AMYOTROPHE LATERALSKLEROSE (ALS)

Neues aus der Forschung

Prof. Dr. Markus Weber

Nationaler ALS Tag, 23. Juni, Eventforum Bern

ALS Forschung

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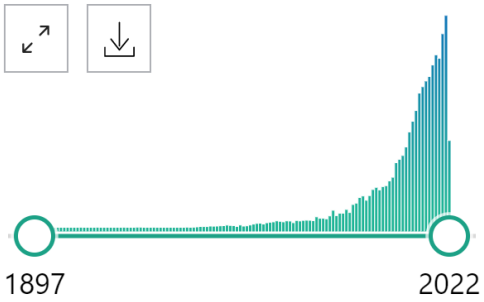
RESULTS BY YEAR



1 Cite Share

Amyotrophic lateral sclerosis.

Hardiman O, Al-Chalabi A, Chio A, Corr EM, Logroscino G, Robberecht W, Shaw PJ, Simmons Z, van den Berg LH.

Nat Rev Dis Primers. 2017 Oct 5;3:17071. doi: 10.1038/nrdp.2017.71.

PMID: 28980624 Free article. Review.

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease, is characterized by the degeneration of both upper and lower motor neurons, which leads to muscle weakness and eventual paralysis. ...

Woher kommt ALS?

