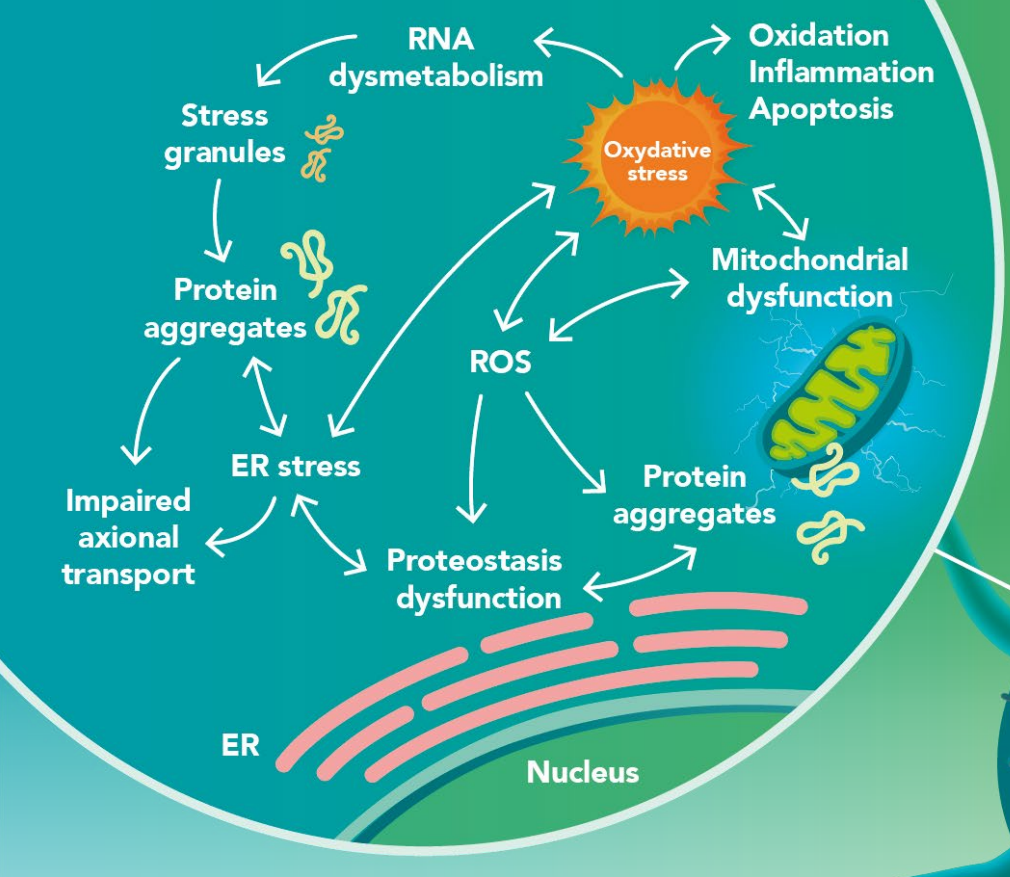
After a participant completes the study, will be offered the possibility to roll over in an open label extension study (ADOREXT) in which all participants will receive daily oral edaravone

- ✔ The ADOREXT protocol has been developed considering pALS and cALS perspective collected in an **Advisory Board**.
- ✔ pALS representatives from international and European pALS organizations participated in the Expert Advisory Board to share their experience and knowledge about ALS.
- ✔ Real-life feedback in clinical development may help to improve overall drug development performance, clinical trial feasibility, patient recruitment, and protocol adherence.

