

5th Congress of the European Academy of Neurology

Oslo, Norway, June 29 - July 2, 2019

Teaching Course 11

Current treatment in neurology (Level 1)

Examples of successful gene treatment - SMA

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Examples of successful gene treatment

— SMA

Tim Hagenacker



Klinik für
Neurologie



NeuroScienceLab
am Universitätsklinikum Essen



Translational
Neuro- and
Behavioral Sciences



Universitätsmedizin Essen

COI

Speaker Honoraria: Biogen, Roche, Novartis

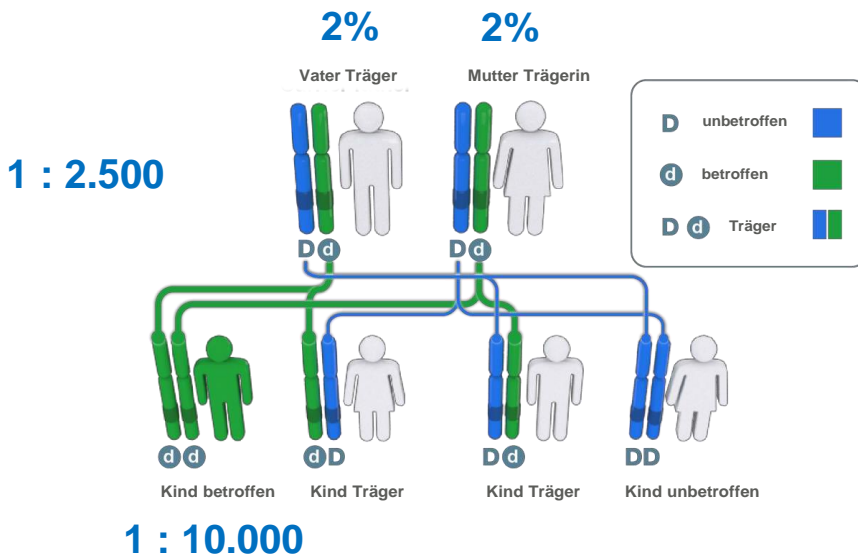
Research support: Biogen

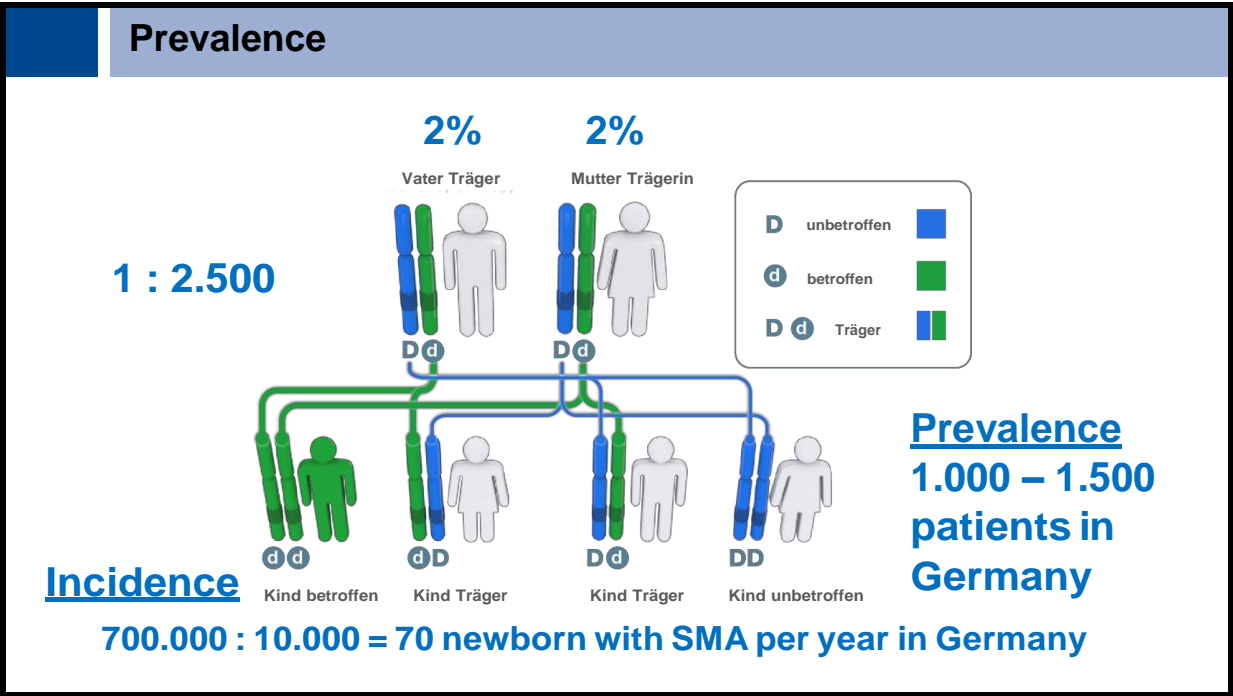
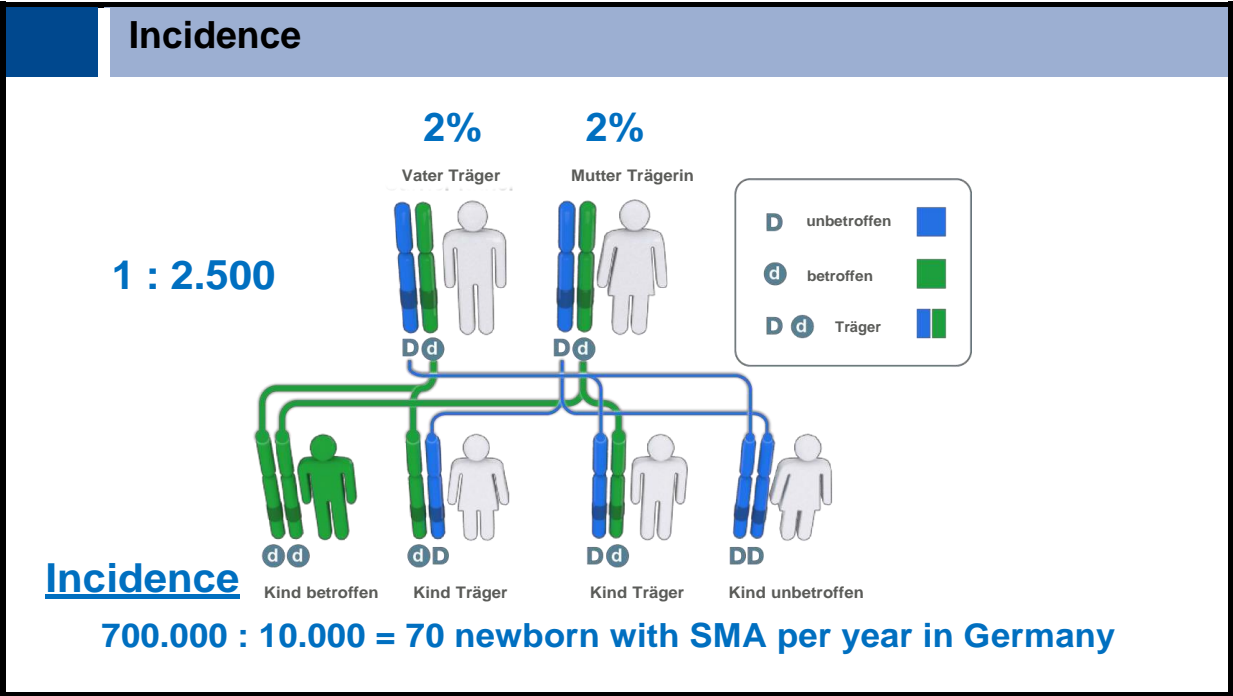
Advisory Board honoraria: Biogen