ALS ist eine komplexe Erkrankung

Erbsubstanz-Genetik

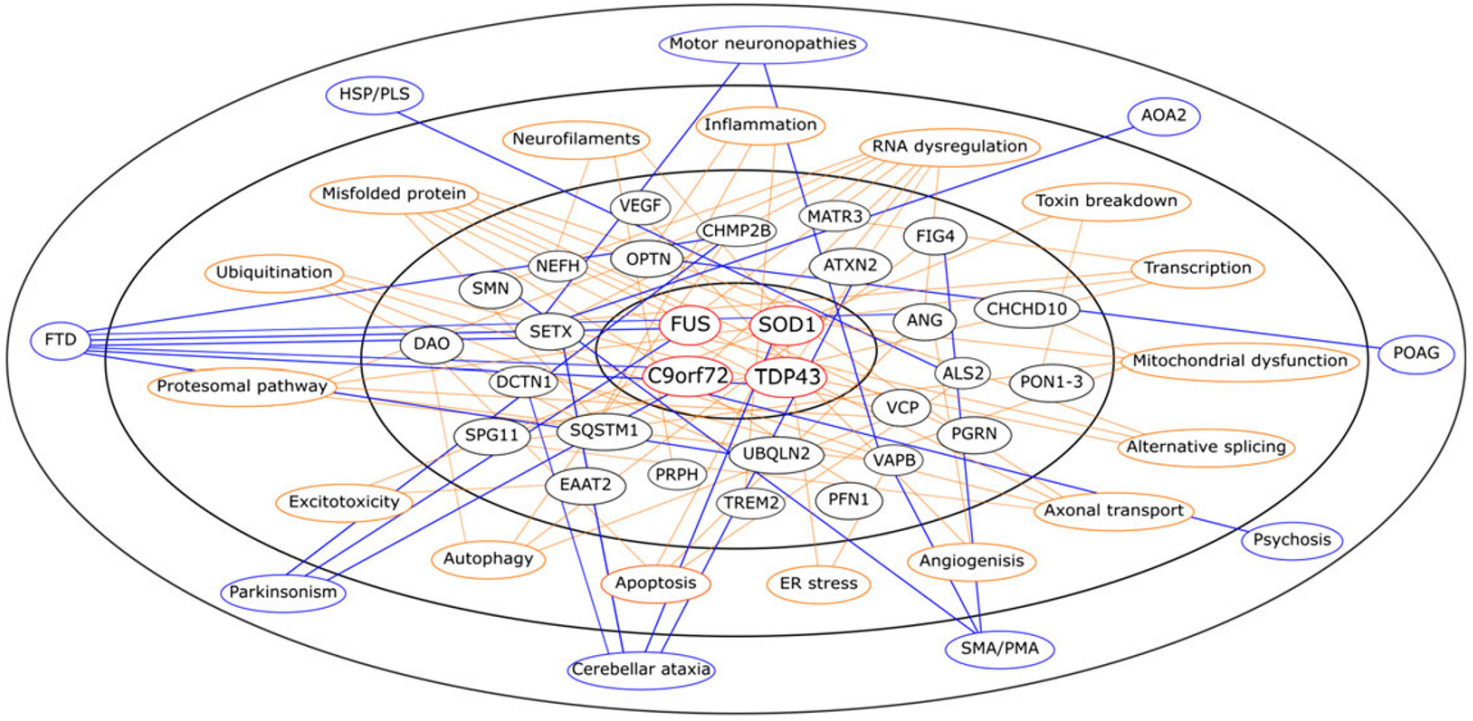


Fig. 2 An illustration of the complexity of ALS pathogenesis. The inner circle includes the associated genes with highest frequency (*C9orf72*, *SOD1*, *TDP-43*/*TARDBP* and *FUS*). The second-order ring includes the large number of genes with a lower frequency of association. The third-order ring includes the possible pathogenic mechanisms that are hypothesized to be associated with these genes. The outer ring includes the other diseases that may be associated with these genes. The complex relationship between genes associated with neurodegeneration, mechanisms of neurodegeneration, and clinical disease phenotypes is apparent. Red = major genes; Black = minor genes; Orange = disease mechanisms; Blue = associated diseases. Mechanistic connections are illustrated by orange lines, and disease associations by blue lines.

