Neues aus der Forschung zur Amyotrophen Lateralsklerose

Priv.-Doz. Dr. Hakan Cetin, PhD
Universitätsklinik für Neurologie, Medizinische Universität Wien
Wien, 19.9.2022

…die nächsten 45 Minuten

1 Grundlagen

2 Diagnose

3 Biomarker

4 Klinische Studien

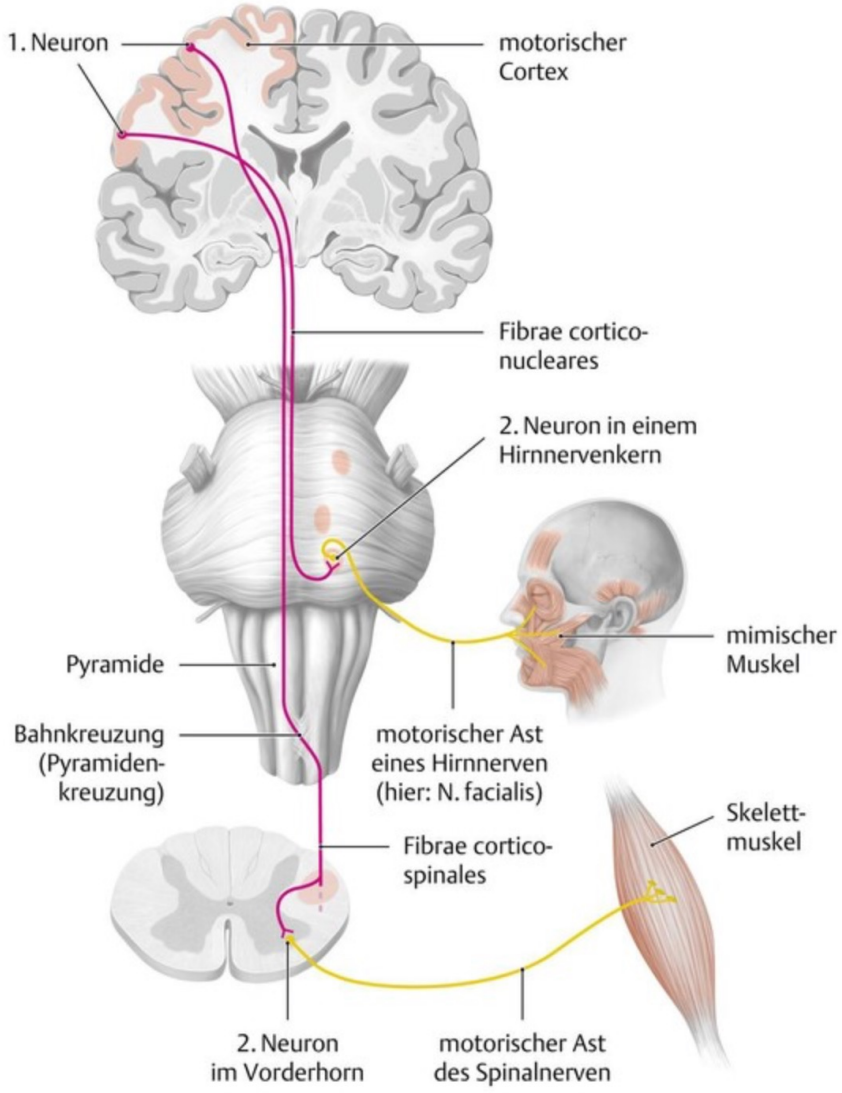
5 Therapiestudien

6 Genetische Therapiestudien

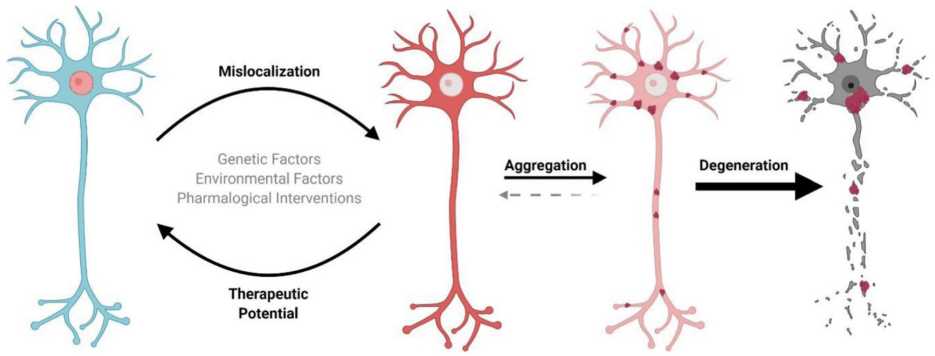
Was ist ALS?

Was sind Motoneuronerkrankungen?

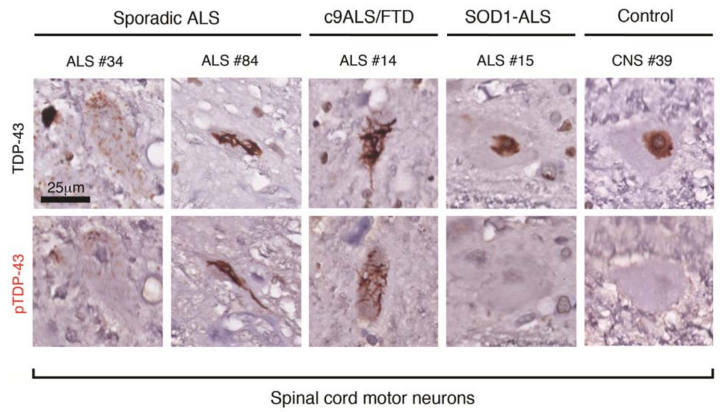
1. und 2. Motoneuron sind primär betroffen



Ablagerung von TDP43 in den Zellen

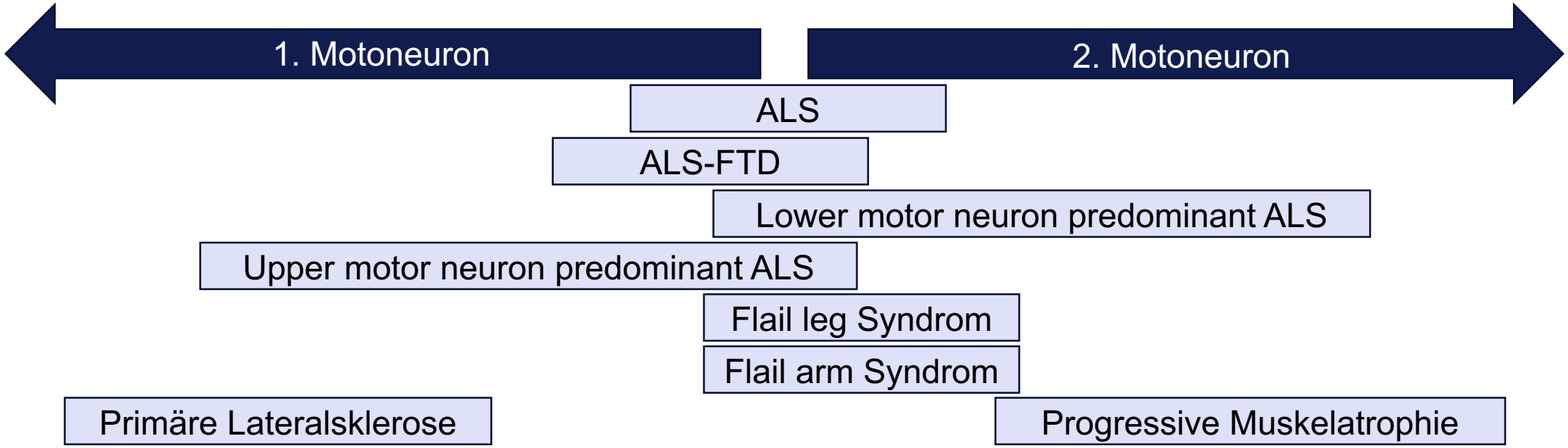


Suk et al, 2020, Mol Neurodegeneration



Melamed et al, 2019, Nat Neurosci

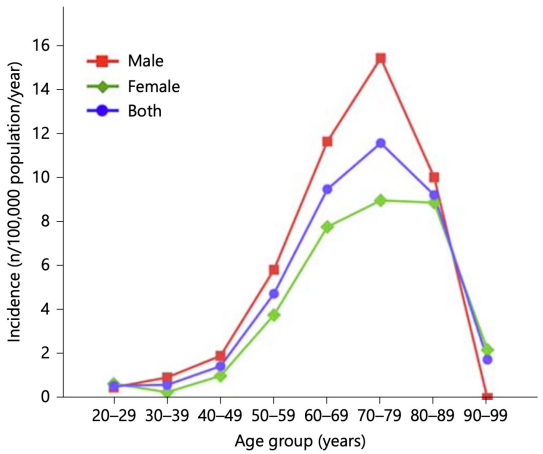
Motoneuronerkrankungen sind heterogen

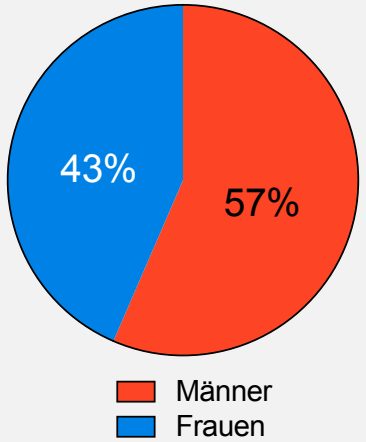


Epidemiologie der ALS

Inzidenz	Punktprävalenz	Lebenszeitprävalenz
~3/100.000/Jahr	~10/100.000	Ca. jede 400. Person erkrankt an ALS

Mediane Alter liegt bei 66 Jahren





Cetin et al, Neuroepidemiology, 2012

Wie wird ALS diagnostiziert?

