European Reference Network
for rare or low prevalence complex diseases

Network Neuromuscular Diseases (ERN EURO-NMD)

Present and future of gene therapy in Neuromuscular Diseases

Satellite Scientific Symposium endorsed by ERN EURO-NMD

February, 22nd 2024

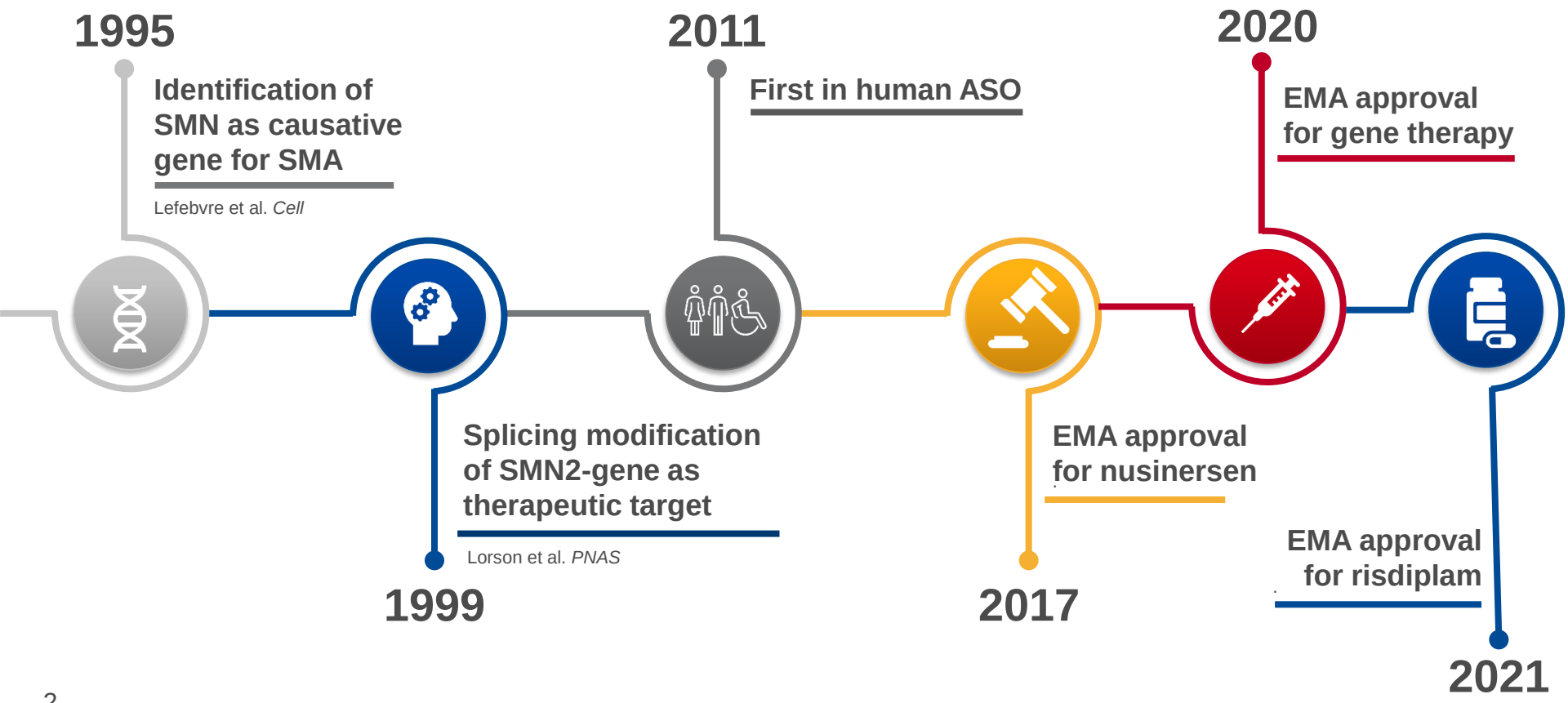
UNIVERSITÄTS KLINIKUM FREIBURG
ZKJ ZENTRUM FÜR KINDER- UND JUGENDMEDIZIN

Latest advances and perspectives for the development of gene therapies

Spinal muscular atrophy

Jan Kirschner
University of Freiburg