SMA is the most common genetic course for infant mortality



Inheritance



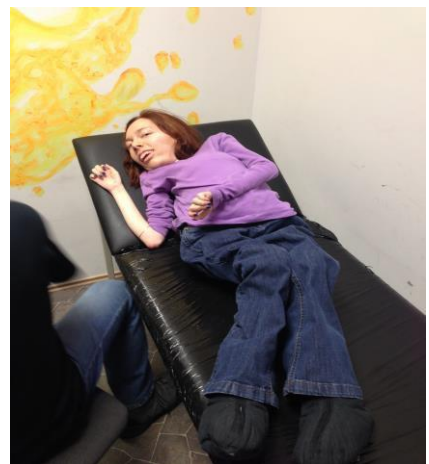


Clinical phenotypes



Clinical phenotypes

Infantile vs. Late-onset SMA

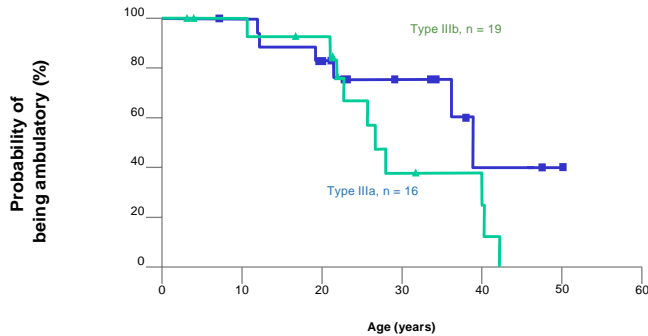


Progression of SMA in adult patients

Disease in adult patients is progressive!!!

Loss of gait/motor function

Increasing need for supportive care

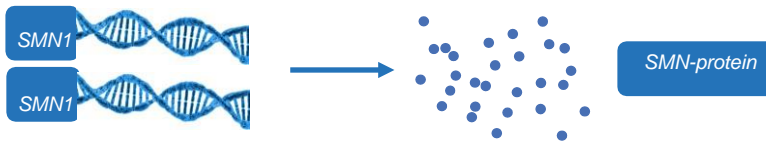


Russman BS, et al. Neurology. 1996;47:973-6.

Chung BH, et al. Pediatrics. 2004;114:e548-53.

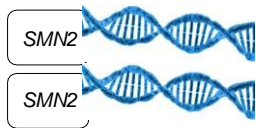
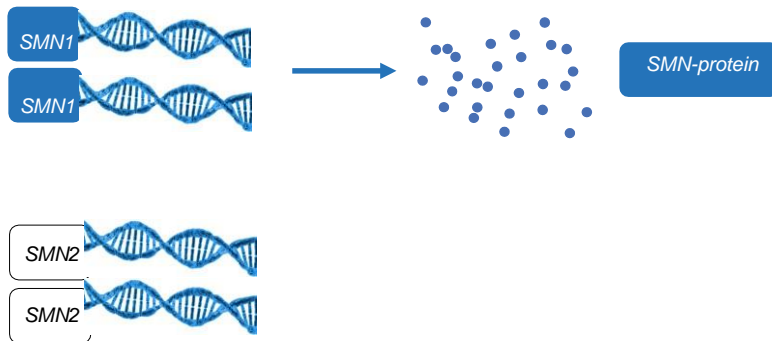
Pathogenesis of SMA

