HTA Austria
Austrian Institute for
Health Technology Assessment
GmbH

SMA therapies

Mid- to long-term follow-up of spinal muscular atrophy (SMA) patients treated for ≥24 months with nusinersen or onasemnogene abeparvovec and ≥12 months for patients treated with risdiplam or combination therapies

Final report

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Mid- to long-term follow-up of spinal muscular atrophy (SMA) patients treated for ≥24 months with nusinersen or onasemnogene abeparvovec and ≥12 months for patients treated with risdiplam or combination therapies

Vienna, November 2023

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List of abbreviations

6 MWT ..... 6-minute walk test
10 MWT ..... 10-minute walk test
AE ..... adverse event
AIHTA ..... Austrian Institute for Health Technology Assessment
ALSFRS ..... Amyotrophic Lateral Sclerosis Functional Scale- revised
ASO ..... antisense oligonucleotide
BiPAP ..... bilevel positive airway pressure
BSID-III ..... Bayley Scales of Infant Development-III
CI ..... confidence interval
CADTH ..... Canadian Agency for Drugs and Technologies in Health
CNS ..... central nervous system
CFS ..... cerebrospinal fluid
CHOP INTEND ..... Children's Hospital of Philadelphia Infant Test of Neuromuscular Disorders
CMAP ..... compound muscle action potential
CoI ..... conflict of interest
DMT ..... Disease modifying therapy
ECG ..... electrocardiogram
EMA ..... European Medicines Agency
EK ..... Egen Klassifikation
FSS ..... fatigue severity scale
FU ..... follow-up
FEV1 ..... forced expiratory volume in 1 minute
FVC ..... forced vital capacity
GAS ..... Global Attainment Scale
HFMSE ..... Hammersmith Functional Motor Scale Expanded for SMA
HINE-2 ..... Hammersmith Infant Neurological Examination
HRQoL ..... health-related quality of life
HTA ..... health technology assessment
IBS ..... irritable bowel syndrome
IHE ..... Institute of Health Economics
INAHTA ..... International Network of Agencies for Health Technology Assessment
IQR ..... interquartile range
IQWiG ..... Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
IV ..... invasive ventilation
LP ..... lumbar puncture
m ..... month
MCID ..... minimal clinically important difference
MFM ..... motor function measure
MMT ..... manual muscle test
MRC ..... Medical Research Council
n ..... number
NG ..... nasogastric
NICE ..... National Institute for Health and Care Excellence
NIV ..... non-invasive ventilation

n.r. ..... not reported
P/C- CGI-C..... Patient/clinician-reported clinical global impression of change
PEG ..... percutaneous endoscopic gastrostomy
p-FOIS ..... The paediatric functional oral intake scale
RCT..... randomized controlled trial
RoB..... risk of bias
(R)ULM ..... (revised) upper limb module for SMA
SAE..... serious adverse event
scAAV9..... systemic complementary adeno-associated virus 9
SF-36 ..... 36-Item Short Form Survey
SMA ..... spinal muscular atrophy
SMAFRS..... spinal muscular atrophy functional rating scale
SMAIS-ULM ..... SMA- Independence Scale -Upper Limb Self Report Module
SMN ..... survival motor neuron
U/L RTI..... upper/lower respiratory tract infection
WHO ..... World Health Organisation
WHO-MGRS ..... WHO Multicentre Growth Reference Study
y ..... year

Zusammenfassung

Hintergrund:

SMA: genetische Erkrankung, SMA Typ 1-4

Spinale Muskelatrophie (SMA) ist eine autosomal-rezessiv vererbte Erkrankung. Ein genetischer Defekt auf Chromosom 5q13 führt zu einer verringerten Expression des SMN-Proteins, was zu progressiver Muskelschwäche führt. Abhängig vom Erkrankungsalter und der maximal erreichten motorischen Leistungsfähigkeit kann SMA in Typ 1 (die schwerste Form) bis Typ 4 eingeteilt werden.

3 zugelassene Therapien: Nusinersen, Risdiplam und Onasmenogene abeparvovec

Bis zur Entwicklung der SMA-Therapien bestand die Behandlung ausschließlich aus „best supportive care“. Derzeit sind drei Behandlungen zugelassen: Nusinersen seit 2017, onasemnogen abeparvovec seit 2020 und risdiplam seit 2021. Nusinersen und risdiplam erhöhen die Verfügbarkeit von funktionellem SMN-Protein in Zellen durch Einfluss auf den mRNA-Spleißprozess. Ein wichtiger Unterschied besteht darin, dass nusinersen intrathekal verabreicht werden muss, während risdiplam oral eingenommen werden kann. Onasemnogene abeparvovec ist eine auf viralen Vektoren basierende Gentherapie.