Gold Coast Kriterien

Gold Coast Kriterien, 2020
Progredienter Erkrankungsverlauf
1.MN und 2.MN in ≥ 1 Region **ODER** 2.MN in ≥ 2 Regionen
Ausschluss von Differentialdiagnosen

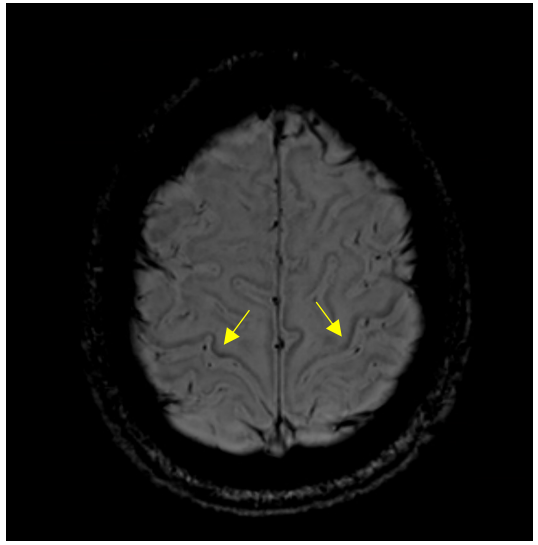
Elektromyographie	Motorisch evozierte Potentiale	MRT
Neurographie	Sonographie	Labor (Serum, Liquor)

Shefner et al, 2020, *Clin Neurophysiol*

Die Suche nach spezifischen Biomarkern?