SMN = Survival of Motorneuron



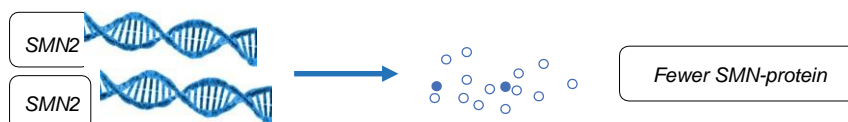
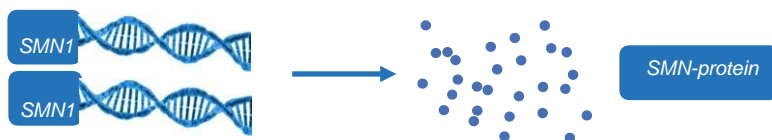
Pathogenesis of SMA

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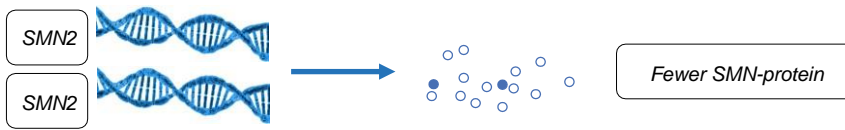
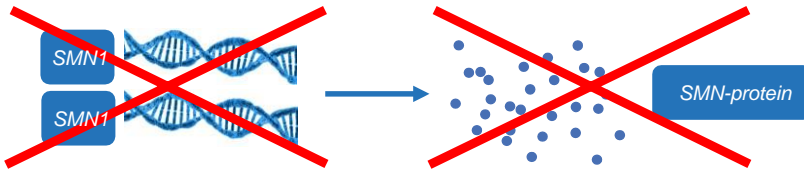
Pathogenesis of SMA

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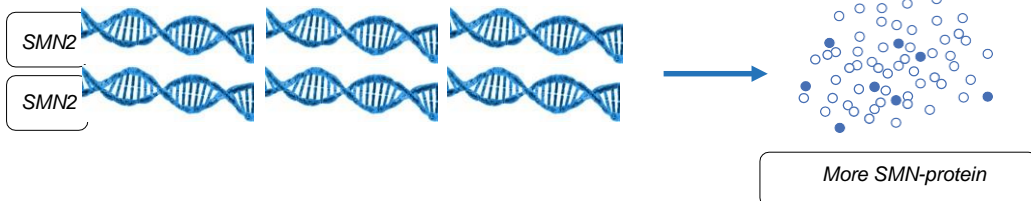
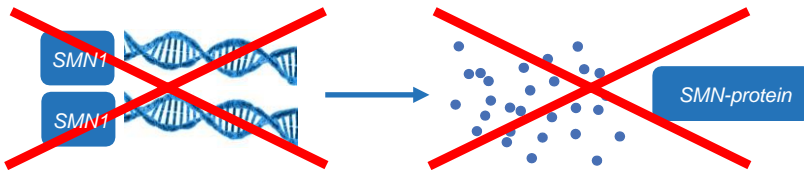
Pathogenesis of SMA