Alle Therapien tragen hohe Kosten, was insbesondere in Gesundheitssystemen mit öffentlicher Finanzierung zu einem Dilemma bei der Erstattungspolitik führt.

Forschungsfrage: Evidenz zur längerfristigen Sicherheit und Wirksamkeit von SMA-Therapien

Ziel unseres Review-Updates ist es, die Evidenz zur längerfristigen Sicherheit und Wirksamkeit (≥24 Monate für nusinersen und onasemnogen abeparvovec und ≥12 Monate für risdiplam) als Monotherapie oder in Kombination zusammenzufassen, mit besonderem Augenmerk auf die Stabilisierung und Persistenz der motorischen Fähigkeiten, dem Einfluss auf die Atmungs- und Ernährungsfunktion und Lebensqualität insgesamt.

Methoden:

systematische Literatursuche, qualitative (narrative) Synthese

Im Juli 2023 wurde eine systematische Literaturrecherche durchgeführt. Die ausgewählten Publikationen wurden auf interne Validität und Verzerrungspotenzial bewertet und alle relevanten Daten in standardisierte Tabellen extrahiert. Die Ergebnisse wurden narrativ zusammengefasst, da extensive Heterogenität der Studien eine quantitative Analyse limitiert.

Ergebnisse:

Ergebnisse: 20 Beobachtungsstudien und 1 RCT, insg. 1374 Patient*innen

In die Synthese wurden zwanzig Beobachtungsstudien und ein RCT einbezogen, die insgesamt über 1374 Patient*innen berichteten. Fünfzehn Studien untersuchten nusinersen in 948 Patient*innen, eine Studie wurde zu onasmenogene abeparvovec identifiziert und untersuchte 12 Patient*innen, und zwei Studien untersuchten risdiplam in 221 Patient*innen. 193 Patient*innen erhielten eine Kombinationstherapie.

Nusinersen bei SMA 1 (n=212)

Nusinersen bei SMA 1: Verbesserung der motorischen Funktion um 63–100%, frühzeitige Behandlung günstig

10 Patient*innen (5%) starben trotz Therapie.

In den Studien, die diese Ergebnisse berichteten, wurde der MCID-Schwellenwert für CHOP INTEND und HINE-2 von 100% bzw. 63–80% der Patient*innen erreicht. Es wurde beobachtet, dass ein früherer Behandlungsbeginn die Verbesserungen positiv beeinflusst, der Einfluss der SMN2-Kopienzahl war jedoch nicht schlüssig. 100% von Kindern mit Therapiebeginn unter 7 Monaten lernten sitzen, aber nur 17.5 % von Kindern älter als 2.

Nusinersen bei SMA 2 bis 4 (n=736)

Nusinersen bei SMA 2-4: verbesserte motorischer Funktion bei ¼ bis ¾ der Ptn, frühzeitige Behandlung günstig

Der HFSME- und RULM-Score verbesserte sich in den ersten 26 Monaten der Behandlung bei etwa ¼ bis ¾ der Patient*innen kontinuierlich, mit moderaten Veränderungen danach. 15% von SMA 2 Patienten, die sitzen konnten, lernten gehen. Die höchsten Verbesserungen traten bei Kindern mit frühem Behandlungsbeginn und/oder hoher motorischer Grundfunktion auf.

Onasemnogen abeparvovec bei SMA 1 (n=12)

Onasemnogen abeparvovec bei SMA 1: 75% lernten sitzen, 100% MCID

Nach 24 Monaten konnten 75% der Patienten ≥ 30 Sekunden lang sitzen und 17% mit Unterstützung stehen. Alle Patient*innen (100%) erreichten den CHOP INTEND MCID-Schwellenwert und 92% erreichten >40 Punkte.

Risdiplam bei SMA 1 (n=41)

Risdiplam bei SMA 1: 44 % lernten sitzen, 90 % MCID

Drei Patient*innen starben trotz Behandlung. CHOP INTEND MCID wurde von 90% der Patient*innen nach 12 bzw. 24 Monaten Behandlung erreicht, wobei 76% bzw. 54% der Patient*innen >4 Punkte erreichten. 44% lernten sitzen, aber keiner lernte gehen.