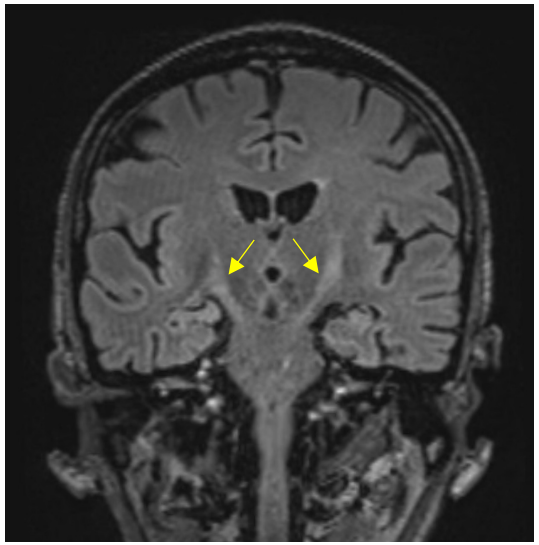
Radiologische Biomarker: MRT

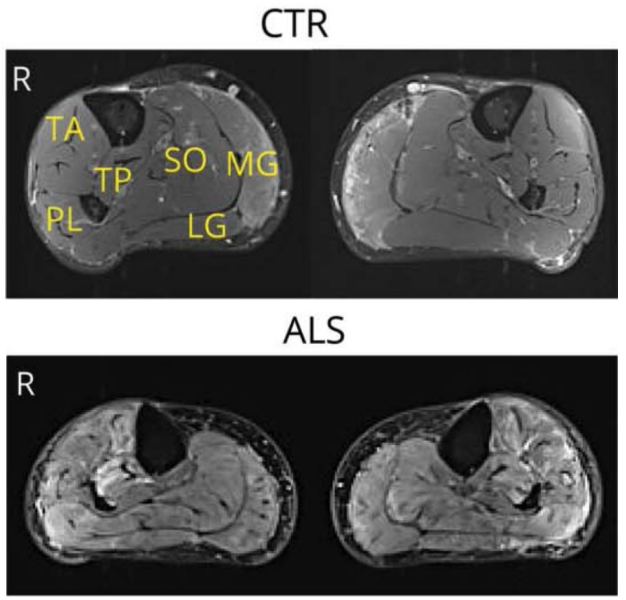
Motor band sign



ALS Patient aus dem AKH

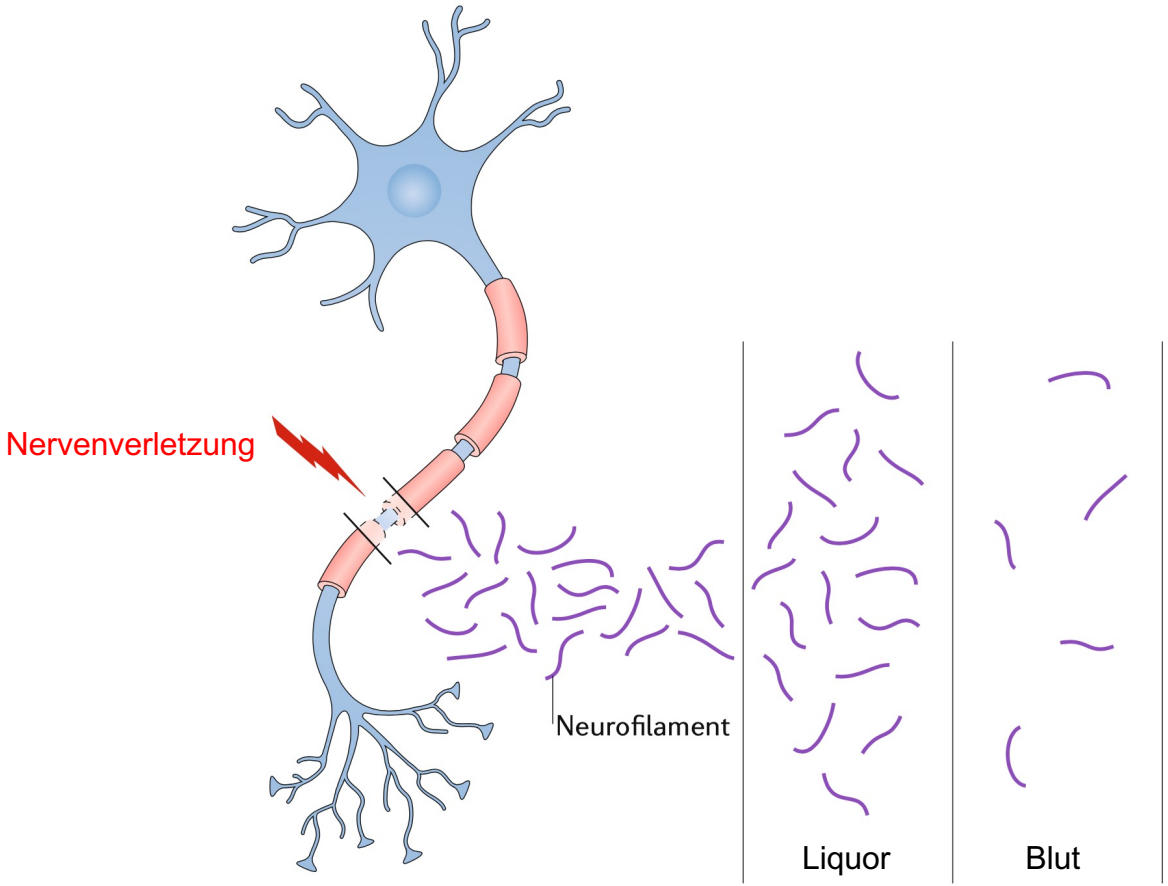
Pyramidenbahn





Klickovic et al, 2019, *Neurology*

Biomarker in Körperflüssigkeiten: Neurofilamente



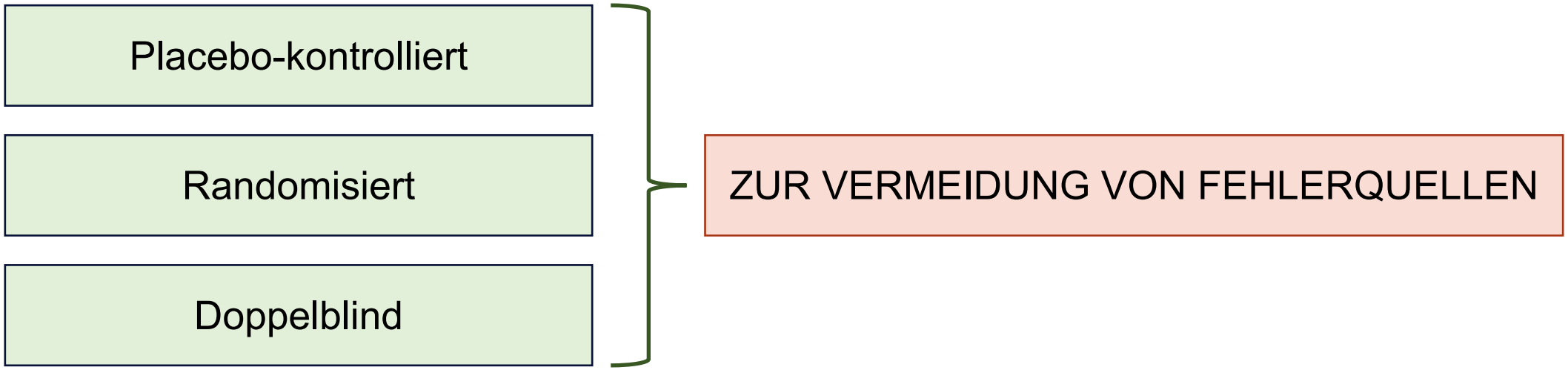
Khalil et al, 2018, *Nature Rev Neurol*

Klinische Studien laufen in Phasen ab

Klinische Studien und ihre Phasen

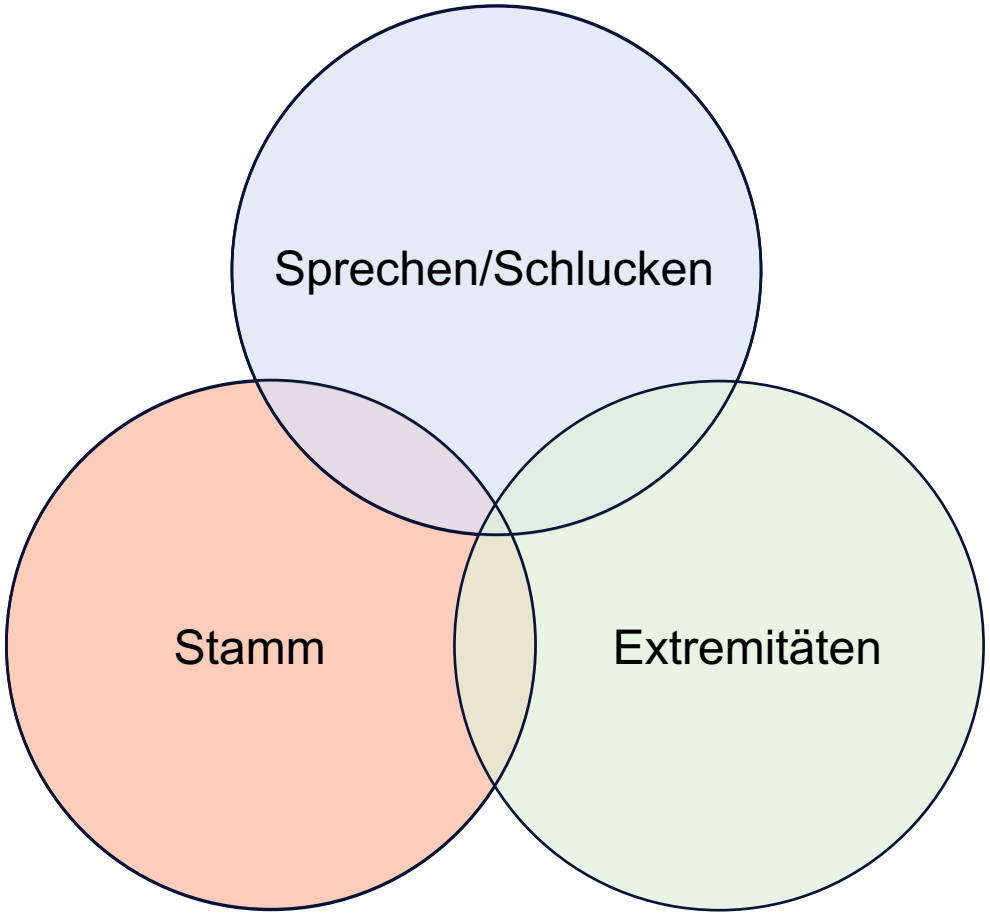
	Wer wird getestet?	Was soll herausgefunden werden?	Placebo	Fallzahl
Phase I	Kleine Zahl gesunder Freiwilliger	Verträglichkeit & Sicherheit	–	10-50
Phase II	Kleine Zahl von Patient*innen	Dosierung & Hinweise auf Wirkung	–/+	100-500
Phase III	Große Zahl von selektionierten Patient*innen und Kontrollen	Wirkung & Verträglichkeit	+	>1000
Phase IV	Nach Zulassung an Gesamtzahl der (nicht selektionierten) Patient*innen	Wirkung & sehr seltene Nebenwirkungen	–	>10.000

Wie läuft eine Studie ab?