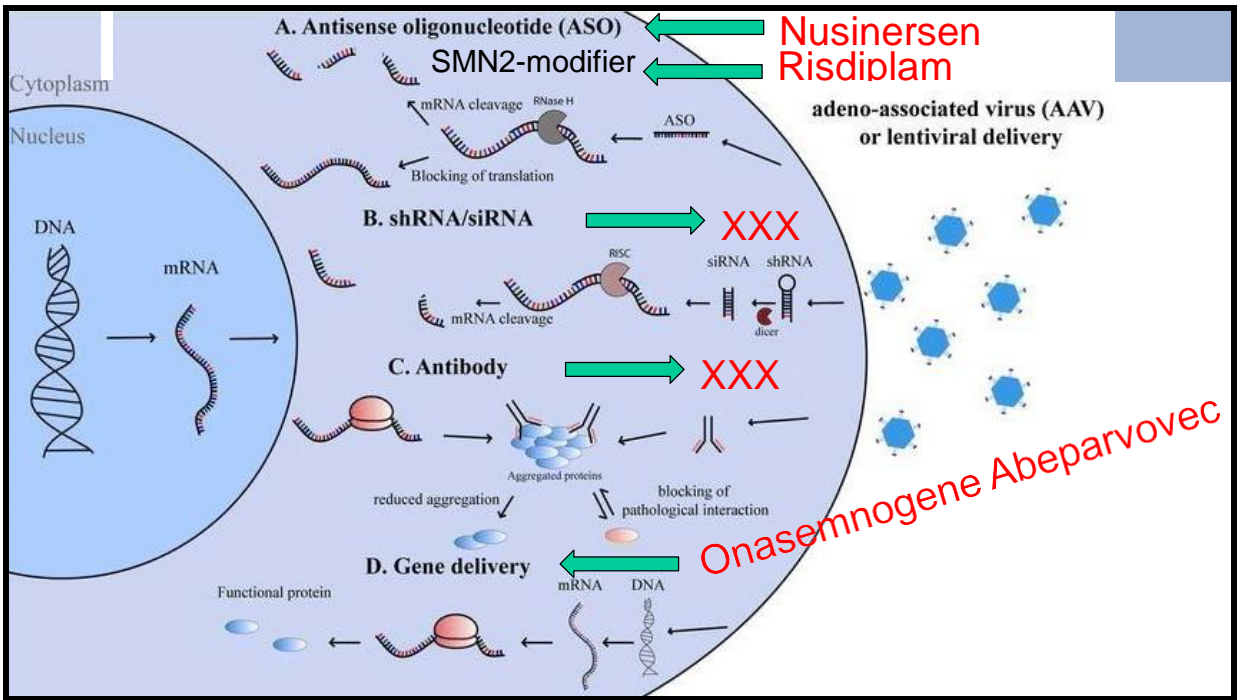
SMN = Survival of Motorneuron



Pathogenesis of SMA

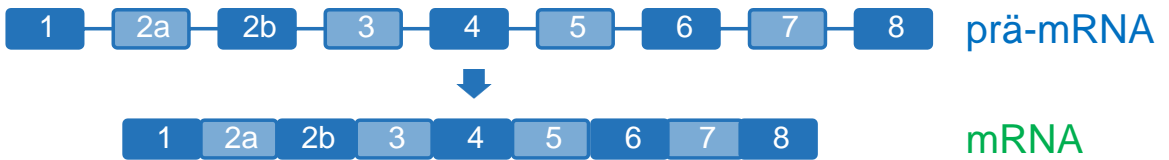
SMN = Survival of Motorneuron



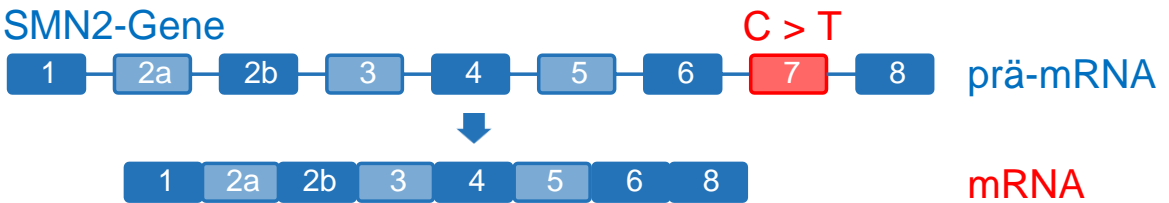


Nusinersen – Mechanism of action

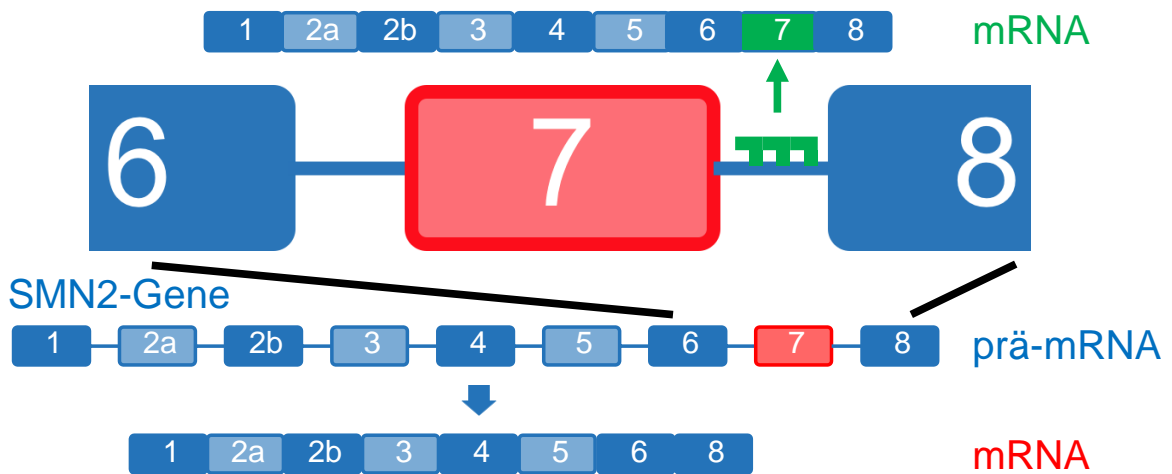
SMN1-Gene



SMN2-Gene

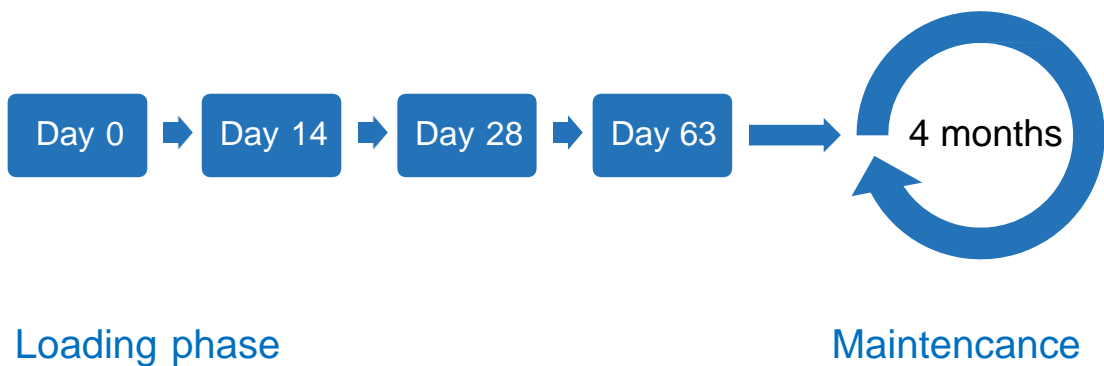


Nusinersen – Mechanism of action



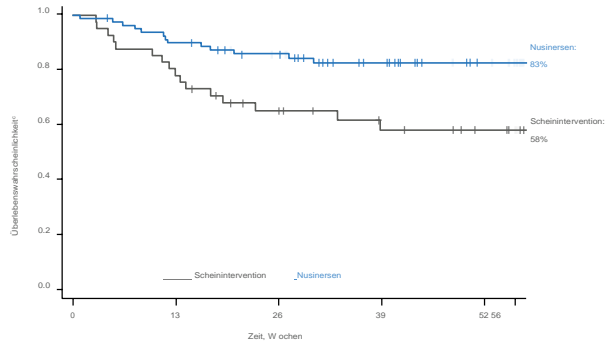
Nusinersen – Mode of application

Intrathecal injection of 12mg, age and weight-independent



Clinical trial data

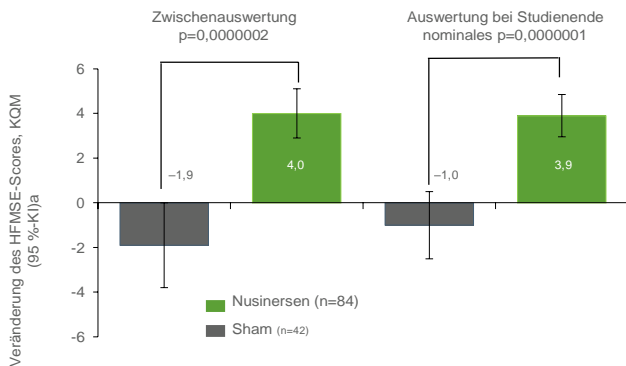
Survival



Scheinintervention	41	33	23	17	12	10
Nusinersen	80	71	58	41	28	23

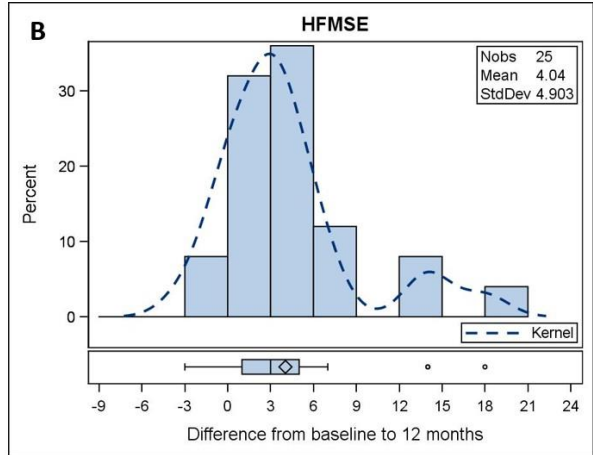
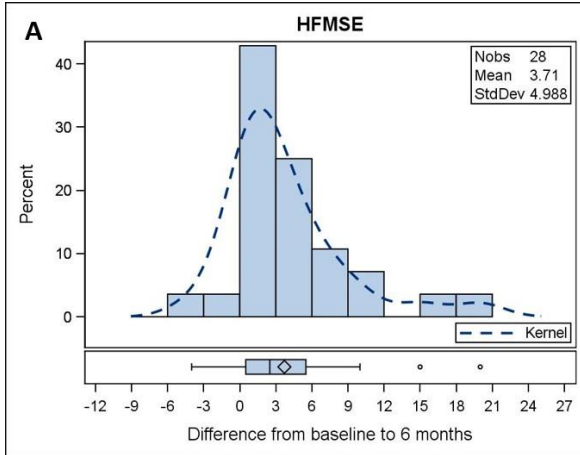
Results in childrens: CHERISH

Increased motor function



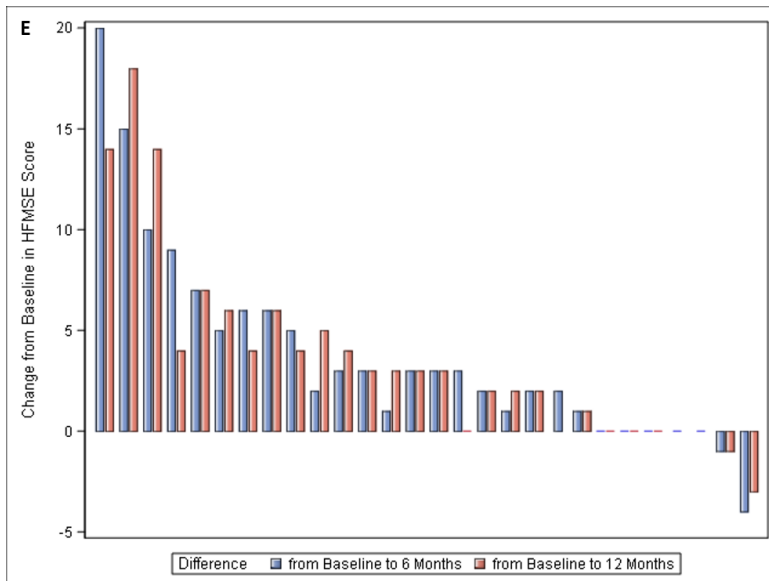
HFMSE: Hammersmith Functional Motor Scale Expanded; KQM: Kleinste-Quadrate-Mittelwerte; SMA: spinale Muskelatrophie. Eine Beschreibung der statistischen Auswertungen findet sich im Notizenext der Folie. a Veränderung zwischen Baseline