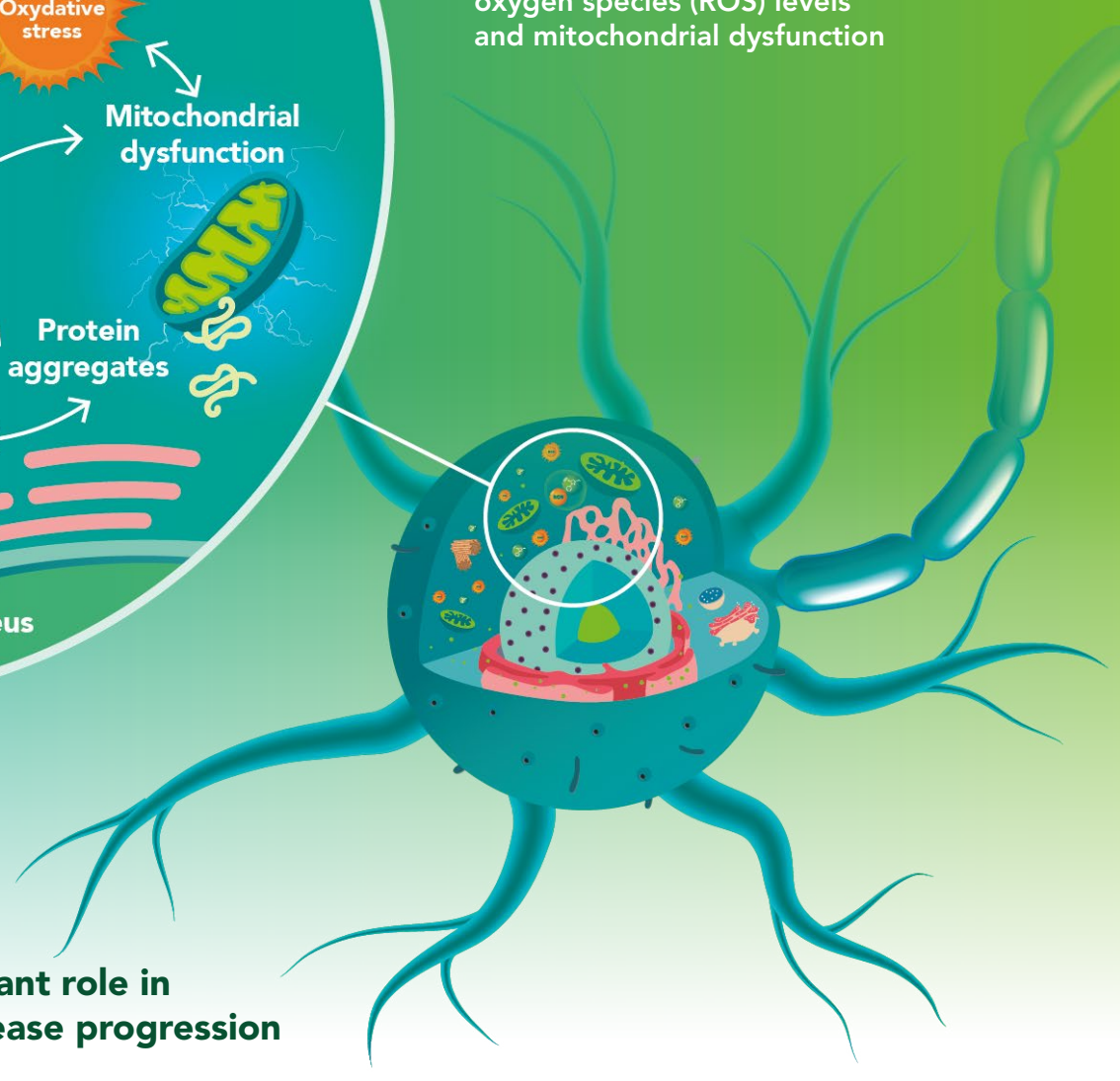
The ADORE Study: an international, phase 3, randomized, placebo-controlled trial with daily oral edaravone (FNP122) in ALS

Graphical Abstract

To describe the design of a Phase 3 trial, assessing the safety and the efficacy on disease progression and survival of once daily oral edaravone in patients with ALS



Distinguishing pathogenic features of neurodegenerative diseases include high reactive oxygen species (ROS) levels and mitochondrial dysfunction



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Edaravone plays an important role in ALS' pathogenesis and disease progression

- ANTIOXIDANT
- ANTI-APOPTOSIS
- ANTI-INFLAMMATION

- Free radical scavenger
- Protects motor neurons from oxidative stress
- Reduces death of neuronal cells
- Modulates mitochondrial function

FNP122 is a newly developed oral formulation of edaravone to be self-administered daily in a liquid form

300 PATIENTS
2:1
FNP122:Placebo

- Multicenter
- Multinational
- Double-blind
- Randomized
- Placebo-controlled

Patients will receive double-blind treatment up to a maximum of 72-weeks

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

Several TRICALS Centers across Europe will participate in this trial

Main inclusion criteria

Definite, probable, probably laboratory supported, or possible ALS (based on the El Escorial and the revised Airlie House diagnostic criteria)