Umwelt

Das et al. N Am J Med Sci. 2012; 4(8): 350–355

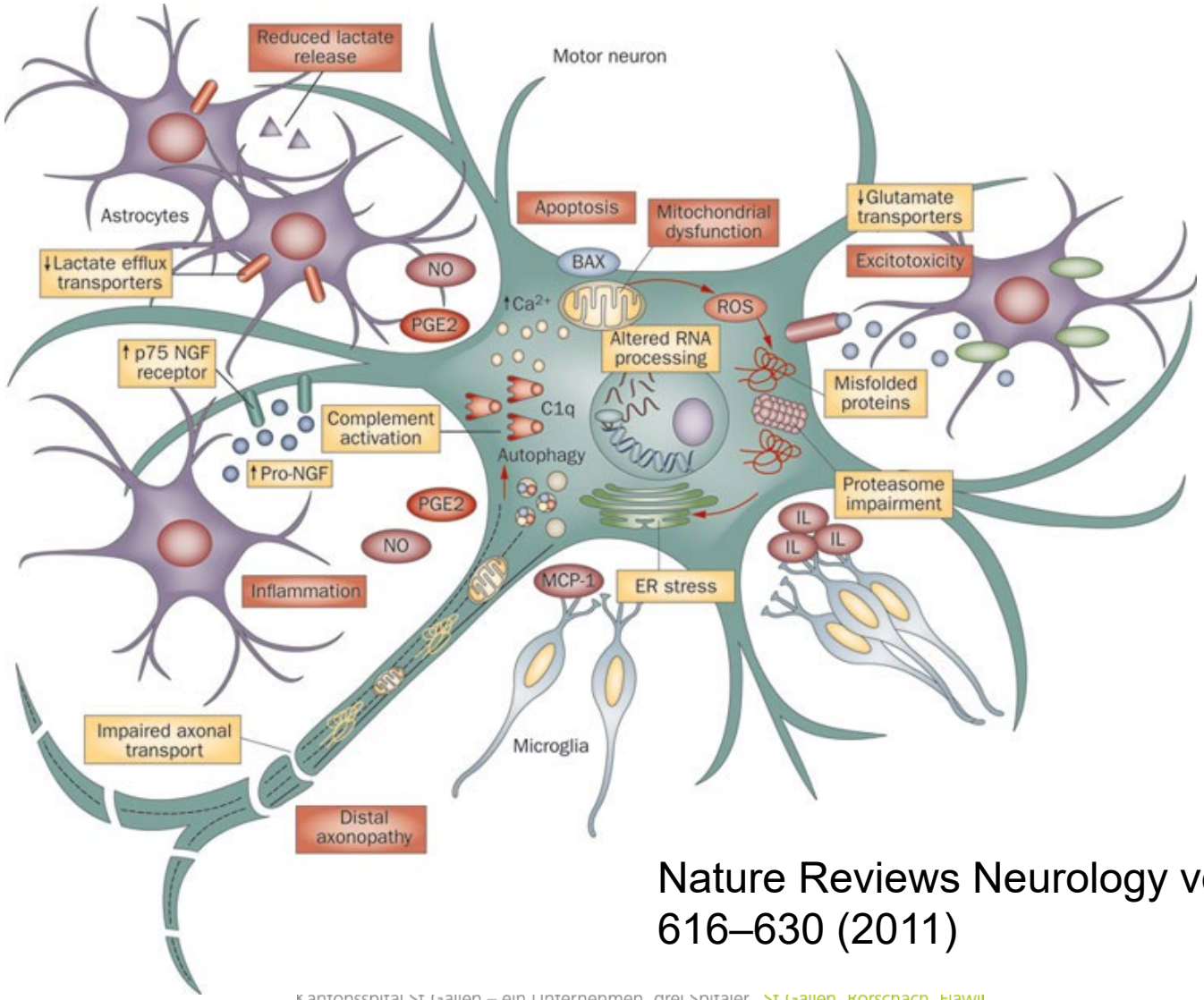
n J Med Sci

Significance level of the risk factors

Risk factors	Total			Male		Female	
	P value	Odds ratio	95% CI	Odds ratio	95% CI	Odds ratio	95% CI
Occupation							
Farming	0.80416	1.07	(0.62–1.85)	0.99	(0.49–1.99)	0.867	(0.26–2.89)
Industrial	0.90126	1.09	(0.29-4.09)	1.05	(0.28–3.93)	–	–
Mining	0.57198	0.55	(0.09–3.53)	0.51	(0.08–3.34)	–	–
Official/Business	0.95314	0.87	(0.28–2.68)	0.83	(0.26–2.57)	–	–
House Work/Students	0.20675	1.57	(0.79–3.12)	1.52	(0.49–4.70)	1.15	(0.35–3.85)
Living places							
Rural	0.037	1.99	(1.02–3.88)	2.45	(1.18–5.75)	1.04	(1.31–3.48)
Urban	0.063	0.50	(0.26–0.98)	0.40	(0.17–1.74)	0.96	(0.28–3.24)
Toxin exposure							
Insecticides/Pesticides	0.030	1.61	(1.27–1.99)	1.09	(1.27–2.79)	3.51	(1.11–12.25)
Heavy metals (iron)	0.811	1.09	(0.29-4.09)	1.05	(0.27–3.93)	–	–
Solvents/Chemicals	–	–	–	–	–	–	–
Smoking							
Smoking present	0.009	1.88	(1.19–2.96)	2.04	(1.23–3.35)	0.91	(0.22–3.66)
Source of drinking water							
Tube Well	0.249	1.41	(0.79–2.54)	1.25	(0.63–2.48)	1.72	(0.52–5.71)
Well Water	0.859	0.99	(0.46–2.14)	1.05	(0.44–2.25)	0.89	(0.18–4.39)
Ponds	0.253	0.46	(0.13–1.65)	0.83	(0.183–3.79)	0.91	(0.11–6.72)
Corporation supplied water	0.288	1.26	(0.80–2.67)	0.51	(1.51–1.76)	0.47	(0.11–2.18)
Others factors							
Electrical trauma	0.003	6.20	(1.75–21.98)	6.64	(1.512–29.16)	6.15	(0.74–51.05)
Working under electromagnetic field	–	–	–	–	–	–	–