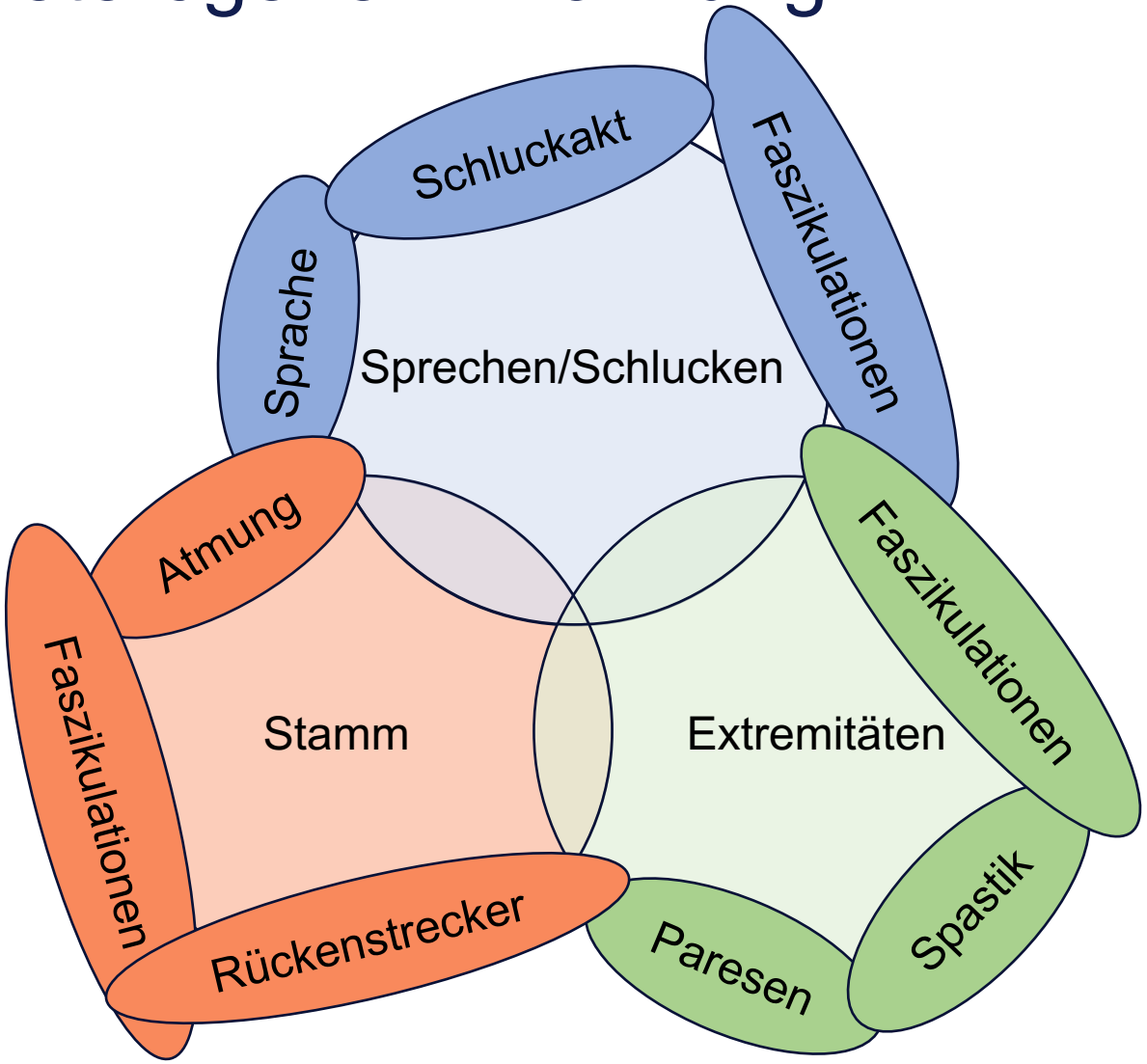


Besonderheiten bei ALS

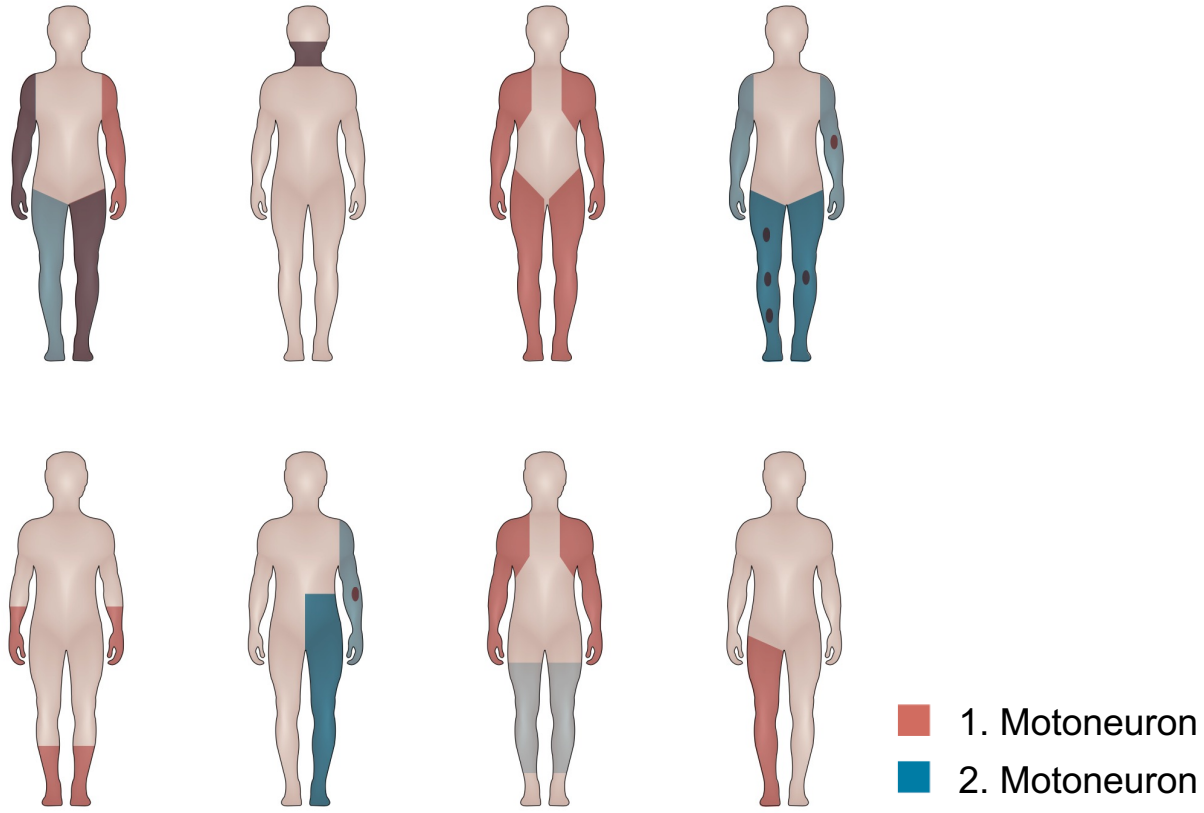
ALS ist eine heterogene Erkrankung



ALS ist eine heterogene Erkrankung



ALS ist eine heterogene Erkrankung



Swinnen & Robberecht, 2014, Nat Rev Neurol

Endpunkte – was wird in Studien gemessen?

- Überlebenszeit
- Körperfunktionen – ALSFRSR
- Lungenfunktion
- Biomarker - Neurofilamente

Endpunkte – ALSFRSR

ALS Functional Rating Scale–Revised (ALSFRS-R)[5]

BULBAR

Speech
- **4** Normal
- **3** Detectable speech disturbance
- **2** Intelligible with repeating
- **1** Speech combined with nonvocal communication
- **0** Loss of useful speech

Salivation
- **4** Normal
- **3** Slight but definite excess of saliva in mouth; may have nighttime drooling
- **2** Moderately excessive saliva; may have minimal drooling
- **1** Marked excess of saliva with some drooling
- **0** Marked drooling; requires constant tissue or handkerchief

Swallowing
- **4** Normal
- **3** Early eating problems—occasional choking
- **2** Dietary consistency changes
- **1** Needs supplemental tube feeding
- **0** NPO (exclusively parenteral or enteral feeding)

FINE MOTOR

Handwriting
- **4** Normal
- **3** Slow or sloppy; all words are legible
- **2** Not all words are legible
- **1** Able to grip pen but unable to write
- **0** Unable to grip pen

Cutting Food*
- **4** Normal
- **3** Somewhat slow and clumsy, but no help needed
- **2** Can cut most foods, although clumsy and slow; some help needed
- **1** Food must be cut by someone, but can still feed slowly
- **0** Needs to be fed

Dressing and Hygiene
- **4** Normal
- **3** Independent and complete self-care with effort or decreased efficiency
- **2** Intermittent assistance or substitute methods
- **1** Needs attendant for self-care
- **0** Total dependence

*There are different assessments for cutting food with gastrostomy.

GROSS MOTOR

Turning in Bed
- **4** Normal
- **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

Walking
- **4** Normal
- **3** Early ambulation difficulties
- **2** Walks with assistance
- **1** Non-ambulatory functional movement only
- **0** No purposeful leg movement

Climbing Stairs
- **4** Normal
- **3** Slow
- **2** Mild unsteadiness or fatigue
- **1** Needs assistance
- **0** Cannot do

RESPIRATORY

Dyspnea
- **4** None
- **3** Occurs when walking
- **2** Occurs with one or more of the following: eating, bathing, dressing (ADL)
- **1** Occurs at rest, difficulty breathing when either sitting or lying
- **0** Significant difficulty, considering using mechanical respiratory support

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

Respiratory Insufficiency
- **4** None
- **3** Intermittent use of BiPAP
- **2** Continuous use of BiPAP
- **1** Continuous use of BiPAP during the night and day
- **0** Invasive mechanical ventilation by intubation or tracheostomy

Aktuelle klinische Studien

Aktuelle klinische Studien

Edaravone

AMX0035

Vitamin B12

Stammzellen

Tofersen

Jacifusen

Edaravone

ALS NEWS TODAY

Home | About ALS | Treatments | News | Columns | Forums

News > FDA Approves Radicava, First New ALS Therapy in 22 Years

FDA Approves Radicava, First New ALS Therapy in 22 Years

by *Magdalena Kegel* | May 8, 2017

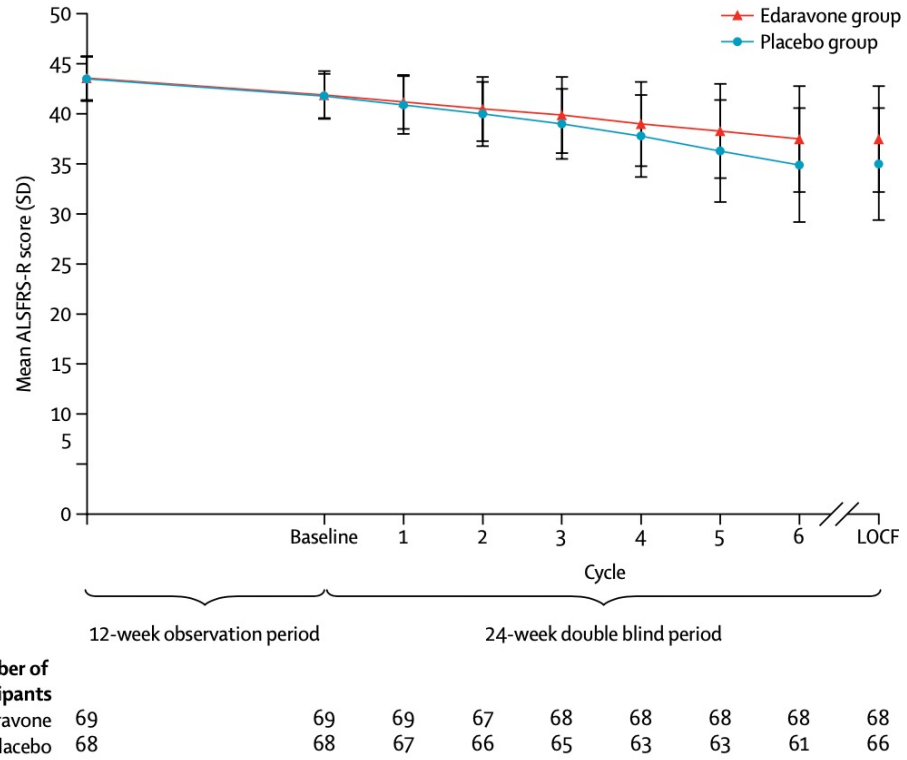
SHARE THIS ARTICLE:

Edaravone

Wirkungsweise unbekannt

Monatliche intravenöse Gabe über 2 Wochen

Edaravone: Phase 3 Studie



	Least-squares mean change		Least-squares mean difference	p value*
	Edaravone (n)	Placebo (n)		
Primary endpoint				
ALSFRS-R score	−5·01, 0·64 (68)†	−7·50, 0·66 (66)†	2·49, 0·76 (0·99 to 3·98)	0·0013
Secondary endpoints				
FVC (%)	−15·61, 2·41 (67)†‡	−20·40, 2·48 (66)†	4·78, 2·84 (−0·83 to 10·40)	0·0942
Modified Norris Scale scores				
Total	−15·91, 1·97 (68)†	−20·80, 2·06 (63)†‡	4·89, 2·35 (0·24 to 9·54)	0·0393
Limb scale	−11·47, 1·61	−14·91, 1·68	3·44, 1·92 (−0·36 to 7·24)	0·0757
Bulbar scale	−4·44, 0·76	−5·89, 0·79	1·46, 0·90 (−0·33 to 3·24)	0·1092
ALSAQ-40 score	17·25, 3·39 (68)†	26·04, 3·53 (64)†‡	−8·79, 4·03 (−16·76 to −0·82)	0·0309
Grip strength (kg)§	−4·08, 0·54 (68)†	−4·19, 0·56 (66)†	0·11, 0·64 (−1·15 to 1·38)	0·8583
Pinch strength (kg)§	−0·78, 0·14 (68)†	−0·88, 0·14 (66)†	0·10, 0·16 (−0·23 to 0·42)	0·5478