Risdiplam bei SMA 2 bis 3 (n=180)

Risdiplam bei SMA 2-3: deutlich verbesserte Motorik und Stabilisierung

Nach 12-monatiger Behandlung wurden signifikante Unterschiede in den MFM32- und RULM-Punkten zwischenbehandelten Patient*innen und der Placebogruppe beobachtet, und nach 24 Monaten signifikante Unterschiede in den MFM 32-Scores zwischen der Risdiplam-Gruppe und der externen, unbehandelten Vergleichsgruppe. Mehr behandelte Patient*innen erreichten den MCID-Schwellenwert von ≥3 Punkten oder Stabilisierung. Es wurde keine Verbesserung der Lebensqualität festgestellt.

Kombinationstherapien

primäre Forschungsfrage nicht auf Kombinationstherapie ausgerichtet, deshalb Ergebnisse weniger aussagekräftig

Onasemnogen abeparvovec + Nusinersen (n=13, SMA 1)

Sieben Patient*innen erhielten gleichzeitig nusinersen. Achtzig Prozent erreichten eine Stabilisierung und zwei Patient*innen (unter Monotherapie) konnten gehen.

Risdiplam + Nusinersen (n=6, SMA 2)

Zwei Patient*innen erhielten zuvor Nusinersen. MCID RULM wurde in 33% erreicht und die Lebensqualität verbesserte sich – ALSFRS-R und EK2 MCID wurden in 50% bzw. 83% erreicht.

Risdiplam + RG7800, Olexosim, Nusinersen oder Onasemnogen apebarvovec

(n=174, SMA 1 bis 3)

Das Hauptziel dieser Studie war die Sicherheit von Risdiplam bei nicht vorbehandelten Patient*innen. Es wurden keine weiteren Endpunkte gemessen. Risdiplam wurde als sicher befunden.

In allen Studien, die diese Endpunkte berichten, wurden unabhängig vom SMA-Typ und der verwendeten Therapie keine signifikanten Verbesserungen der Atmungs- und Ernährungsfunktion verzeichnet, wobei die meisten Studien keine Veränderung oder einen Anstieg des Bedarfs an Beatmung und Ernährungsunterstützung berichten.

keine Verbesserung der Atmungs- und Ernährungsfunktion unerwünschte Ereignisse häufig aber selten behandlungsbedingt

Unerwünschte Ereignisse traten in allen Studien, in denen darüber berichtet wurde, häufig auf, wurden jedoch selten als behandlungsbedingt eingestuft. In den Nusinersen-Studien wurde häufig über ein postlumbales Punktionssyndrom berichtet, und insgesamt waren krankheitsbedingte Atemwegskomplikationen häufig.

Schlussfolgerung:

Es liegen Daten für die Sicherheit und Wirksamkeit aller Therapien auf die motorische Funktion bei Patient*innen mit allen SMA-Typen vor. Es gibt klare Hinweise darauf, dass ein früher Behandlungsbeginn zu besseren Ergebnissen führt, was die Wichtigkeit des Neugeborenen-Screenings unterstreicht. Verbesserungen und Stabilisierung bei älteren SMA-Patient*innen mit späterem Krankheitsbeginn waren ebenfalls erkennbar, was auf eine Steigerung der Gesamtfunktionalität bei Patient*innen mit leichteren Krankheitsverläufen hindeutet.

Evidenz für Verbesserung der Motorfunktion in allen SMA-Typen, keine Verbesserung der Atem-/ Ernährungsfunktion, unerwünschte Ereignisse häufig, aber selten behandlungsbedingt

Es gibt keine eindeutigen Hinweise für eine Verbesserung der Atmungs- und Ernährungsfunktion, unabhängig vom SMA-Typ oder der Therapie. Viele Fragen zu Langzeit-Permanenz oder Regression der Motorfunktionen, zur Auswirkung der Therapien auf die Lebensqualität, zum Behandlungszeitrahmen sowie zu klaren Indikatoren für einen Abbruch und zu den veränderten medizinischen Bedürfnissen behandelter SMA-Patient*innen bleiben unbeantwortet.

keine kurativen, sondern krankheitsmodifizierende Therapien

Auf jeden Fall gibt es keine stichhaltigen Beweise, dass es sich bei den Behandlungen um "kurative“ Therapien handeln, sondern "krankheitsmodifizierende" Therapieansätze.