und Monat 15; Zwischenauswertung: erhobene Daten: Scheinintervention, n = 19; Nusinersen, n = 35; imputierte Daten: Scheinintervention, n = 23; Nusinersen, n = 49. Auswertung bei Studienende: erhobene Daten: Scheinintervention, n = 34; Nusinersen, n = 66; imputierte Daten: Scheinintervention, n = 8; Nusinersen, n = 18. 1. Finkel RS et al. Primary efficacy and safety results from the phase 3 ENDEAR study of nusinersen in infants diagnosed with spinal muscular atrophy (SMA). *Vorgelegt auf der 43. Jahrestagung der British Paediatric Neurology Association*, 11.-13. Januar 2017, Cambridge, Vereinigtes Königreich. 2. Finkel RS et al. *Lancet*, 2016;388(10063):3017-3026. 3. Bertini E et al. Nusinersen in pre-symptomatic infants with spinal muscular atrophy (SMA): interim efficacy and safety results from the phase 2 NURTURE study. *Vorgelegt auf dem 21. Internationalen Kongress der World Muscle Society*, 4.-8. Oktober 2016, Granada, Spanien. 4. Wang CH et al., Teilnehmer der internationalen Fachtagung zu Versorgungsstandards der SMA. *J Child Neurol*, 2007;22(8):1027-1049.