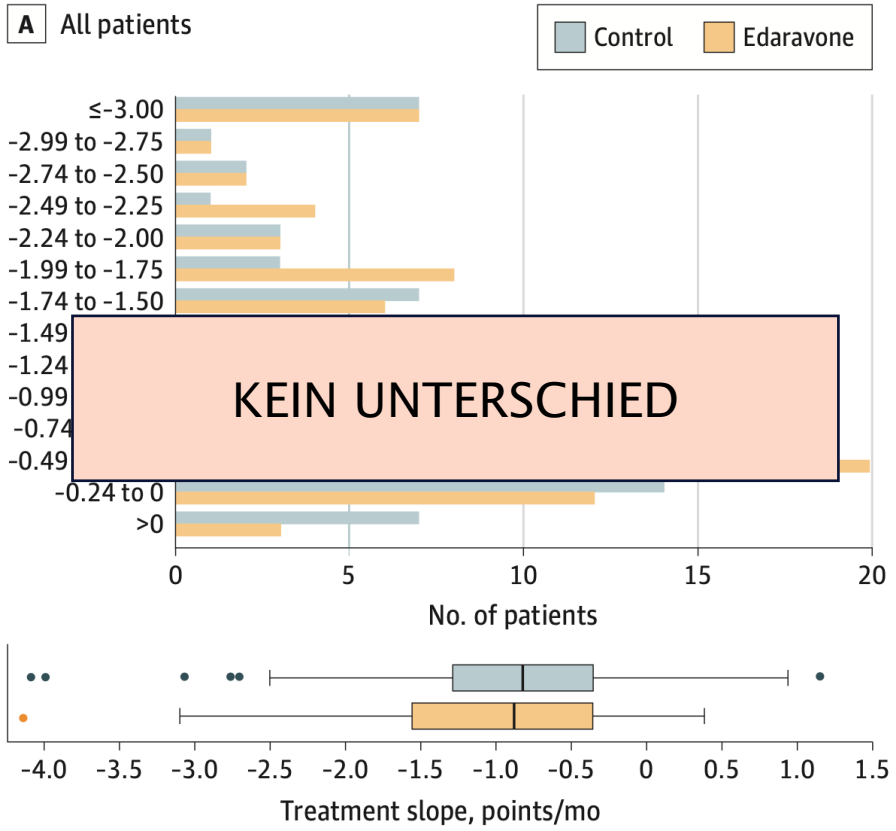
Akimoto et al, 2017, *Lancet Neurol*

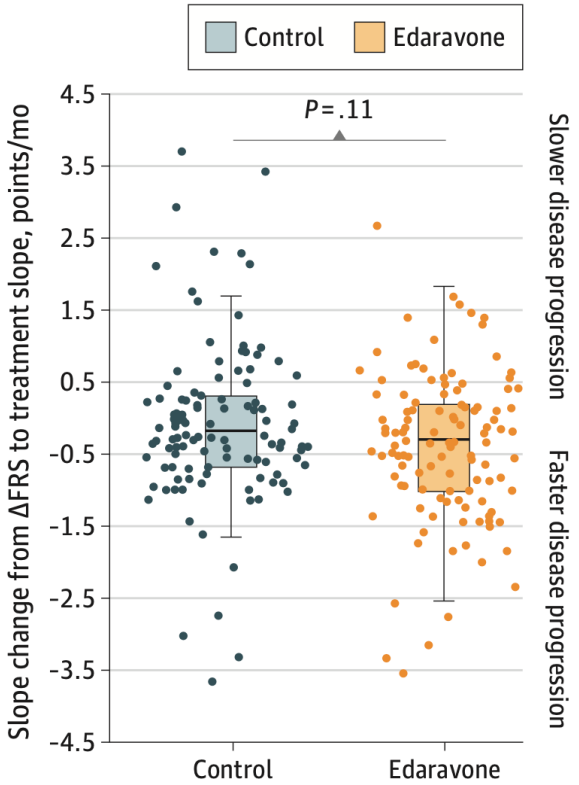
Edaravone: neue Phase 4 Studie

JAMA Neurology | Original Investigation

Safety and Effectiveness of Long-term Intravenous Administration of Edaravone for Treatment of Patients With Amyotrophic Lateral Sclerosis

Characteristic	No. (%) of patients Total[a] Edaravone (n = 130)	Matched controls (n = 130)
Sex		
Female	48 (37)	47 (36)
Male	82 (63)	83 (64)
Symptom onset		
Spinal	97 (75)	97 (75)
Bulbar	33 (25)	33 (25)
Age, median (IQR), y		
At disease onset	56.1 (49.0 to 63.3)	55.4 (48.0 to 62.3)
At baseline	57.5 (50.5 to 64.5)	56.7 (49.8 to 63.8)
Baseline, median (IQR)		
Disease duration, mo	16.4 (10.3 to 23.0)	15.5 (10.1 to 24.3)
ALSFRS-R, score	38 (32.7 to 42)	39 (35 to 42)
ΔFRS, median (IQR), points/mo	−0.58 (−1.07 to −0.31)	−0.52 (−1.02 to −0.32)
Follow-up, median (IQR), mo	12.7 (7.6 to 18.5)	11.1 (6.4 to 19.2)





Witzel et al, 2022, *JAMA Neurol*

AMX0035

Natriumphenylbutyrat + Taurursodiol

Neuroprotektiv – Reduktion der Abbauvorgänge in der Zelle

CENTAUR Phase 2 Studie wurde 2020 publiziert

Laufende PHOENIX Phase 3 Studie

AMX0035: CENTAUR Phase 2 Studie

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline (Modified Intention-to-Treat Population).*

Characteristic	Sodium Phenylbutyrate–Taurursodiol (N=87)	Placebo (N=48)	Overall (N=135)
Male sex — no. (%)	61 (70)	32 (67)	93 (69)
White race — no. (%)†	82 (94)	46 (96)	128 (95)
Age — yr	57.6±10.4	57.3±7.6	57.5±9.5
Bulbar onset — no. (%)	26 (30)	10 (21)	36 (27)
Riluzole or edaravone use — no. (%)‡	62 (71)	42 (88)	104 (77)
Riluzole	59 (68)	37 (77)	96 (71)
Edaravone	22 (25)	24 (50)	46 (34)
Both	19 (22)	19 (40)	38 (28)
Prebaseline ALSFRS-R slope§	0.95±0.43	0.93±0.60	0.94±0.49
Slow vital capacity — % of predicted normal value	83.6±18.2	83.9±15.9	83.7±17.4
ALSFRS-R total score§	35.7±5.8	36.7±5.1	36.0±5.5
Bulbar score	9.5±2.4	10.0±2.6	9.7±2.5
Fine-motor score	8.0±2.7	8.0±2.6	8.0±2.7
Gross-motor score	7.5±2.8	7.6±2.6	7.6±2.8
Breathing score	10.6±1.9	11.0±1.8	10.8±1.9
ATLIS upper-limb score — % of predicted normal value¶	54.8±24.4	51.4±25.2	53.6±24.6
ATLIS lower-limb score — % of predicted normal value¶	57.6±24.9	57.1±25.8	57.4±25.1
ATLIS total score — % of predicted normal value¶	56.8±20.1	53.9±20.9	55.8±20.4
Months since ALS symptom onset	13.5±3.8	13.6±3.6	13.5±3.8
Months since ALS diagnosis	5.9±3.3	6.3±3.2	6.0±3.3
Body-mass index‖	26.9±4.4	26.4±5.8	26.7±4.9

87 Patienten mit AMX0035

48 Patienten mit Placebo

Einnahme über 24 Wochen

AMX0035: CENTAUR Phase 2 Studie

Table 1. Demographic and Clinical Characteristics of the Participants at Baseline (Modified Intention-to-Treat Population).*