Drug development for SMA



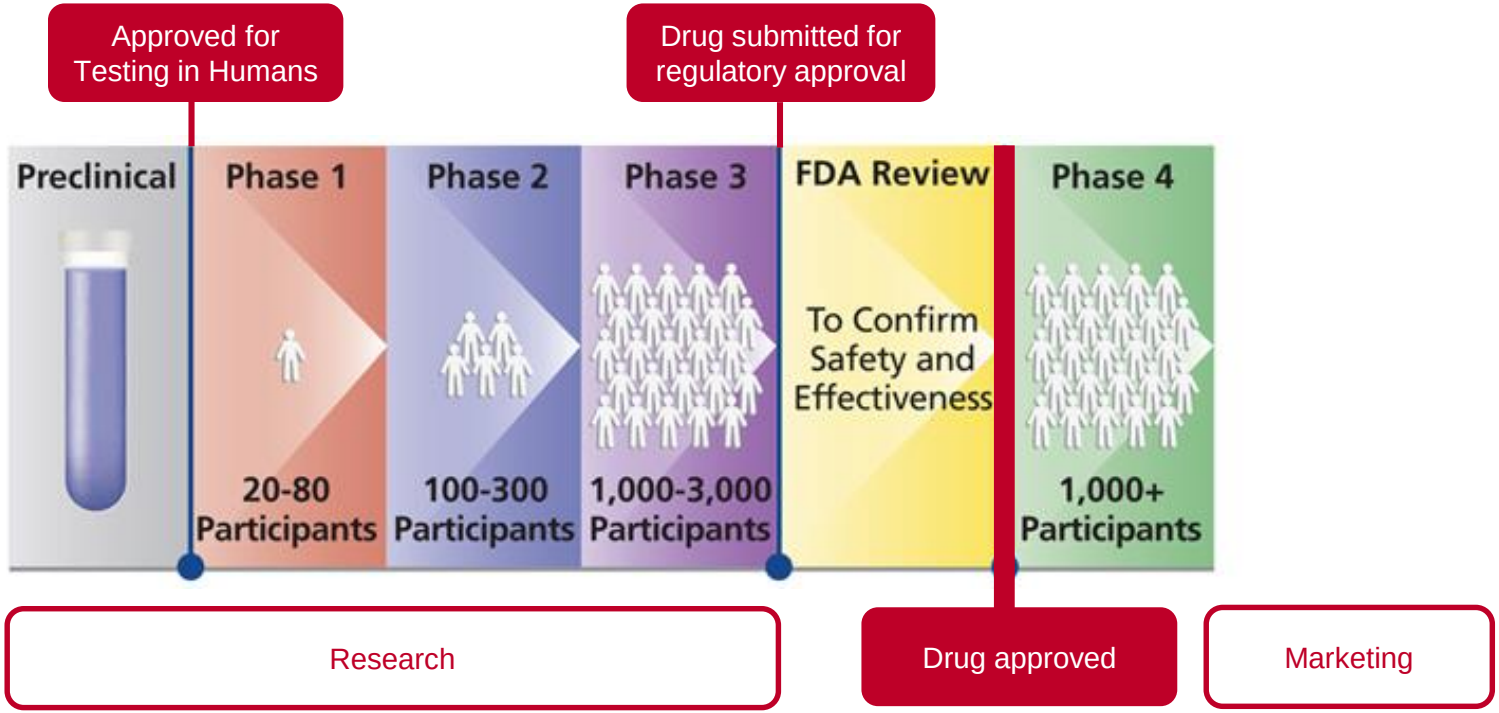
Gene therapies for rare diseases

» only about 5% of 7000 rare diseases have an approved drug treatment
» about 80% of rare diseases are due to genetic mutations
» most begin during childhood and have significant impact on health and QoL

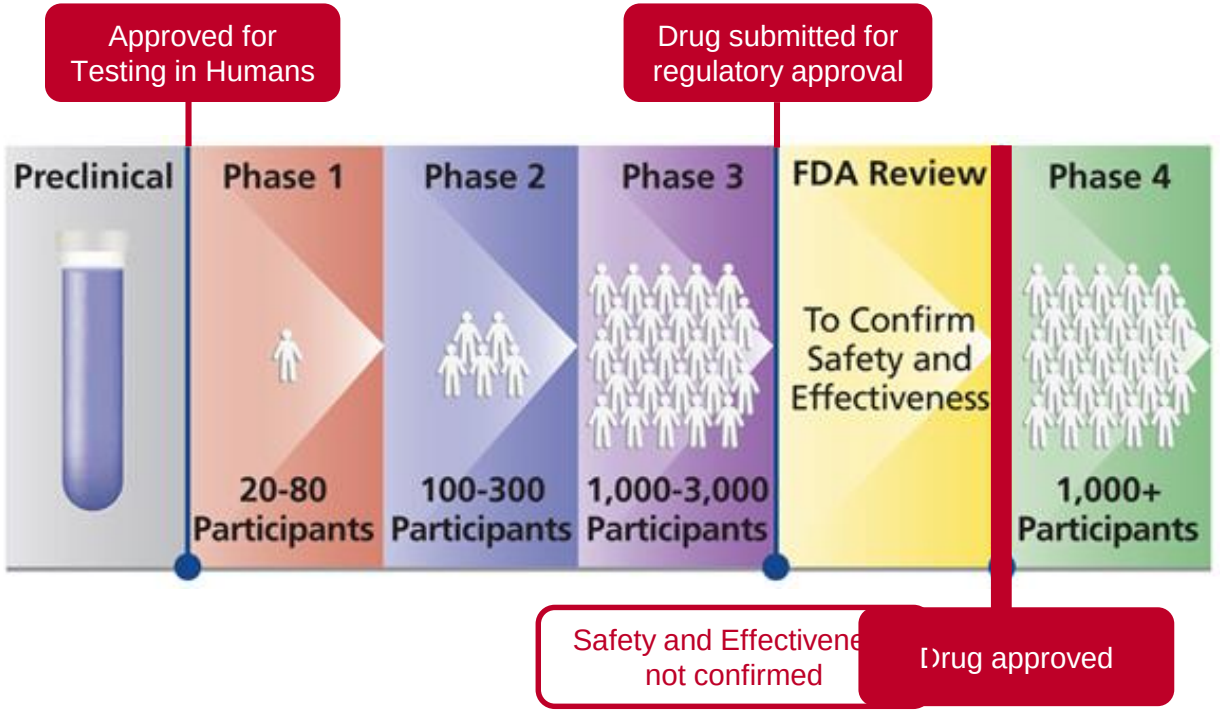
» gene therapy offers potential to address underlying biology
» small populations
» often difficult to conduct placebo-controlled trials