Results of own patients (Motor function)



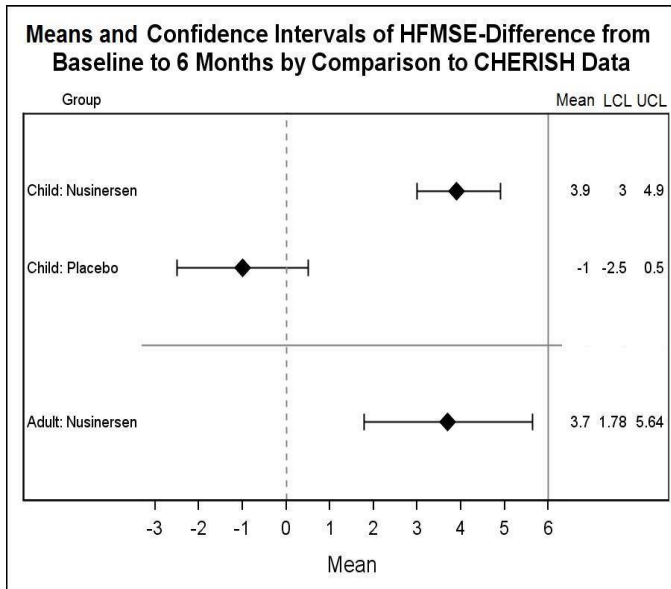
Hagenacker et al., 2019 subm.

Results of own patients (Motor function)



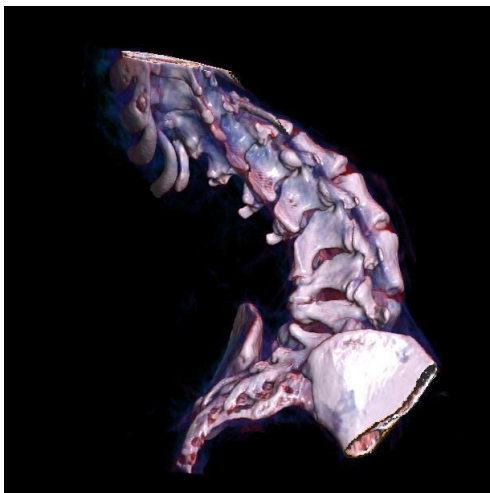
Hagenacker et al., 2019 subm.

Results of own patients (Motor function)



Hagenacker et al., 2019 subm.

Challenges: Scoliosis



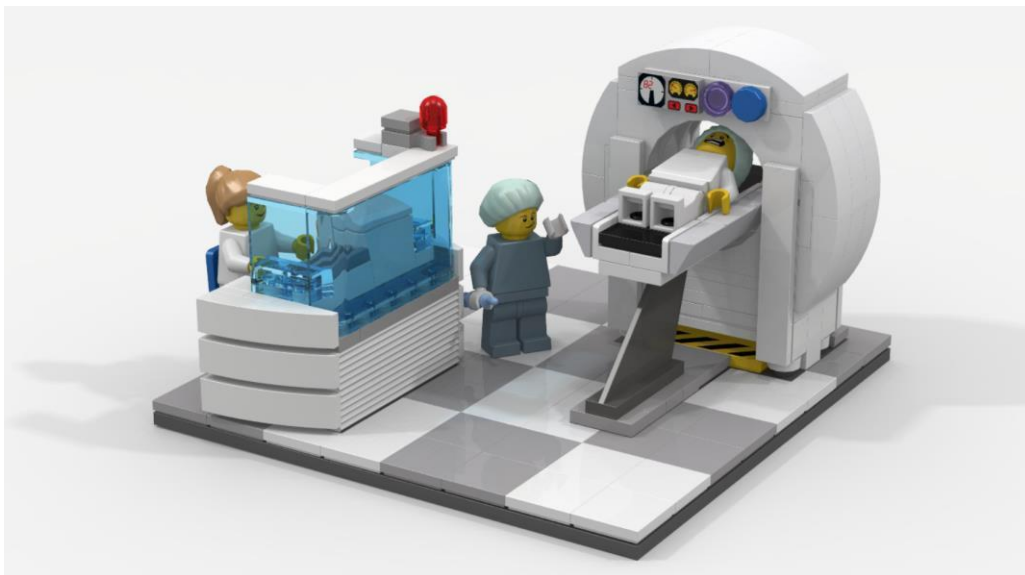
Stolte et al., 2018

Challenges: Spondylodesis

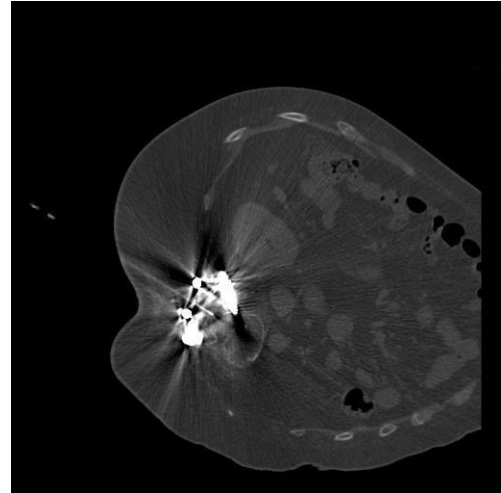
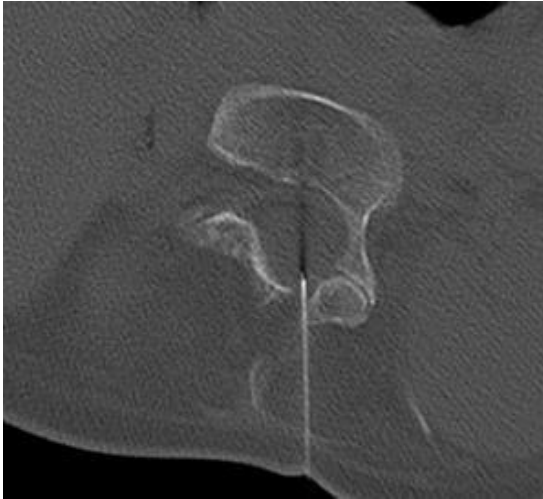