Slow Vital Capacity (SVC) **≥70%**

Onset of first symptoms **≤24 months** prior to randomization

Change **≥0.35 and ≤1.5 points per month** in ALSFRS-R score between first symptoms and screening visit

Study visits

Enrollment started on October 2021

- Up to 8 visits (V) up to W72
- 7 monthly calls (C) up to W48

Primary efficacy endpoint

- Change from baseline in ALSFRS-R total score after 48w

Secondary efficacy endpoints

- Function and survival · *CAFS at 48 and 72w*
- Survival time · *Over 72w*
- Pulmonary function · *Change from baseline in SVC*
- Muscle strength · *Change from baseline in HHD score*
- QoL · *Change from baseline in ALSAQ-40 and EQ-5D-5L scores*
- Cognition · *Change from baseline in ECAS score*

Safety endpoints

- TAEs, vital signs, ECG, laboratory tests

Exploratory endpoints

- ALS biomarkers

OLE Study: ADOREXT

All ADORE patients will be offered the possibility to roll over in an open label extension in which all patients will receive daily oral edaravone (FNP122)

Study strenghts

- ✔ Robust trial design: In line with EMA's ALS guideline
- ✔ Large phase 3 study (300 patients)
- ✔ New daily oral formulation of edaravone
- ✔ Active treatment vs. placebo
- ✔ Low burden of study visit schedules
- ✔ Sensitive and reliable outcome measures
- ✔ Longer term efficacy & safety (up to 72w of treatment vs. placebo)
- ✔ Possibility to continue with FNP122 after the end of the study to all patients

The ADORE study is a phase 3 trial designed to compare active treatment vs. placebo for a longer duration (up to 72w of treatment) in patients with ALS

The results will provide relevant safety and efficacy data on this new daily oral formulation of edaravone (FNP122)

TRICALS: Treatment Research Initiative to Cure ALS; **CAFS**: Combined assessment of function and survival; **ALSFRS-R**: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; **SVC**: slow vital capacity; **HHD**: hand-held dynamometer; **ROS**: Reactive oxygen species; **ER**: endoplasmic reticulum; **TAEs**: Treatment Emergent Adverse Events; **ECG**: electrocardiogram.

REFERENCES

Link A Multicenter, Randomized, Double-blind, Placebo-controlled Study to Investigate the Efficacy and Safety of FAB122 in Patients With Amyotrophic Lateral Sclerosis (ADORE). ClinicalTrials.gov [Internet]. January 5, 2022. Accessed April 07, 2022

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TOP LINE RESULTS OF THE ADORE STUDY:
AN INTERNATIONAL, PHASE 3 TRIAL TO INVESTIGATE THE EFFICACY AND SAFETY OF DAILY ORAL EDARAVONE (FNP122) IN ALS

van Eijk R[1], Povedano M[2], van Damme P[3], Chiò A[4], McDermott C[5], Al-Chalabi A[6], Hardiman O[7], Kuźma-Kozakiewicz M[8], Mascías J[9], Silani V[10], Lisewski P[11], Antczak J[12], Vázquez Costa JF[13], Mora Pardina JS[14], Ludolph A[15], Calvo A[16], Sansone V[17], Attarian S[18], Borghero G[19], Pardo J[20], Petri S[21], Sorarù G[22], Trojsi F[23], Hobson E[24], Mandrioli J[25], Ingre C[26], Salachas F[27], Soriani MH[28], Corcia P[29], Meyer T[30], Gunther R[31], Reyes Garrido V[32], Turner M[33], Brylev L[34], de Carvalho M[35], Ealing J[36], Camu W[37], Danel Brunaud V[38], Varona C[39], Tarragó C[40], Nadal T[41], Albareda N[41], van den Berg LH[42].

Objective

To outline the baseline characteristics of the participants in the ADORE study and the results of the primary, key secondary efficacy endpoints and safety analysis.

Methods

The ADORE study was a **multicenter, multinational, double-blind, randomised (2:1), placebo controlled, Phase 3 study to investigate the efficacy and safety of 100 mg edaravone (FNP122), administered orally once daily, in patients with ALS.**

Main inclusion criteria

- Definite, probable, probably laboratory-supported or possible ALS.
- Slow Vital Capacity (SVC) ≥70%.
- Onset of first symptoms ≤24 months prior to randomization.
- Change ≥ 0.35 and ≤1.5 points/month in ALSFRS-R score between first symptoms and screening visit.