Balance between high medical need and limited evidence

Drug development pipeline



Drug development pipeline for orphan drugs



The “evidence gap”

- No randomized trials
- Extrapolation (age, disease stage)
- Surrogate parameters
- No data on long-term effectiveness

- (Rare) side effects are not known

Treatment with onasemnogene abeparvovec (Zolgensma®)

» Clinical studies in infants with SMA type 1 up to 6 months of age

- Motor milestone achievement that are not expected in natural history
- Ongoing effectiveness after one-time treatment

» EMA approval (5/2020)

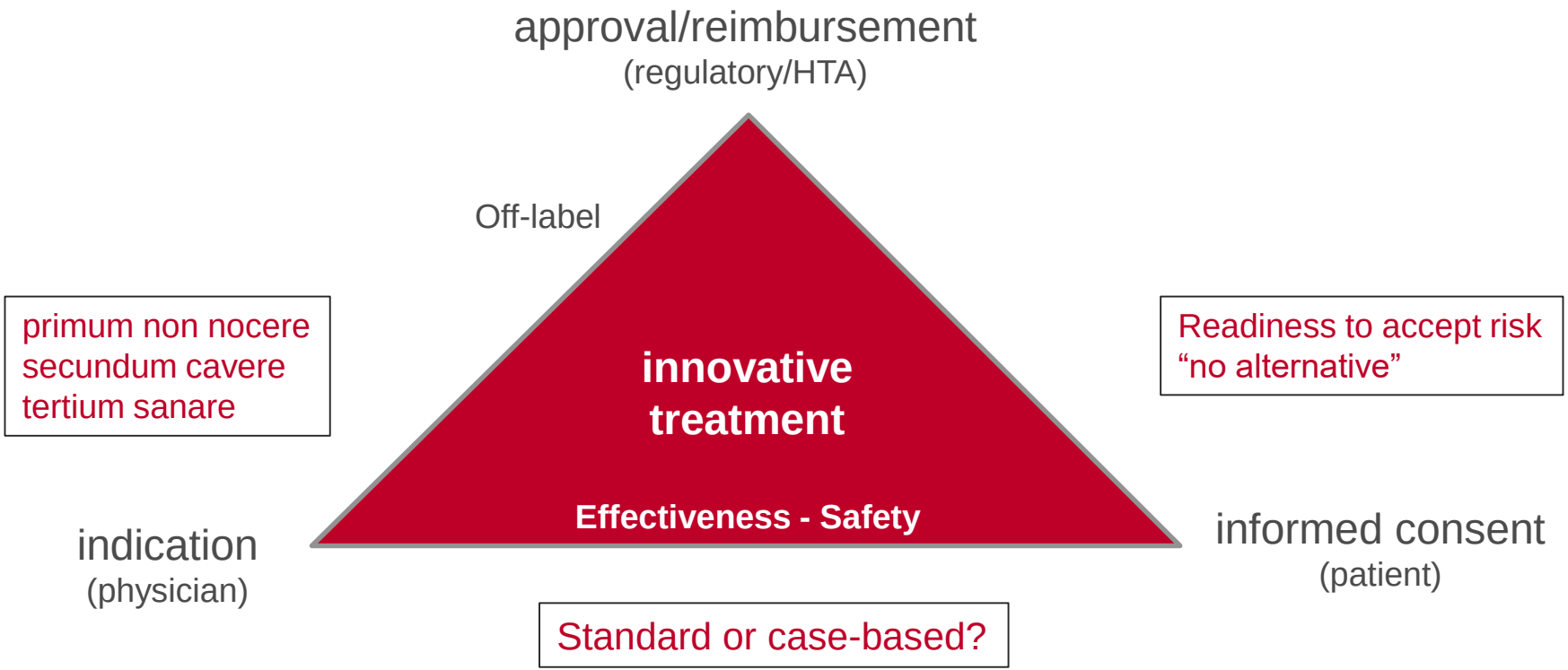
- Patients with SMA type 1 (symptom onset before 6 months of age)
- Patients with up to 3 *SMN2* copies, including SMA type 2/3
- No clear age or body weight limit

» Ongoing developments

- Use in older/heavier patients
- Clinical studies with intrathecal administration

Decision-makers for innovative treatments

Decision-makers for innovative treatments



How to bridge the “evidence gap”?