Characteristic	Sodium Phenylbutyrate–Taurursodiol (N=87)	Placebo (N=48)	Overall (N=135)
Male sex — no. (%)	61 (70)	32 (67)	93 (69)
White race — no. (%)†	82 (94)	46 (96)	128 (95)
Age — yr	57.6±10.4	57.3±7.6	57.5±9.5
Bulbar onset — no. (%)	26 (30)	10 (21)	36 (27)
Riluzole or edaravone use — no. (%)‡	62 (71)	42 (88)	104 (77)
Riluzole	59 (68)	37 (77)	96 (71)
Edaravone	22 (25)	24 (50)	46 (34)
Both	19 (22)	19 (40)	38 (28)
Prebaseline ALSFRS-R slope§	0.95±0.43	0.93±0.60	0.94±0.49
Slow vital capacity — % of predicted normal value	83.6±18.2	83.9±15.9	83.7±17.4
ALSFRS-R total score§	35.7±5.8	36.7±5.1	36.0±5.5
Bulbar score	9.5±2.4	10.0±2.6	9.7±2.5
Fine-motor score	8.0±2.7	8.0±2.6	8.0±2.7
Gross-motor score	7.5±2.8	7.6±2.6	7.6±2.8
Breathing score	10.6±1.9	11.0±1.8	10.8±1.9
ATLIS upper-limb score — % of predicted normal value¶	54.8±24.4	51.4±25.2	53.6±24.6
ATLIS lower-limb score — % of predicted normal value¶	57.6±24.9	57.1±25.8	57.4±25.1
ATLIS total score — % of predicted normal value¶	56.8±20.1	53.9±20.9	55.8±20.4
Months since ALS symptom onset	13.5±3.8	13.6±3.6	13.5±3.8
Months since ALS diagnosis	5.9±3.3	6.3±3.2	6.0±3.3
Body-mass index‖	26.9±4.4	26.4±5.8	26.7±4.9

AMX0035 verlangsamt Erkrankung (ALSFRSR)

Kein Einfluss auf Lungenfunktion

Kein Einfluss auf Überlebenszeit

AMX0035: PHOENIX Phase 3 Studie

600 Patient*innen

Einnahme über 48 Wochen

ALSFRSR + Überleben

Ergebnisse im Jahr 2024 erwartet

AMX0035: CENTAUR Phase 2 Studie

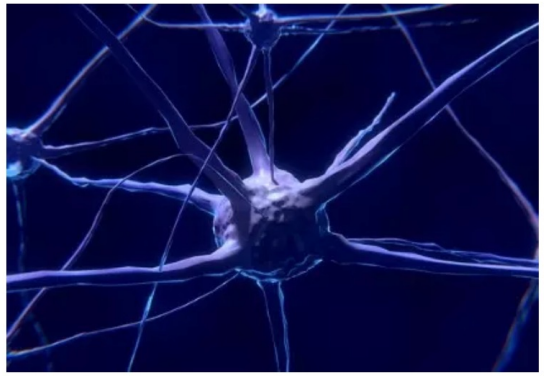


Foto: Pixabay

Amyotrophe Lateralsklerose: Neue ALS-Therapie in Kanada zugelassen

Gesundheitsnews, Medizin und Forschung

Torsten Lorenz, Beitrag vom 13. Juni 2022

ALS-Forschung – Neuroprotektive Therapie von Amyotropher Lateralsklerose: Die kanadische Gesundheitsbehörde Health Canada hat den Wirkstoff AMX0035 (Natriumphenylbutyrat und Ursodoxicoltaurin) unter bestimmten Bedingungen für die Behandlung von Amyotropher Lateralsklerose (ALS) zugelassen.

FDA Committee, in Reversal, Favors AMX0035 Approval for ALS

After rare 2nd review, advisors vote 7–2 to support Amylyx therapy

by *Marisa Wexler, MS* | September 8, 2022

VITAMIN B12: Phase 3 Studie

Aktive Form von Vitamin B12

Neuroprotektiv – Reduktion der Abbauvorgänge in der Zelle

Intramuskuläre Injektion von 50mg, 2x in der Woche

Einschluss von Patien*innen im frühen Stadium

Ausschluss von Patient*innen mit schnellem/langsamem Verlauf

VITAMIN B12: Phase 3 Studie

JAMA Neurology | Original Investigation

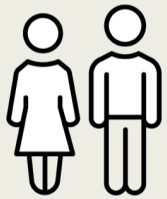
Efficacy and Safety of Ultrahigh-Dose Methylcobalamin in Early-Stage A… A Randomized …

Ryosuke Oki, MD; Yuishin Izum… Satoshi Sakaguchi, MD, PhD; H… Yuki Hatanaka, MD, PhD; Masa… Kazumoto Shibuya, MD, PhD; … Kiyonobu Komai, MD, PhD; Hit… Hidefumi Ito, MD, PhD; Makiko… Takayoshi Shimohata, MD, PhD… Nobuyuki Araki, MD, PhD; Mits… Hirokazu Furuya, MD, PhD; Sat… Satoshi Kuwabara, MD, PhD; R…

RCT: Efficacy and Safety of Ultrahigh-Dose Methylcobalamin in Early-Stage Amyotrophic Lateral Sclerosis: A Randomized Clinical Trial

POPULATION

74 Males, 55 Females



Adults with amyotrophic lateral sclerosis diagnosed within 1 y from onset

Mean age, 61.0 y

SETTINGS / LOCATIONS

25 Neurology centers in Japan

INTERVENTION

129 Patients

65 Ultrahigh-dose methylcobalamin

Intramuscular injection of methylcobalamin, 50 mg, twice weekly for 16 wk

64 Placebo

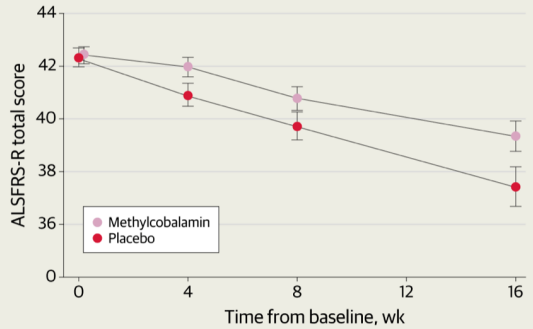
Intramuscular injection of placebo twice weekly for 16 wk

PRIMARY OUTCOME

Change in Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) total score (range, 0-48, with lower scores indicating more severe symptoms) from baseline to week 16

FINDINGS

The methylcobalamin group had a significantly lower reduction in ALSFRS-R total score, representing slower function decline, compared with the placebo group



Mean (SE) change in ALSFRS-R total score:
Methylcobalamin, −2.66 (0.61)
Placebo, −4.63 (0.60)

Least square means difference:
1.97; 95% CI, 0.44-3.50; *P* = .01

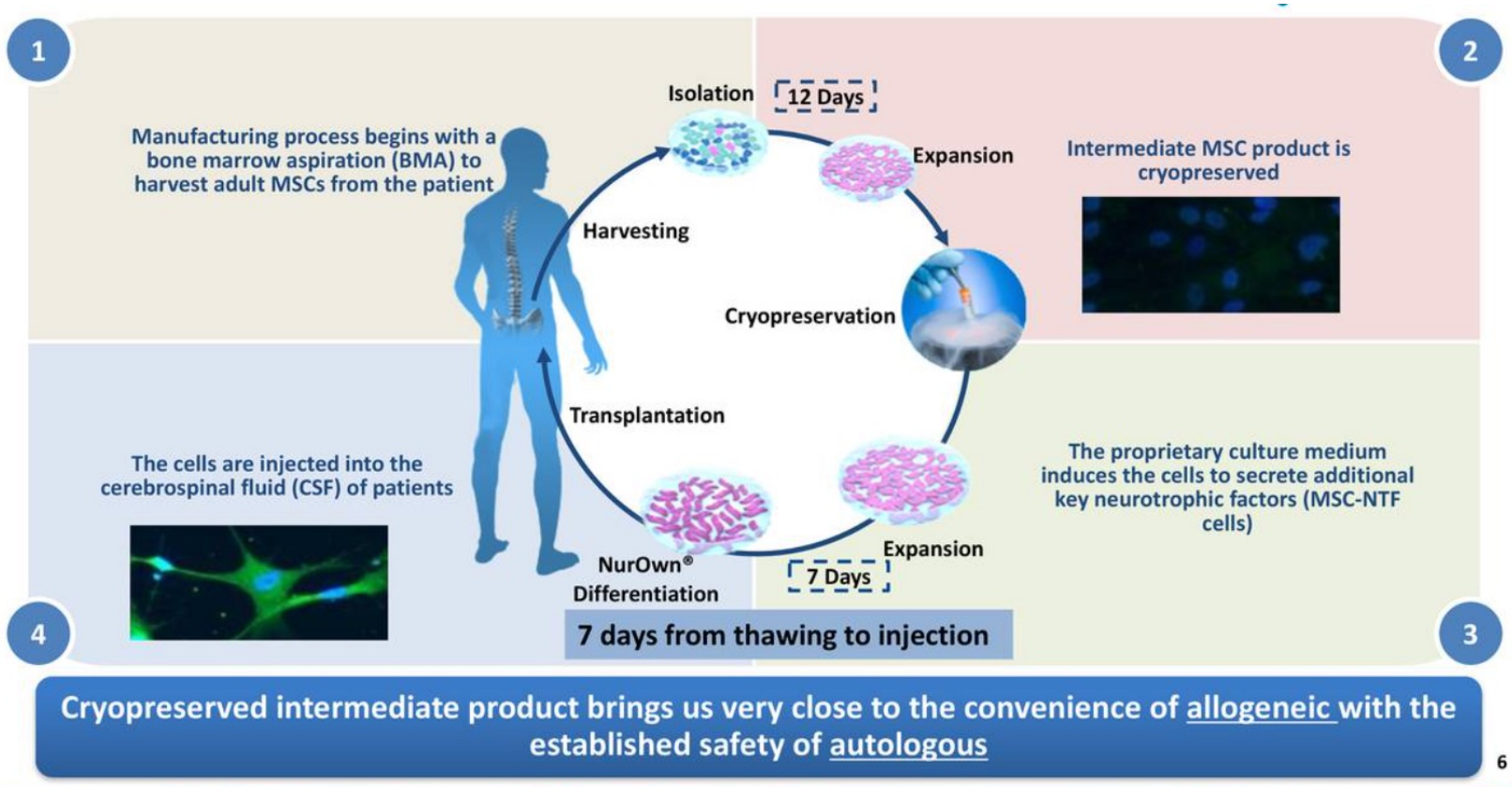
Oki R, Izumi Y, Fujita K, et al; Japan Early-Stage Trial of Ultrahigh-Dose Methylcobalamin for ALS (JETALS) Collaborators. Efficacy and safety of ultrahigh-dose methylcobalamin in early-stage amyotrophic lateral sclerosis: a randomized clinical trial. *JAMA Neurol.* Published online May 9, 2022. doi:10.1001/jamaneurol.2022.0901