Stolte et al., 2018

CT



CT



Success rates

	SMA type 2	SMA type 3	Total
Number of patients	9	19	28
Conventional	0	14	14
Fluoroscopy	0	3*	3*
CT	9**	2	11**
Number of procedures (%)	33	89	122
Conventional	0 (0%)	65 (73.0%)	65 (53.3%)
Fluoroscopy	0 (0%)	14 (15.7%)	14 (11.5%)
CT	33 (100%)	10 (11.2%)	43 (35.2%)
Success rate***	97.0%	98.9%	98.4%
Conventional	-	100%	100%
Fluoroscopy	-	92.9%	92.9%
CT	97.0%	100%	97.7%

Stolte et al., 2018

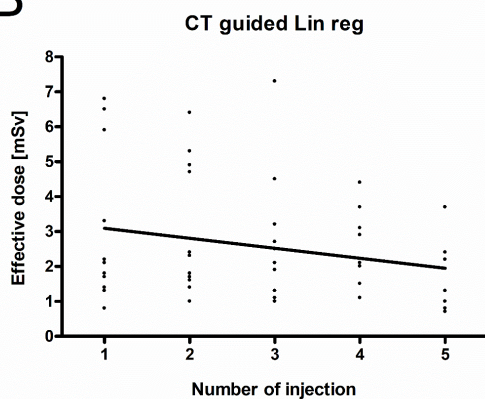
Challenge: Radiation exposure



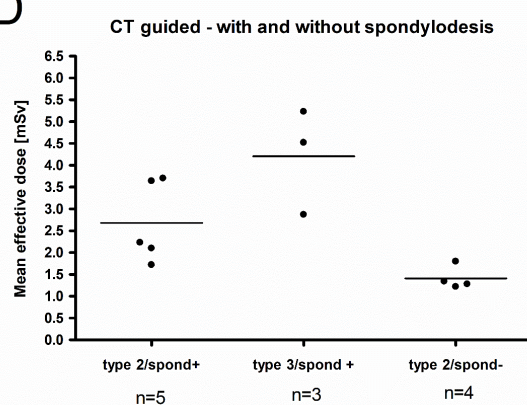
Challenge: Radiation exposure

Effective dose in CT in SMA-patients

B



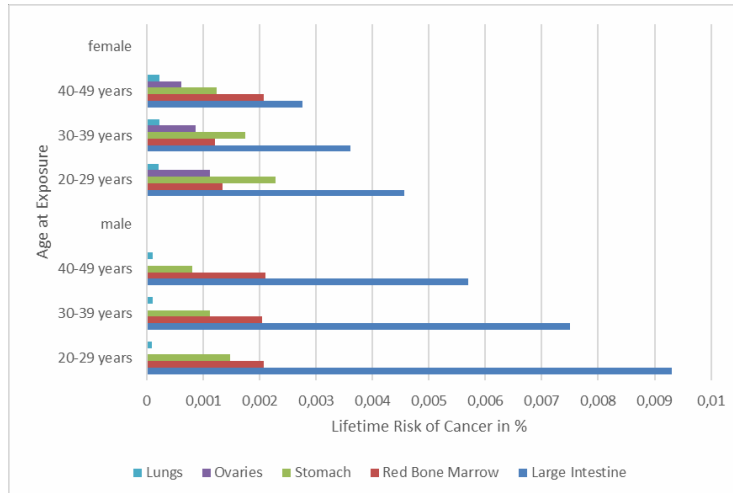
D



Kizina, et al., 2019 subm.

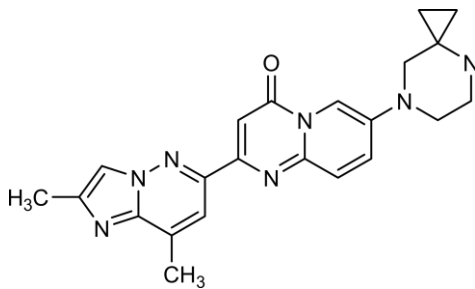
Challenge: Radiation exposure

Risk of malignancy after CT-injection (mSv)



Oldenburg et al., Neuroradiology 2019

Risdiplam



Oral available SMN2-Splicing modifier

Small molecule

2x/d

Firefish (SMA I)



Sunfish (SMA II and III)



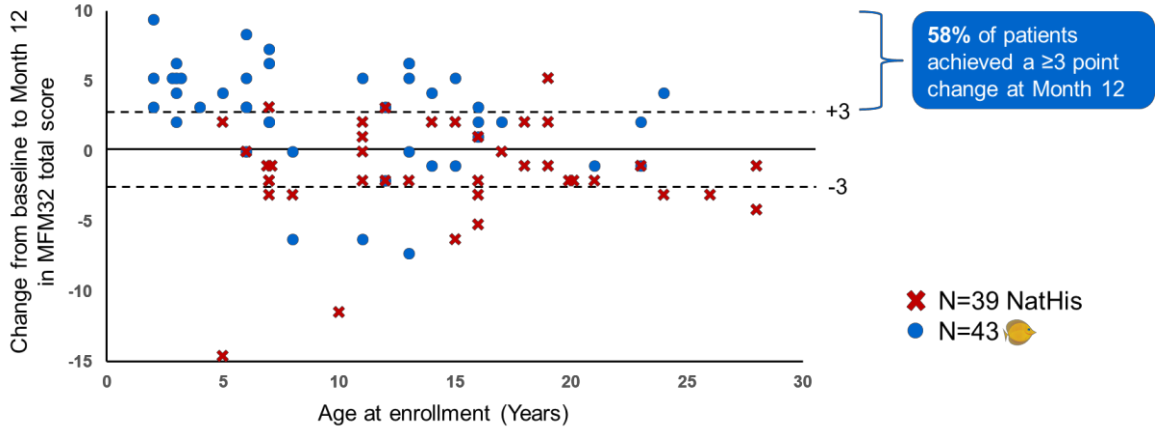
Jewelfish (prior treated with x)