» Educate the community about evidence gap (experts and patients)
» Continue clinical research (“as good as possible”)
» Continous evaluation rather than “one-time” approval
» Dynamic pricing models
» Update the community on growing evidence

» cross-disease, cross-company, cross-country … sharing and networking

Comparison of three approved treatments for SMA

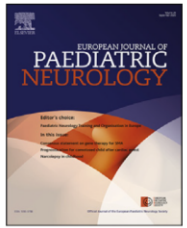
	Nusinersen (Spinraza®)	**Onasemnogene-abeparvovec (Zolgensma®)**	**Risdiplam (Evrysdi®)**
Approval	2017 all SMA patients	2020 SMA type 1, or up to 3 *SMN2* copies	2021 SMA types 1-3, or up to 4 *SMN2* copies
Experience	> 15 000 patients	> 3 000 patients	> 8 000 patients
Dosing	Standard dose, every 4 months	bw dependent, one-time treatment	bw dependent, daily
Administration	intrathecal	intravenous	oral solution
Effectiveness	depends on disease stage at initiation		
Price	600.000 €/ year, follwing yrs 320.000 €/year	1.5 million € once	85.000 - 290.000 €/year

Treatment with onasemnogene abeparvovec

European Journal of Paediatric Neurology 28 (2020) 38–43

Contents lists available at ScienceDirect

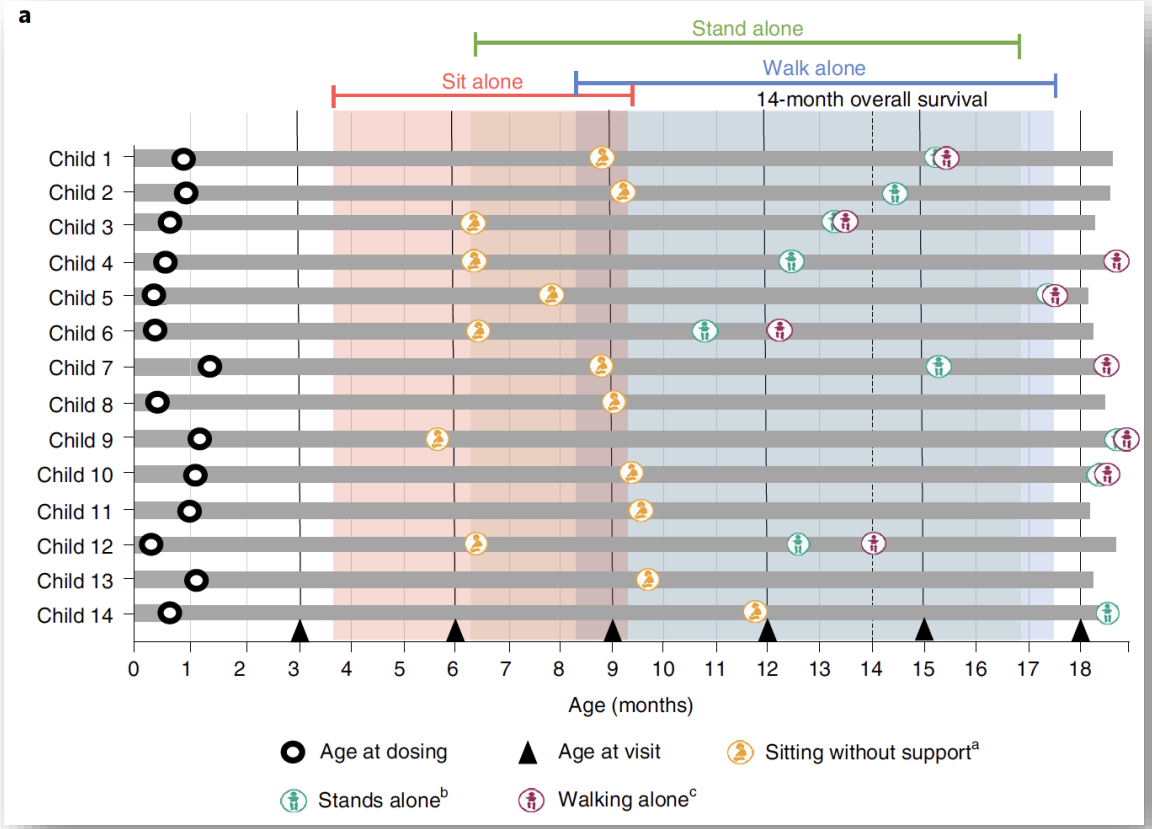
European Journal of Paediatric Neurology



European ad-hoc consensus statement on gene replacement therapy for spinal muscular atrophy

Janbernd Kirschner [a, *], Nina Butoianu [b], Nathalie Goemans [c], Jana Haberlova [d], Anna Kostera-Pruszczyk [e], Eugenio Mercuri [g, h], W. Ludo van der Pol [k], Susana Quijano-Roy [i], Thomas Sejersen [j], Eduardo F. Tizzano [f], Andreas Ziegler [l], Laurent Servais [m, n, 1], Francesco Muntoni [o, 1]