N Am J Med Sci

Viele Krankheitsmechanismen

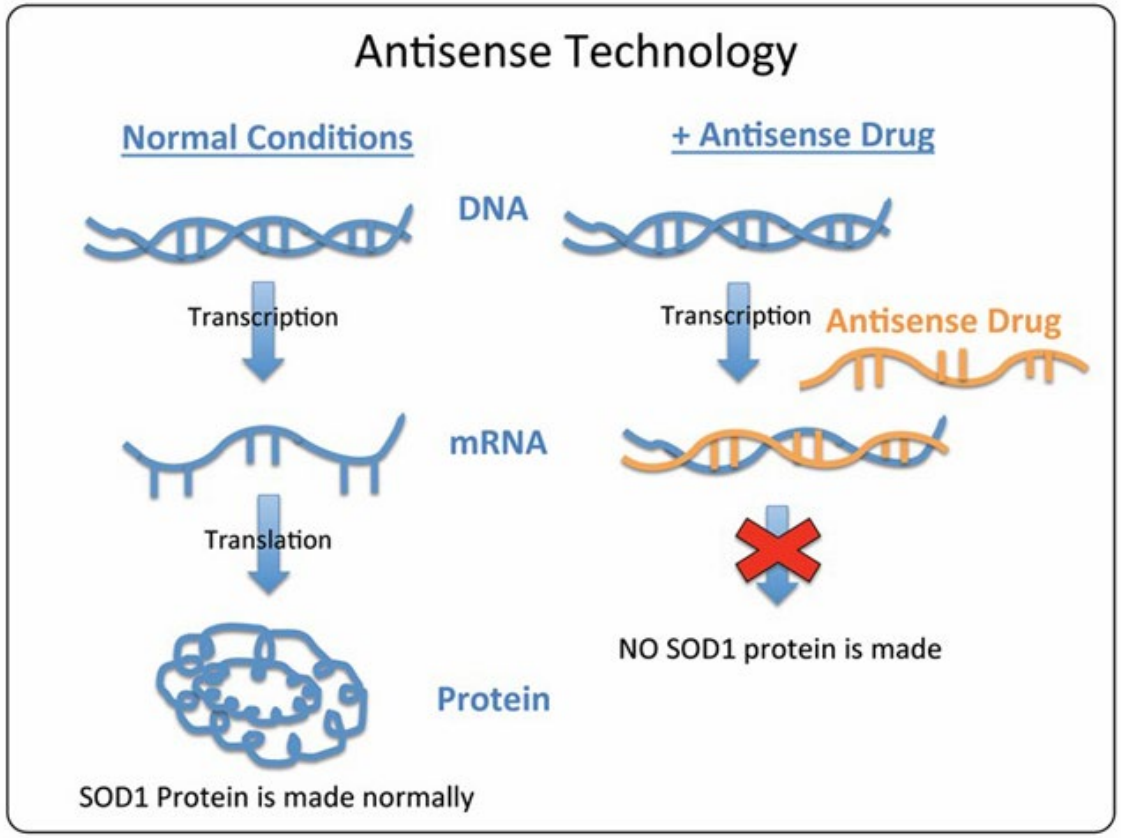


Nature Reviews Neurology volume 7, pages 616–630 (2011)

Was sind die Herausforderung bei der Entwicklung neuer Medikamente ?

- Unklar inwieweit Forschungsergebnisse von Tiermodellen auf Menschen übertragbar sind.
- ALS ist sehr variabel (heterogen)
  - «jeder hat seine eigene Krankheit»
- Es braucht für Studien hunderte Patienten und eine lange Studiendauer
  - teuer
- Was sind die besten einfachen Messgrössen zum Nachweis von Therapieeffekten (Biomarker)?