Endpoints

Primary efficacy endpoint

- Change from baseline in ALSFRS-R total score after 48 weeks.
- The primary analysis population was the modified intention to treat (mITT).
- A number of sensitivity analyses were performed for the primary endpoint utilizing the primary analysis population (mITT), the per protocol (PP) and intention-to-treat (ITT) population.

Secondary endpoints

- CAFS at week 48 and 72 and survival time over 72 weeks.
- Safety and tolerability of FNP122.

All participants were followed up for 48 weeks and the first one hundred participants randomised were followed up for 72 weeks (or until an intercurrent event was reached).

Results

Study population

- Overall, 302 subjects were included in the mITT population and in the SAF population. The PP population consisted of 247 subjects, excluding 55 subjects due to major protocol deviations.
- Baseline characteristics were similar across treatment groups.
- The majority of subjects was co-medicated with riluzole (95.0%), had an ALS progression rate of <1.0 (76.2%) and median ALS duration (time since symptom onset) was 14.0 months.

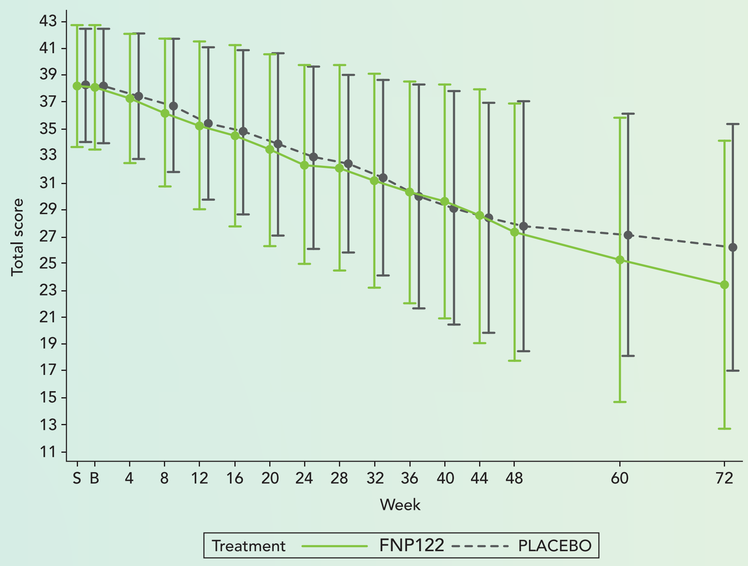
Demographics – SAF

	FNP122 (N=205)	Placebo (N=97)	Overall (N=302)
Sex, n (%)			
Male	123 (60.0)	62 (63.9)	185 (61.3)
Female	82 (40.0)	35 (36.1)	117 (38.7)
Age (years)			
Mean (SD)	59.3 (10.5)	59.3 (10.0)	59.3 (10.3)
Median	59.0	60.0	59.0
Min, Max	32-80	32-78	32-80
Race, n (%)			
Asian	2 (1.0)	0 (0.0%)	2 (0.7)
Black Or African American	0 (0.0%)	1 (1.0)	1 (0.3)
White	185 (90.2)	90 (92.8)	275 (91.1)
Other	1 (0.5)	1 (1.0)	2 (0.7)
Not Reported	17 (8.3)	5 (5.2)	22 (7.3)
BMI (kg/m²)			
Mean (SD)	25.36 (3.83)	24.82 (3.23)	25.19 (3.65)
Median	24.93	24.67	24.91
Min, Max	18.1-42.9	18.2-32.5	18.1-42.9
Additional riluzole co-medication use, n (%)			
Yes	194 (94.6)	93 (95.9)	287 (95.0)
No	11 (5.4)	4 (4.1)	15 (5.0)
ALS progression rate (slope ALSFRS-R), n (%)			
<1.0	158 (77.1)	72 (74.2)	230 (76.2)
≥1.0	47 (22.9)	25 (25.8)	72 (23.8)

Note: N indicates the number of subjects included in the treatment group or total, n presents the number of non-missing observations.
SAF=safety population; BMI=body mass index.