Presymptomatic Treatment with onasemnogene abeparvovec



SPR1NT Trial

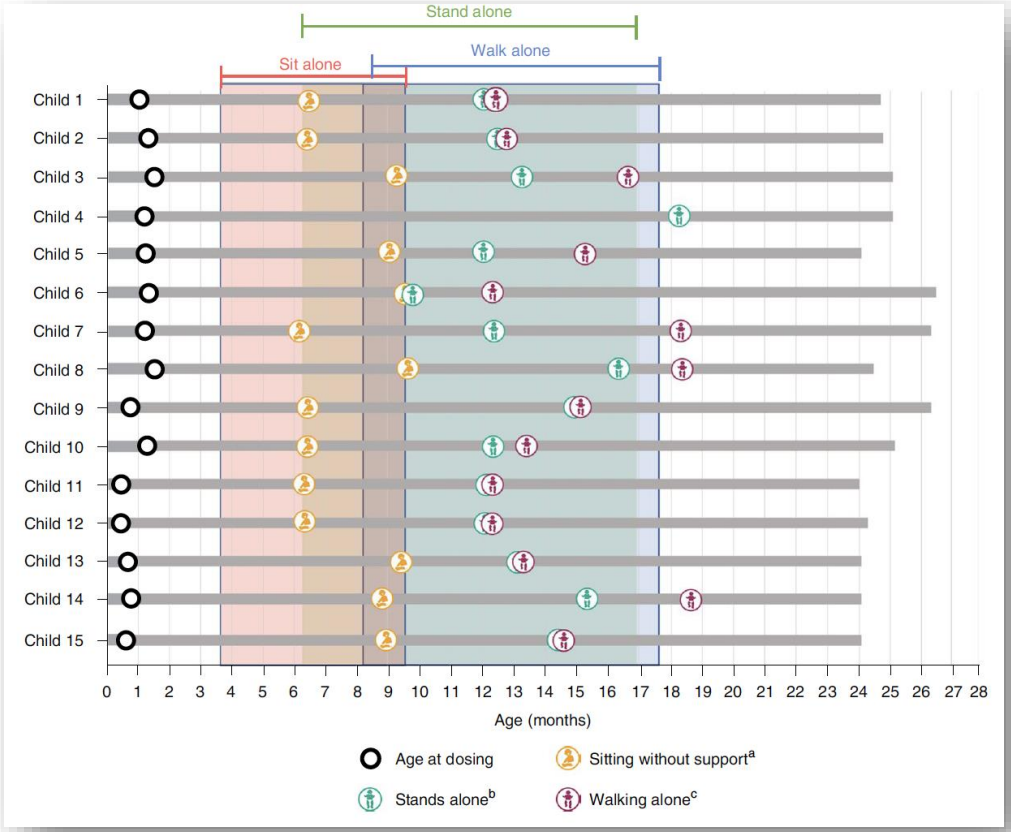
14 children with 2 *SMN2* copies

Treated before symptom onset

Within six postnatal weeks

Strauss et al. *Nature Medicine* 2022

Presymptomatic Treatment with onasemnogene abeparvovec



SPR1NT Trial

15 children with 3 *SMN2* copies

Treated before symptom onset

Within six postnatal weeks

Strauss et al. *Nature Medicine* 2022

Real-world experience with Onasemnogene abeparvovec

Restore Registry

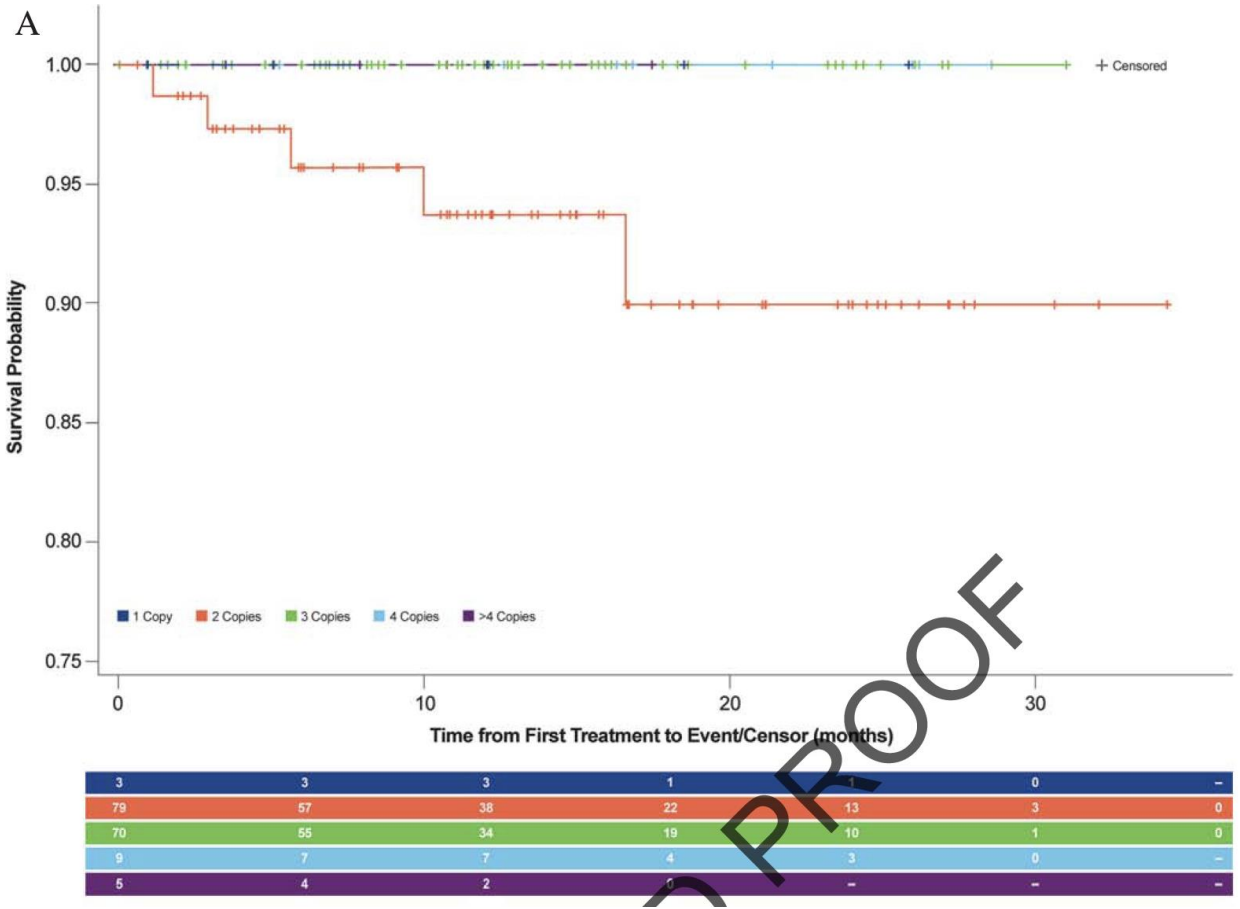
Table 1
Demographics and baseline clinical characteristics for all patients identified by newborn screening, clinical diagnosis, and in the overall cohort