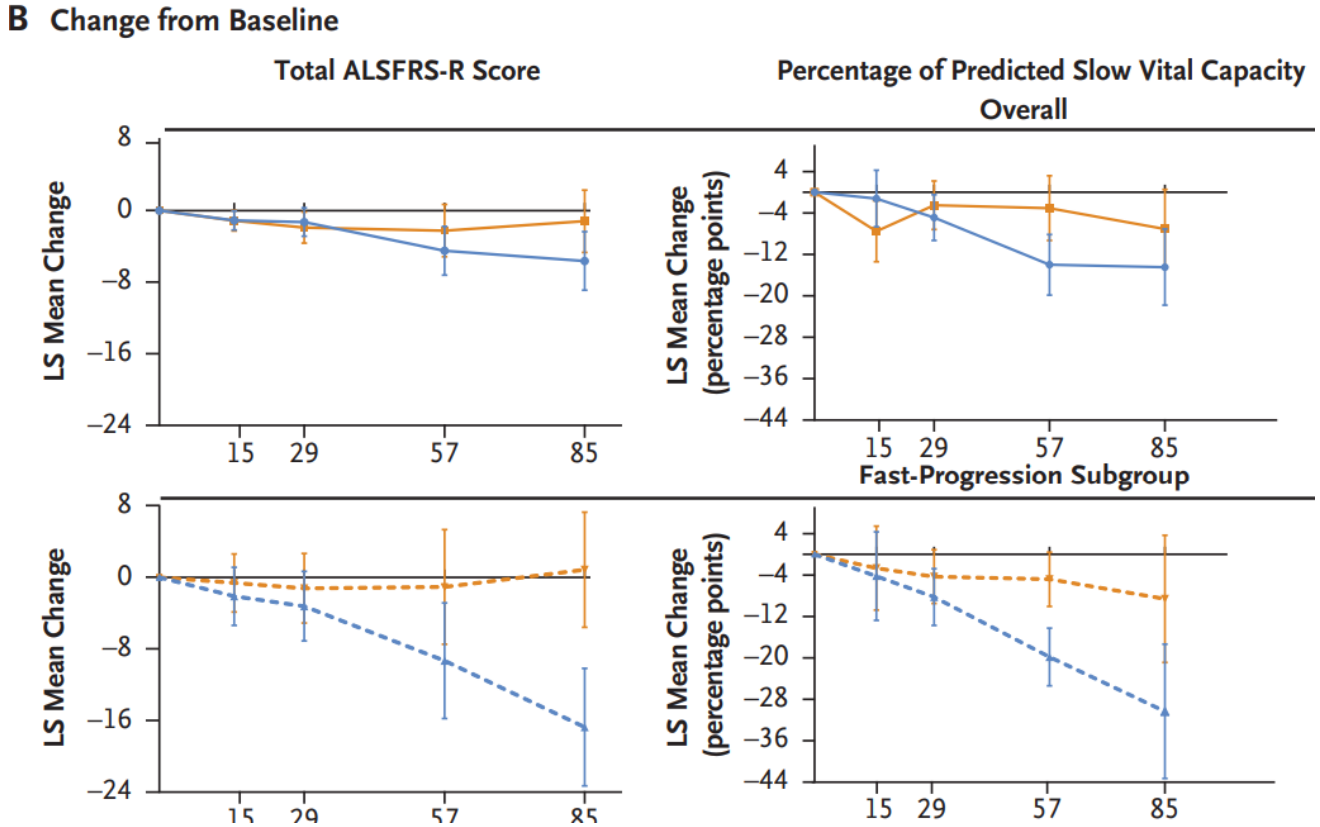
Antisense Technology



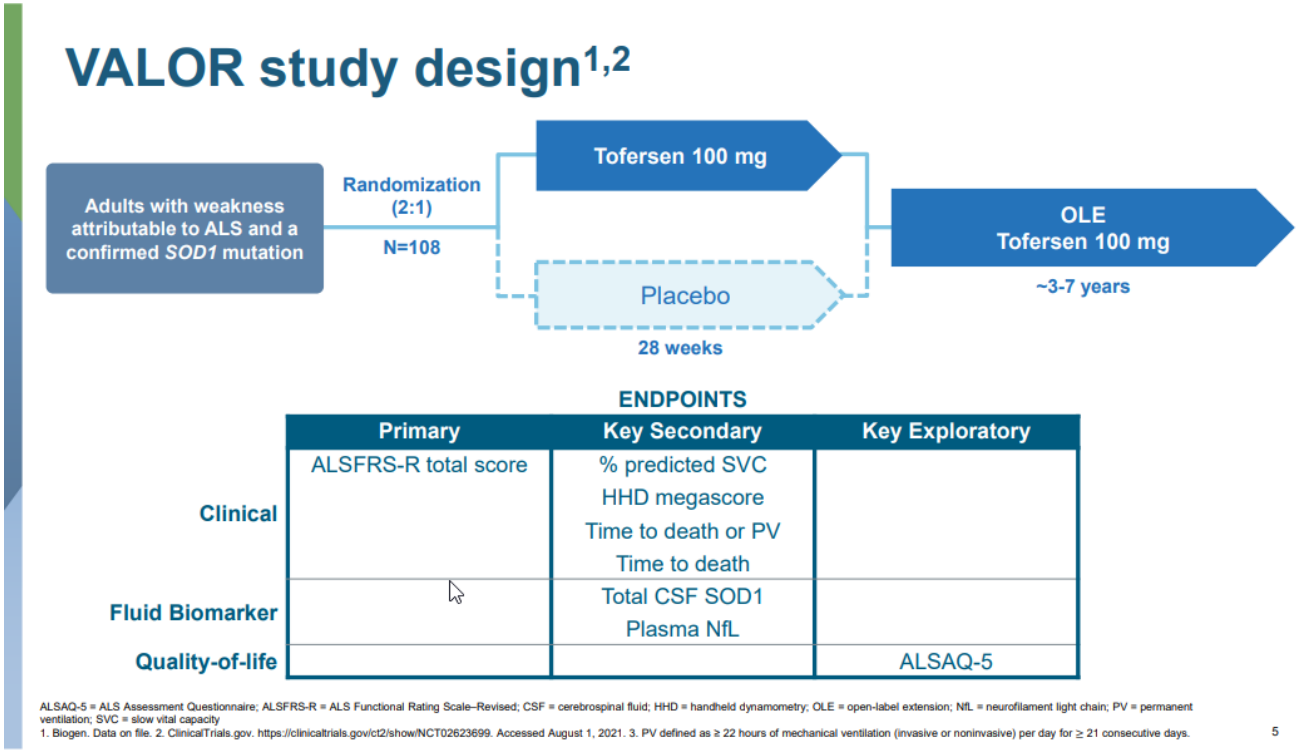
Antisense technology works to eliminate mutated protein by preventing it from being created.