VITAMIN B12 – Phase 3 Studie

Teilnehmerzahl zu niedrig (129 Patient*innen)

Studiendauer zu niedrig (16 Wochen)

Stammzellen in der ALS-Forschung: NurOwn Studie



NurOwn: Phase 3 Studie

Stammzellen werden aus dem Knochenmark entnommen

3-malige Verabreichung in den Spinalkanal (Woche 0, 8, 16)

Endpunkt: Verlangsamung um 1,25 Punkte im ALSFRSR

95 Patient*innen mit Stammzellen: **32,6%**

94 Patient*innen mit Placebo: **27,8%**

KEIN UNTERSCHIED

NurOwn: Phase 3 Studie

CLINICAL RESEARCH ARTICLE

MUSCLE&NERVE WILEY

A randomized placebo-controlled phase 3 study of mesenchymal stem cells induced to secrete high levels of neurotrophic fa

Merit E. Cudkowicz MD | Stacy R. Lindborg PhD | Namita A. Goyal MD |
Nathan P. Staff MD | Margaret A. Owegi DO | Donald A. Berry PhD |
Yael Gothelf PhD |
Ralph Z. Kern MD |

Patient*innen im frühen Stadium (ALSFRSR >35 Punkte)

26 Patient*innen mit Stammzellen: **34,6%**

32 Patient*innen mit Placebo: **15,6%**

KEIN UNTERSCHIED

NurOwn: Weitere Analysen

ERRATUM

MUSCLE&NERVE WILEY

An erratum is being issued to the article published in March 2022 in Muscle&Nerve 65(3):291–302, to ensure that data from the trial is shown correctly per the prespecified analysis plan. Subgroup analyses reported in the original publication for the key secondary endpoint, average change from baseline to endpoint in ALSFRS-R, used an incorrect model and incorporated interaction terms between the subgroup and treatment. These analyses have been corrected to employ the pre-specified efficacy model for subgroup analysis. The following corrections and clarifications apply to this publication and its supplement document.

DOI: 10.1002/mus.27478

UNTERSCHIED bei anderen Grenzwerten

ALS NEWS TODAY

Home About ALS Treatments

News > BrainStorm Plans to File for NurOwn Approval in US for ALS

BrainStorm Plans to File for NurOwn Approval in US for ALS

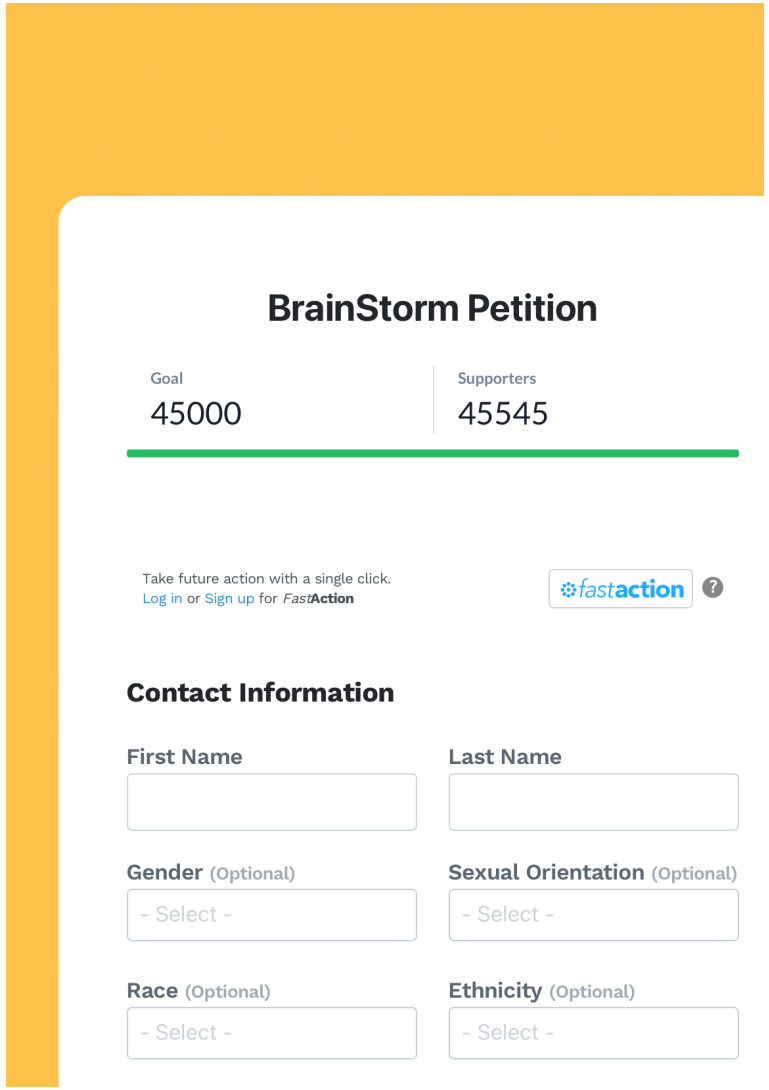
Corrected trial data show better efficacy than initially reported

by *Marta Figueiredo, PhD* | August 19, 2022

TAKE ACTION

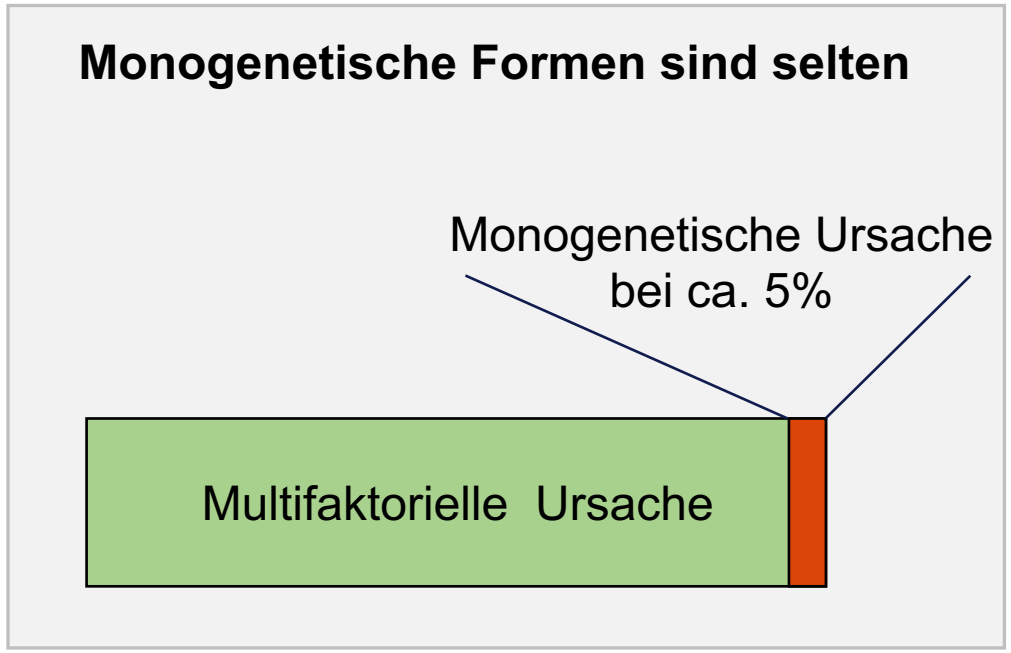
ALS community petitions BrainStorm and the FDA to urgently determine a path forward for NurOwn