Characteristics	Newborn screening ($n = 98$)	Clinical diagnosis ($n = 70$)	All patients (N = 168)
Age, months			
At initial SMA diagnosis			
Mean (SD)	1.34 (7.12)	9.49 (6.54)	4.73 (7.96)
Median (IQR)	0 (0–1)	8.5 (4–14)	1 (0–6)
Min, Max	0, 70	0, 27	0, 70
At onasemnogene abeparvovec infusion			
Mean (SD)	3.30 (7.99)	10.70 (6.66)	6.38 (8.29)
Median (IQR)	1 (1–2)	9.5 (5–15)	3 (1–10)
Min, Max	0, 72	0, 28	0, 72

Servais et. al 2024

Real-world experience with Onasemnogene abeparvovec

Restore Registry

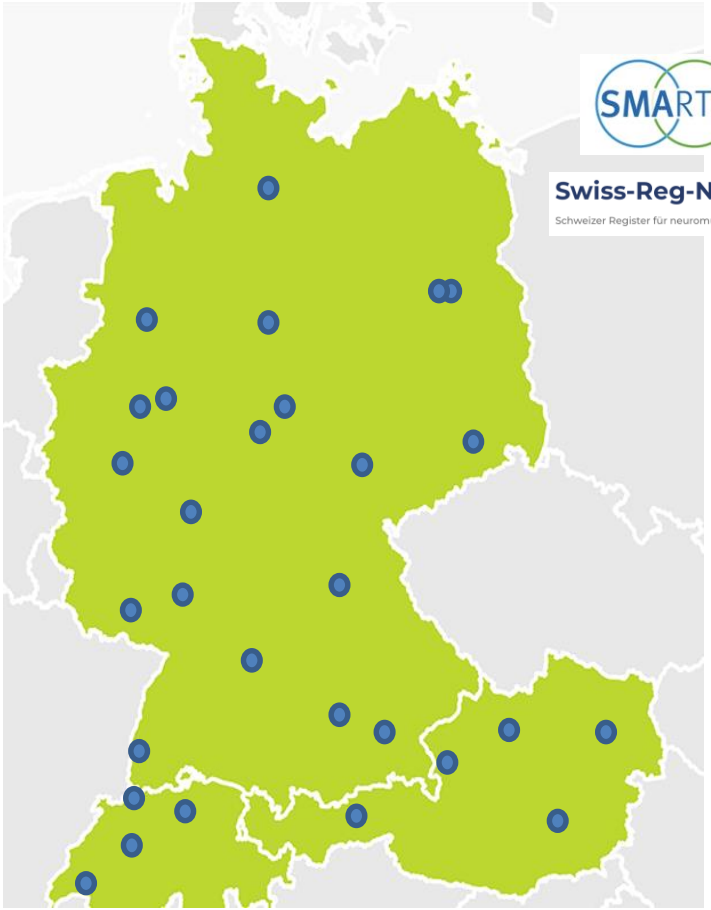


 Servais et. al 2024

Real-world experience with gene therapy for SMA in Germany, Austria and Switzerland

Study [1]:

- Protocol-based according to published care recommendations[1]
- Prospective registry study (single arm, no control group)
- multicentre (all **29 treatment centres** in D-A-CH-region
- Data cut 02/2023
- Prespecified statistical analysis plan (SAP)