Phase 1–2 Studie of Antisense Oligonucleotide Tofersen bei familiärer SOD1 ALS

T. Miller, M. N Engl J Med, July 9, 2020



VALOR



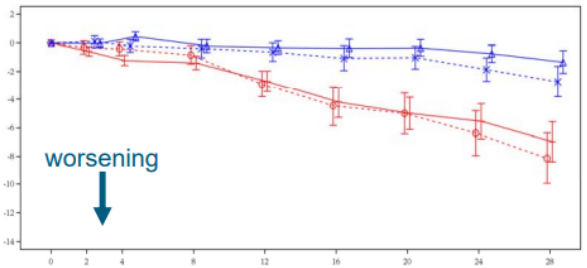
https://investors.biogen.com/static-files/b2154d4e-f69f-49d4-9a61-e834387293ea

Effect on clinical function

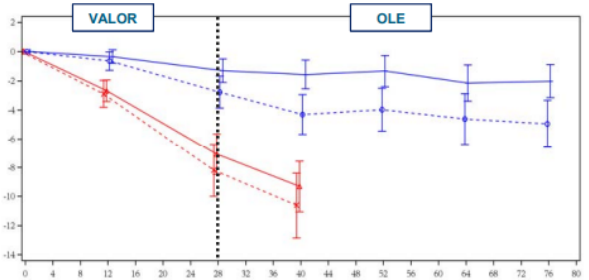
Adjusted mean (± SE) change from baseline in ALSFRS-R

Faster-progressing (mITT), tofersen (n=39)
Faster-progressing (mITT), placebo → tofersen (n=21)
Slower-progressing (non-mITT), tofersen (n=33)
Slower-progressing (non-mITT), placebo → tofersen (n=15)

VALOR
(Primary endpoint)



VALOR + OLE



	Placebo	Tofersen	Difference Tofersen vs Placebo (p-value)
Faster-progressing (mITT); Week 28	-8.14	-6.98	1.2 (p=0.97 joint rank)
Slower-progressing (non-mITT); Week 28	-2.73	-1.33	1.4

	Placebo → tofersen	Early-start tofersen	Difference Tofersen vs Placebo (95% CI)
Faster-progressing (mITT); Week 40	-10.6	-9.3	1.3 (-4.1, 6.7)
Slower-progressing (non-mITT); Week 76	-4.9	-2.0	2.9 (-0.7, 6.6)

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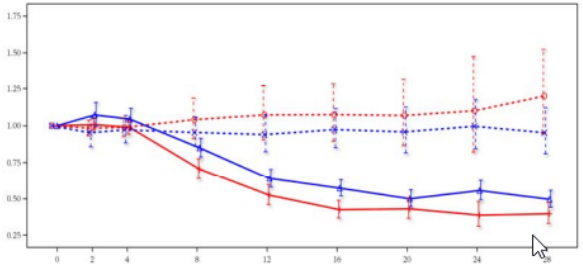
Effect on neurofilament

LS geometric mean ratio (95% CI) to baseline of plasma NfL

Faster-progressing (mITT), tofersen (n=39)
Faster-progressing (mITT), placebo → tofersen (n=21)
Slower-progressing (non-mITT), tofersen (n=33)
Slower-progressing (non-mITT), placebo → tofersen (n=15)

VALOR

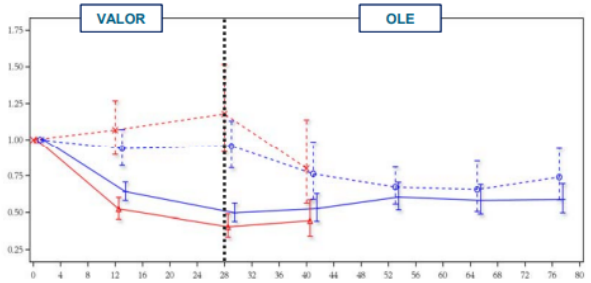
(Key secondary endpoint)