Efficacy

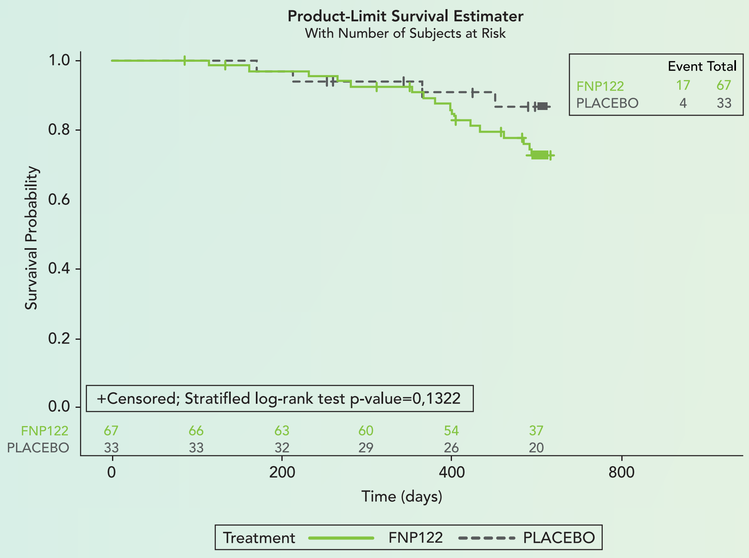
ALSFRS-R Total Score Mean (SD) versus Time – mITT



ALSFRS-R=4Amyotrophic Lateral Sclerosis Functional Rating Scale – Revised; mITT=modified intention-to-treat; B=Baseline; S=Screening; SD=standard deviation.

- The mean change in ALSFRS-R score per month in the period from onset of first symptoms to the Screening Visit was 0.753.
- Changes in LS mean (SE) ALSFRS-R total score during 48 weeks of treatment were -12.6 (0.7) for the FNP122 treatment group and -13.4 (0.9) for the placebo group. The difference between the 2 groups (0.777 (1.127)) was not statistically significant (p=0.4910).

Kaplan-Meier (KM) Curve of Survival Time (Progression-free Survival)[a] over 72 Weeks – mITT 72 Weeks Subgroup (N =100)



[a]Survival time (progression-free survival) is defined as alive and no tracheostomy, or no initiation of noninvasive ventilation for more than 20 hours a day for more than 10 consecutive days

- Survival time over 72 weeks, was analyzed descriptively by KM curve and stratified log-rank test and Cox model. No significant difference was found between the FNP122 group and the placebo group using a hazard ratio (p=0.1135) or the log-rank test (p=0.1322).

Safety

- FNP122 was safe and well tolerated.

Number (%) of Subjects Experiencing at Least 1 Adverse Event - SAF

Category	FNP122 (N=205)		Placebo (N=97)		Overall (N=302)	
	n (%)	m	n (%)	m	n (%)	m
Any TEAE	180 (87.8)	861	82 (84.5)	454	262 (86.8)	1315
Any serious AE	62 (30.2)	85	28 (28.9)	36	90 (29.8)	121
Any serious TEAE	62 (30.2)	85	28 (28.9)	36	90 (29.8)	121
Any TEAE leading to treatment discontinuation	21 (10.2)	26	9 (9.3)	15	30 (9.9)	41
Any AE leading to death	20 (9.8)	20	7 (7.2)	7	27 (8.9)	27
Any AESI	31 (15.1)	34	13 (13.4)	13	44 (14.6)	47
TEAE by relationship						
Unrelated	176 (85.9)	775	82 (84.5)	422	258 (85.4)	1197
Related	49 (23.9)	86	23 (23.7)	32	72 (23.8)	118
TEAE by severity						
Mild	167 (81.5)	578	78 (80.4)	325	245 (81.1)	903
Moderate	92 (44.9)	214	38 (39.2)	102	130 (43.0)	316
Severe	50 (24.4)	69	18 (18.6)	27	68 (22.5)	96

AE=adverse event; AESI=adverse event of special interest; N=sample size of group; n=number of individuals occurring per adverse event category; m=number of events, TEAE=treatment-emergent adverse event.

CAFS scores showed a marked decrease from Week 48 to Week 72 in both the FNP122 group and the placebo group, but the differences between the two study groups at Week 48 and Week 72 were not statistically significantly different, as assessed using a Mann-Whitney U test (respectively, p=0.6091 and p=0.3882).

Conclusions

In summary, 100 mg daily oral edaravone (FNP122) did not show a significant benefit over placebo in slowing disease progression measured by ALSFRS-R score and CAFS. FNP122 was safe and well tolerated. These findings provide valuable insights for future research endeavors aimed at addressing the challenges in ALS management.

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