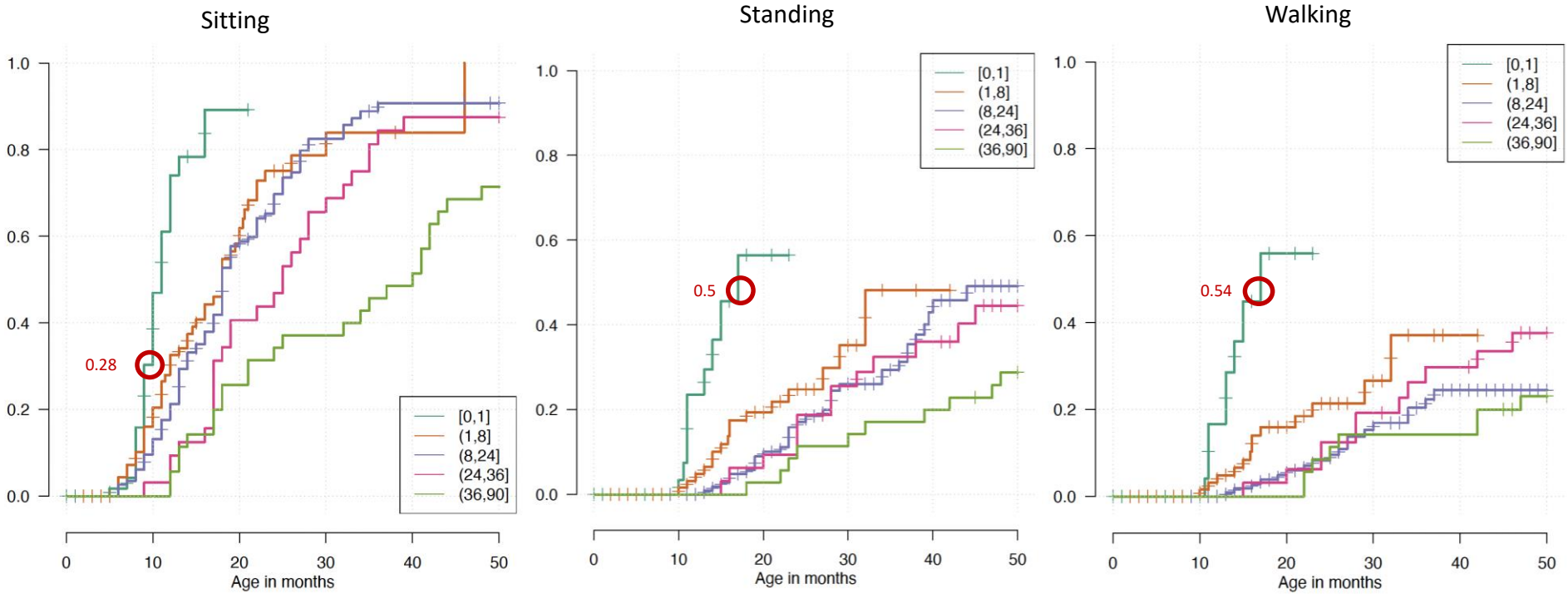


[1]: Ziegler et al., Nervenarzt. 2020 Jun;91(6):518–529. doi: 10.1007/s00115-020-00919-8.

Cohort of patients treated

Characteristic		total n = 347
Sex, N (%)	female	186 (54)
	male	161 (46)
SMA type, N (%)	Pre-symptomatic	134 (39)
	1	153 (44)
	2	55 (16)
	3	5 (1)
SMN2 copy number, N (%)	1	2 (0.6)
	2	207 (60)
	3	136 (39)
	4	2 (0.6)
Pre-treatment, N (%)	naïv	177 (51)
	Nusinersen	152 (44)
	duration, months, mean±SD (range)	12.1±12.8 (0-55)
	time between nusinersen to GT, days, mean±SD (range)	75.8±44.5 (1-317)
	Risdiplam	16 (5)
	duration, months, mean±SD (range)	4±4.7 (0.5-19)
	time between risdiplam to GT, days, mean±SD (range)	11.1±12.7 (1-44)
	Nusinersen+Risdiplam	1 (0.3)
Age at infusion, months, mean±SD (range)		14.0±15.4 (0-90)
Weight at infusion, kg, mean±SD (range)		7.7±3.4 (1.7-17.6)
Follow up, months, mean±SD (range)		13.7±9.5(0-43)