Weeks from VALOR baseline

	Placebo	Tofersen	Geo mean ratio Tofersen:Placebo (p-value)
Faster-progressing (mITT); Week 28	1.20 (20% incr)	0.40 (60% decr)	0.33 (p<0.0001)
Slower-progressing (non-mITT); Week 28	0.95 (5% decr)	0.50 (50% decr)	0.52

VALOR + OLE



Weeks from VALOR baseline

	Placebo → tofersen	Early-start tofersen	Geo mean ratio Tofersen:Placebo (95% CI)
Faster-progressing (mITT); Week 40	0.80 (20% decr)	0.45 (55% decr)	0.56 (0.36, 0.86)
Slower-progressing (non-mITT); Week 76	0.74 (26% decr)	0.59 (41% decr)	0.79 (0.60, 1.05)

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https://investors.biogen.com/static-files/b2154d4e-f69f-49d4-9a61-e834387293ea

Biogen

Update on Tofersen Early Access Program Part 1

Part 1 of Biogen's Early Access Program (EAP) for the most rapidly progressing SOD1-ALS patients is now open. Beginning June 25, 2021, physicians may submit requests on behalf of patients who meet the inclusion/exclusion criteria by emailing MedicineAccess@clinigengroup.com. Biogen will be ready to ship tofersen to eligible sites to be available for administration as early as July 15, once appropriate documentation and regulatory requirements have been met.

We plan to initiate the Part 2 EAP for the broad SOD1-ALS population, if results from the Phase 3 study indicate that tofersen is safe and effective, and if no further studies are required.

Update on Tofersen Clinical Program:

Dear members of the ALS community,

C9Orf

Row	Saved	Status	Study Title	Conditions	Interventions
9	☐	Completed	A Study to Assess the Safety, Tolerability, and Pharmacokinetics of BIIB078 in Adults With **C9ORF**72-Associated Amyotrophic Lateral Sclerosis	• Amyotrophic Lateral Sclerosis	• Drug: BIIB078 • Drug: Placebo
10	☐	Active, not recruiting	Study to Assess the Safety, Tolerability, Pharmacokinetics, and Effect on Disease Progression of BIIB078 Administered to Previously Treated Adults **C9ORF**72-Associated Amyotrophic Lateral Sclerosis (ALS)	• Amyotrophic Lateral Sclerosis	• Drug: BIIB078

ARTICLES
https://doi.org/10.1038/s41591-021-01615-z
nature medicine

Check for updates

OPEN

Antisense oligonucleotide silencing of FUS expression as a therapeutic approach in amyotrophic lateral sclerosis

Vladislav A. Korobeynikov[1,2,6], Alexander K. Lyashchenko[1,2,6], Beatriz Blanco-Redondo[1,5,6], Paymaan Jafar-Nejad[3] and Neil A. Shneider[1,4] ✉

Fused in sarcoma (FUS) is an RNA-binding protein that is genetically and pathologically associated with rare and aggressive

Anna 8.11.2021 (started on Jacifusen 7/2021)

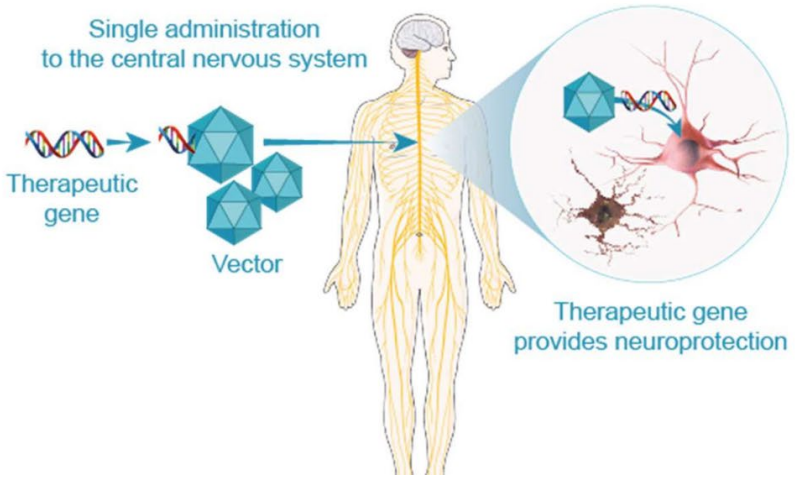
Anna 04.02.22

Viren können auch nützlich sein: Vektoren

Avrion Therapeutics

What is gene therapy:
A new therapeutic modality based on treatment of diseases by altering genes in patients' cells (Fig. 2)
The field of gene therapy has been booming in the last 2-3 years due to several disruptive products on the market today (Luxturna, Zolgensma), with important partnerships and acquisitions by pharma companies.