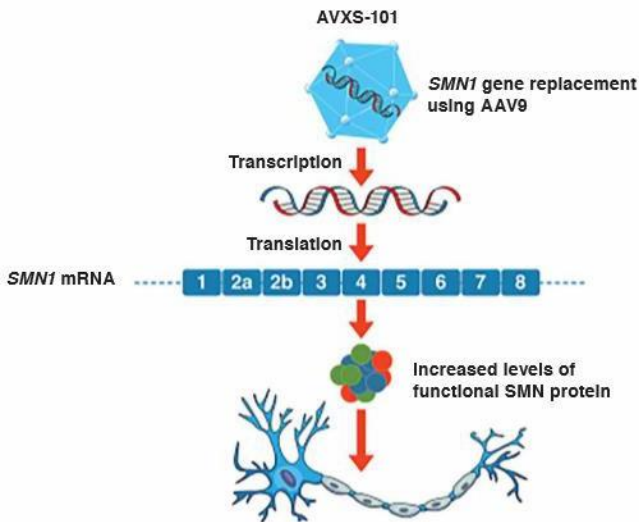
Rainbowfish (presympt.)



Risdiplam



Onasemnogene Apeparvovec (AVXS-101)



Single i.v.-administration

AAV9-linked

„Vaccination“? Immunity?

„Irreversible“

FDA-approval for SMA I < 2 y

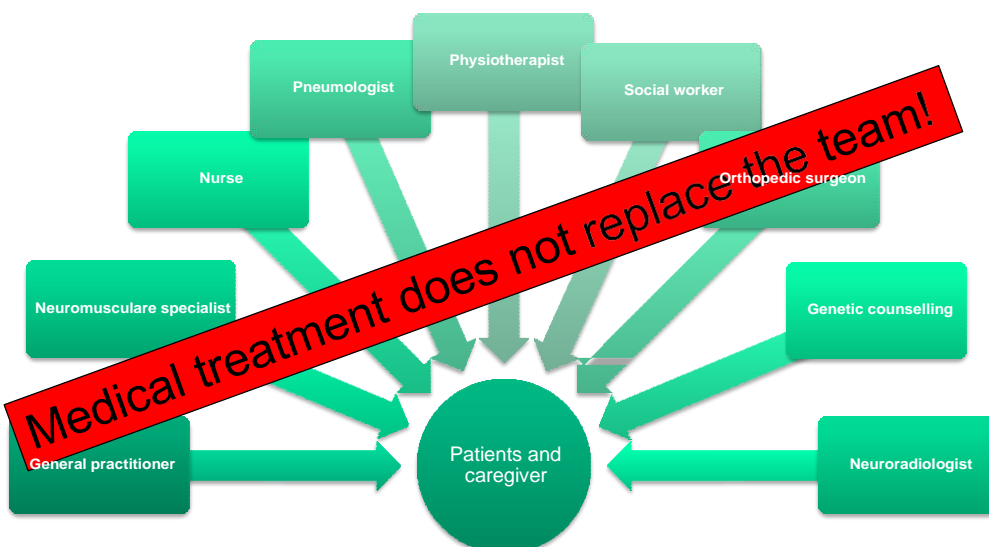
Onasemnogene A베parvovec (AVXS-101)

AL-ZAIDY ET AL.

WILEY  183**TABLE 2** Motor milestone achievements impacting QoL

Patients	Age at GT (mos)	Motor milestone achievement							
		Brings hand to mouth	Head control	Roll ^a	Sitting with assistance	Sitting unassisted			Standing assisted
						≥5 s ^b	≥10 s ^c	≥30 s ^d	
E.04	6	✓	✓	✓	✓	✓	✓ [*]	✓ [*]	
E.05	4	✓	✓	✓	✓	✓	✓	✓	
E.06	2	✓	✓	✓	✓	✓	✓	✓	✓
E.07	4	✓	✓	✓	✓	✓	✓	✓ [*]	
E.08	8	✓							
E.09	5	✓	✓	✓	✓	✓	✓	✓	
E.10	1	✓	✓	✓	✓	✓	✓	✓	✓
E.11	2	✓	✓	✓	✓	✓	✓	✓	✓ [*]
E.12	3	✓	✓	✓	✓	✓	✓	✓	
E.13	1	✓	✓		✓	✓	✓	✓	
E.14	4	✓	✓	✓	✓	✓	✓	✓	✓ [*]
E.15	2	✓	✓		✓	✓	✓	✓	
Total (%)	N/A	100	92	75	92	92	92	92	33

Summary



„Team SMA“ at UKE



Dr. Andreas Totzeck



Dr. Benjamin Stolte



Dr. Kathrin Kizina



Melina Schlag,
Study Nurse/
Physiotherapist



Dr. Markus Leo, M.Sc.



Linda Schmitt, B.Sc.



Thank you!

Neuromuscular Unit

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