Motor milestones Meilensteine sind altersabhängig



Adverse events

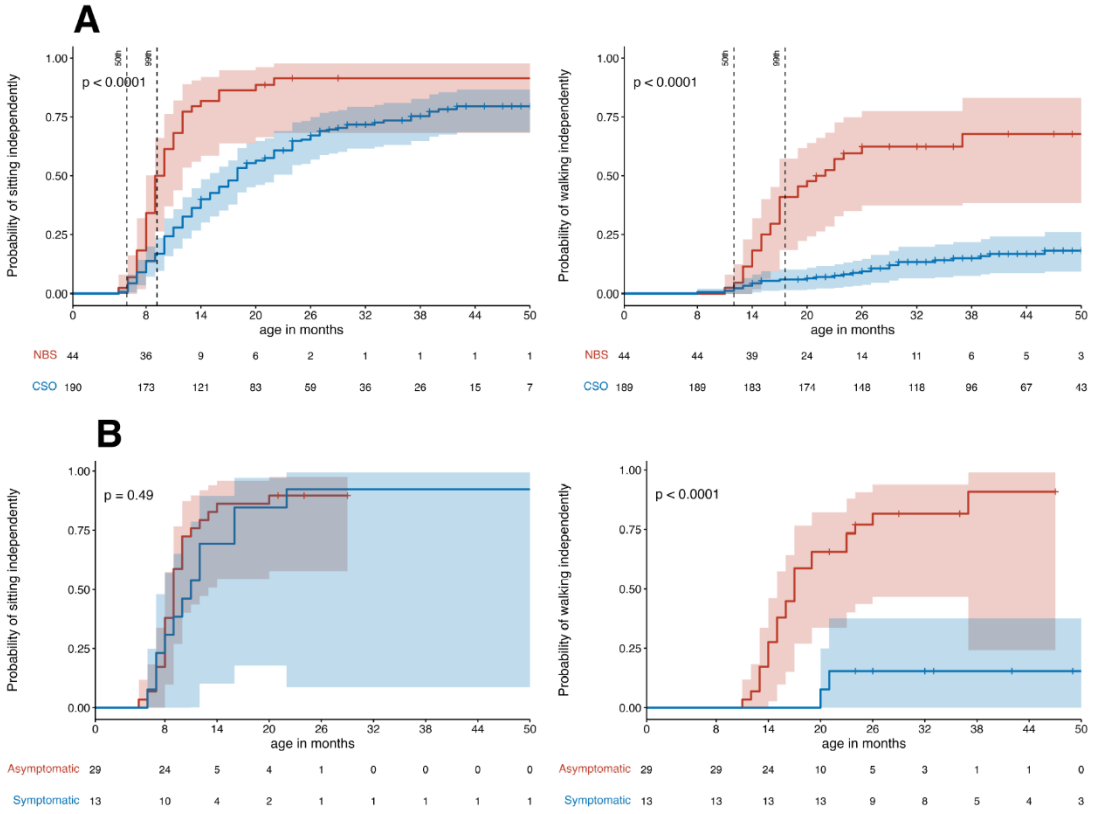
Background

Hepatotoxity common, often requiring extended use of steroid (if transaminases > 2fold ULN

Thrombocytopenia common during the first two weeks

Rare cases with severe adverse events like thrombotic microangiopathy, liver failure
Only seen in real-world data, not in clinical trials

Controlled cohort-study on the effect of newborn screening

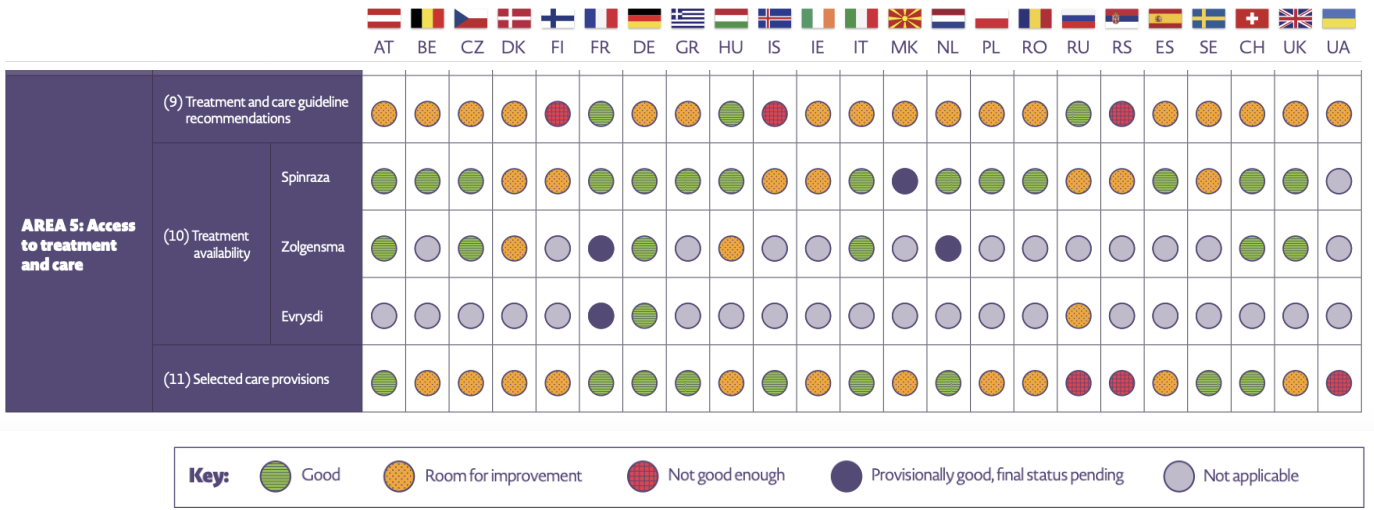


Schwartz et. al 2024 – accepted for JAMA Pediatrics

Access to treatment across Europe

Figure 1: Summary of metric status for each country

Refer to Table 19 in appendix for a fuller explanation of red, yellow and green assessment criteria for each metric



AT – Austria; BE – Belgium; CZ – Czech Republic; DK – Denmark; FI – Finland; FR – France; DE – Germany; GR – Greece; HU – Hungary; IS – Iceland; IE – Ireland; IT – Italy; MK – North Macedonia; NL – The Netherlands; PL – Poland; RO – Romania; RU – Russia; RS – Serbia; ES – Spain; SE – Sweden; CH – Switzerland; UK – United Kingdom; UA – Ukraine

CRA in collaboration with SMA Europe and support from Biogen (8/2021)

Conclusion and perspectives

» Initiating new drug treatments with limited evidence can be challenging.

» Treatment effects are most impressive when initiated pre-symptomatically.

» Genetic newborn screening should be standard in countries, where at least one treatment is available.

» Additional real-world data help to close the evidence gap.

» Symptomatic patients remain with significant disease burden despite treatment. Combination with other drug targets might be needed (e.g. myostatin inhibition).

» Identifying predictors of outcome and managing expectations is essential.

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Thank you!