Figure 2:
'*In vivo*' gene therapy is based on vectors to deliver therapeutic gene sequences to the central nervous system. The most commonly used vectors are derived from adeno-associated (AAV) or lentiviral viruses. Gene therapy can provide neuroprotection via the replacement, addition, silencing or editing of genetic information. **Gene therapy is typically based on a 'single administration' treatment.**

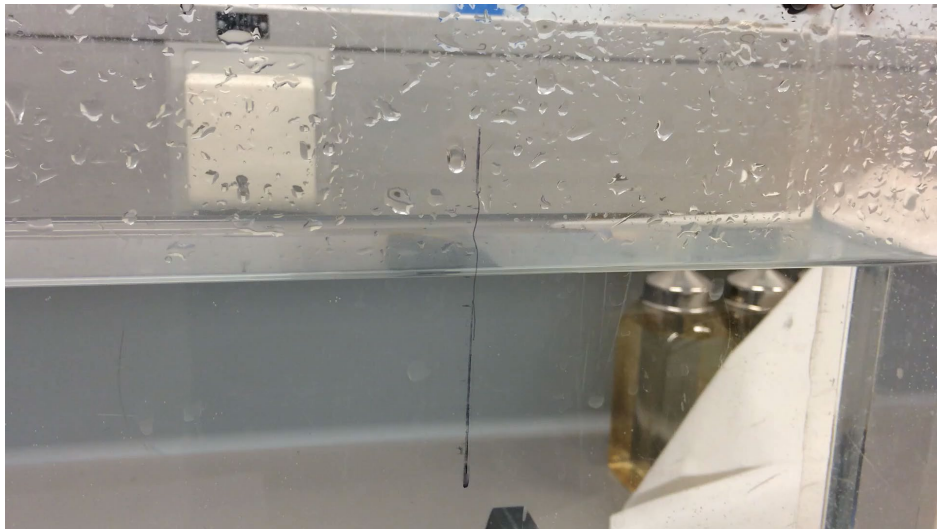


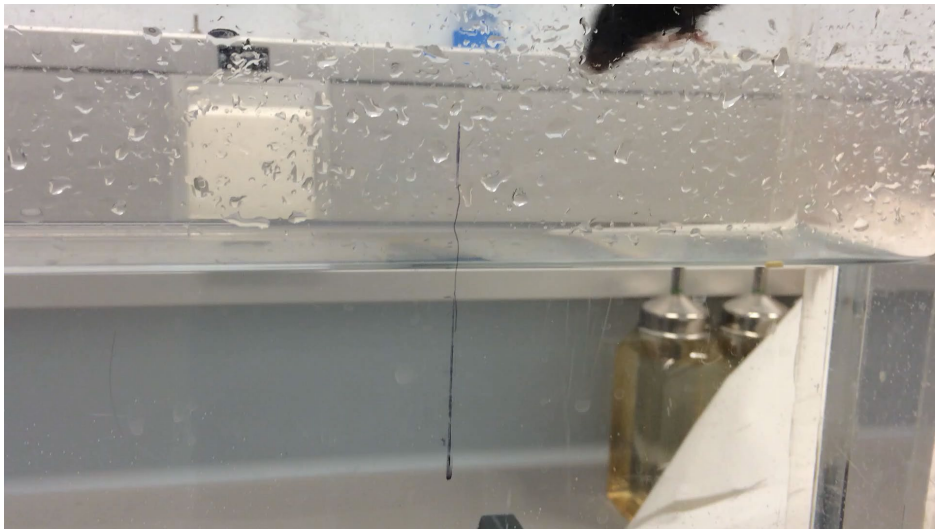
Motorische Funktion bei behandelten Mäusen

fALS SOD1^{G93A} (PBS injected)

fALS SOD1^{G93A}

AAV9-gfaABC$_1$D/syn1-miR SOD1





Muskelzentrum/ALS Clinic

Edaravone (Radicava)

U.S. FOOD & DRUG ADMINISTRATION

FDA Approves Oral Form for the treatment of adults with amyotrophic lateral sclerosis (ALS)

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Action

FDA has approved Radicava ORS (edaravone) oral suspension for the treatment of adults with amyotrophic lateral sclerosis (ALS). Radicava ORS is an orally administered version of Radicava, which was originally approved in 2017 as an intravenous (IV) infusion to treat