Share

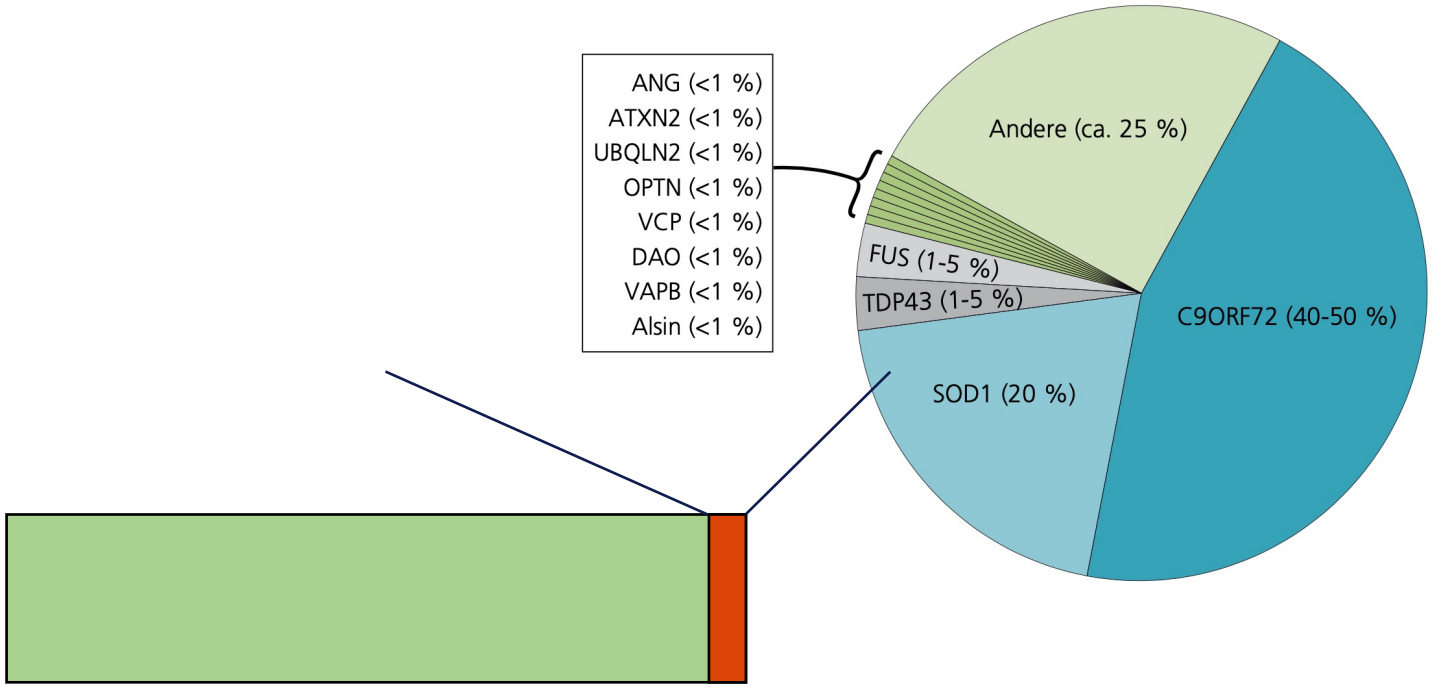


Genetische Therapien

Genetik der ALS

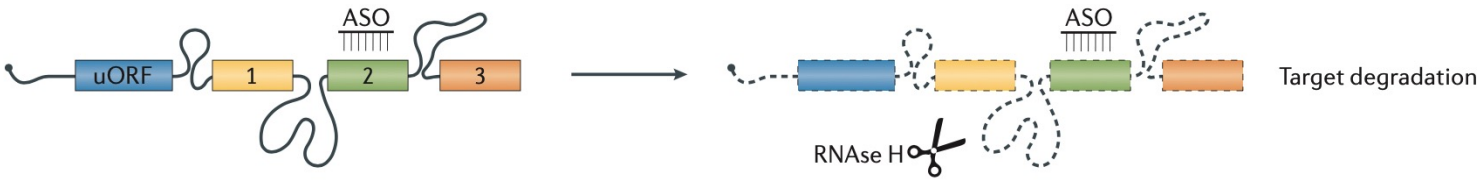


Genetik der ALS



Monogenetische Ursache

Tofersen gegen SOD1-ALS: VALOR Phase 3 Studie



Antisense-Oligonukleotid (ASO) gegen SOD1-mRNA

Rinaldi & Wood, 2017, *Nat Rev Neurol*

Tofersen gegen SOD1-ALS: Phase 3 Studie

Injektion von 100mg Tofersen in den Spinalkanal

72 Patient*innen mit Tofersen

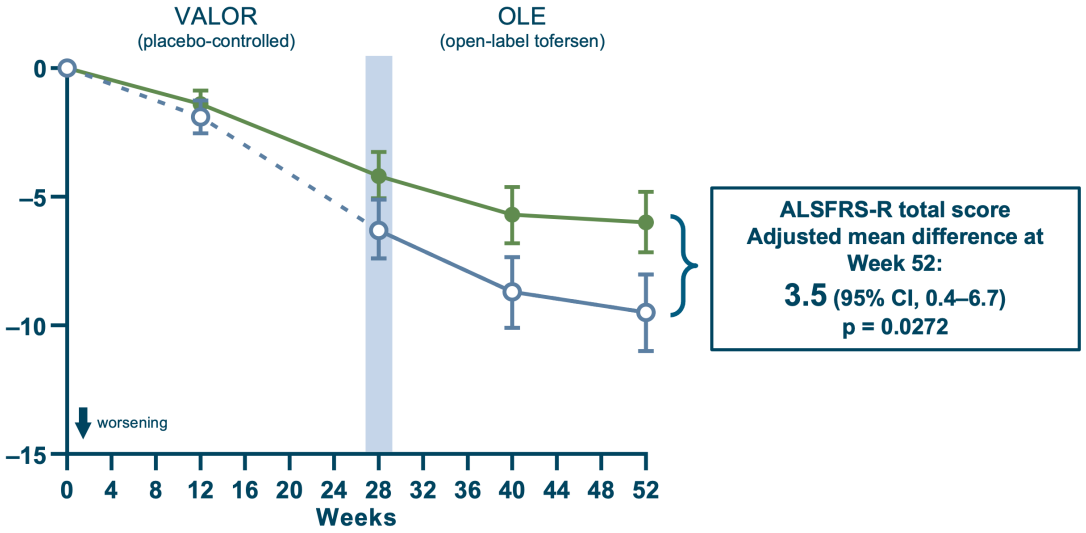
36 Patient*innen mit Placebo

Endpunkt: ALSFRSR, Lungenfunktion, Überleben, Neurofilamente

Beurteilung nach 28 und 52 Wochen

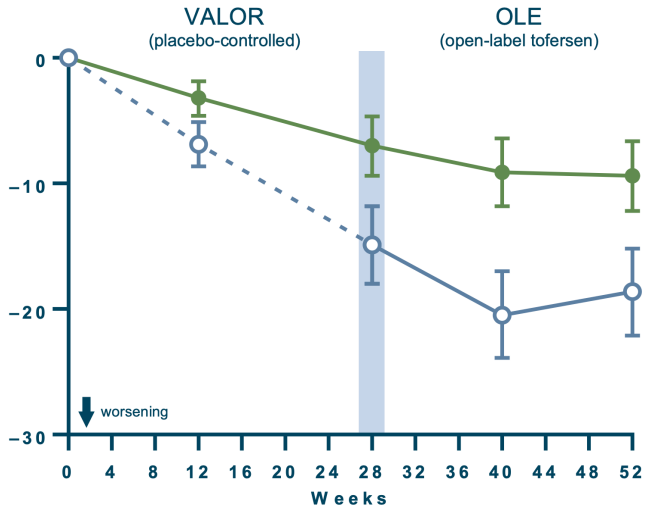
Tofersen gegen SOD1-ALS: Phase 3 Studie

ALSFRSR



ALSFRS-R total score
Adjusted mean difference at Week 52:
3.5 (95% CI, 0.4–6.7)
p = 0.0272

Lungenfunktion



Percent-predicted SVC
Adjusted mean difference at Week 52:
9.2 (95% CI, 1.7–16.6)
p = 0.0159

ALS NEWS TODAY

Home About ALS Treatments

News > Tofersen Early Access Program Now Open to SOD1-ALS Patients

Tofersen Early Access Program Now Open to SOD1-ALS Patients

by *Marta Figueiredo, PhD* | July 2, 2021

ZERBOR/SHUTTERSTOCK

Auch in Wien !

Jacifusen gegen FUS-ALS

KURIER

ABO ANMELDEN

FORSCHUNG

30.08.2022

Muskellähmung gestoppt: Hoffnung für ALS-Patienten

Ein neues Medikament zeigt bei einer Patientin, dass sich die genetisch bedingte Form der unheilbaren Nervenkrankheit aufhalten lässt.

Jacifusen gegen FUS-ALS

Jacifusen in den Spinalkanal, 77 Patient*innen

Teil 1 für 61 Wochen

Teil 2 für 85 Wochen (OLE)

Endpunkt: ALSFRSR, Lungenfunktion, Überleben, Neurofilamente

Ergebnisse 2025 erwartet

Danke für die Aufmerksamkeit!

ALS Charity Radtour, Wien 2021
@Neurobikedownthedanube
Michael Craig Gradwell

Bei Fragen: hakan.cetin@meduniwien.ac.at