Executive Summary

Background:

SMA: genetic disease, SMA type 1-4

Spinal muscular atrophy (SMA) is an autosomal recessively inherited disease. A genetic defect on chromosome 5q13 leads to expression of reduced levels of the SMN protein, which causes progressive muscle weakness. Dependent on the age of onset and maximum achieved motor ability, SMA can be classified into type 1 (most severe form) to type 4.

3 approved therapies: nusinersen, risdiplam, and onasmenogene abeparvovec

Until the advent of SMA therapies, the only treatment was best supportive care. Three treatments have been approved: nusinersen in 2017, onasemnogene abeparvovec in 2020 and risdiplam in 2021. Nusinersen and risdiplam both work by increasing the availability of functional SMN protein in cells by interfering with the mRNA splicing process, with the important difference that nusinersen needs to be administered intrathecally whilst risdiplam can be taken orally. Onasemnogene abeparvovec is a viral vector-based gene therapy.

All therapies are prohibitively expensive, causing dilemmas for reimbursement policies, particularly in health systems with public funding.

research question: evidence on longer-term safety and efficacy of SMA therapies

The present review aims to update the evidence on longer-term safety and efficacy (≥24 months for nusinersen and onasemnogene abeparvovec and ≥12 months for risdiplam) as monotherapies or in combination with particular attention to stabilisation and persistence of motor skills, effect on respiratory and nutritional function and overall quality of life in patients with SMA 1 to 4.

Methods:

systematic literature search, qualitative (narrative) synthesis

A systematic literature search was conducted in July 2023. The selected publications were assessed for internal validity and risk of bias and all relevant data were extracted into standardised tables. Results were summarized narratively as substantial heterogeneity of studies prevents meaningful quantitative analysis.

Results:

20 observational studies, 1 RCT, in total 1374 patients

Twenty observational studies and one RCT were included in the synthesis, reporting on 1374 patients in total. Fifteen studies investigated nusinersen in 948 patients, one study was identified on onasmenogene abeparvovec, evaluating 12 patients and two studies investigated risdiplam in 221 patients. A combination of therapies was received by 193 patients.

Nusinersen in SMA 1 (n=212)

nusinersen in SMA 1: motoric function improvement in 63-100%, early treatment favourable

10 patients (5%) died despite therapy.

Across all studies reporting these outcomes, MCID for CHOP INTEND and HINE-2 was reached by 100% and 63-80% of patients, respectively. Earlier treatment initiation was shown to positively influence improvements but the influence of SMN2 copy number was inconclusive. 100% of children who initiated treatment before age 7 months achieved sitting, compared to only 17.5% in children older than 2.

Nusinersen in SMA 2 to 4 (n=736)

HFSME and RULM scores continuously improved in the first 26 months of treatment in approximately ¼ to ¾ of patients, with only moderate changes thereafter. 15% of SMA 2 sitters learned to walk. The highest improvement occurred in children with early treatment initiation and/or high baseline motor function.

nusinersen in SMA 2-4: motor improvement in ¼ to ¾ of patients, early treatment favourable

Onasemnogene abeparvovec in SMA 1 (n=12)

After 24 months, 75% of patients achieved sitting ≥ 30 s and 17% achieved standing with support. All patients (100%) achieved the CHOP INTEND MCID and 92% achieved >40 points. Patients experienced deterioration in respiratory function and no change in nutritional status despite therapy.

onasemnogene abeparvovec in SMA 1: 75% learned to sit,100% MCID

Risdiplam in SMA 1 (n=41)

Three patients died despite treatment. CHOP INTEND MCID was reached by 90% of patients after 12 and 24 months of treatment with 76% and 54% of patients achieving >4 points, respectively. 44% achieved sitting but none achieved walking. Worsening of respiratory function and nutritionalstatus occurred despite therapy.

risdiplam in SMA 1: 44% learned to sit, 90% MCID

Risdiplam in SMA 2 to 3 (n=180)

After 12 months of treatment, significant differences in MFM32 and RULM scores were observed between treated patients and the placebo group, and after 24 months, significant differences in CHOP INTEND scores between the risdiplam group and the external untreated comparator. More patients achieved the MCID ≥3 points and stabilisation in the treated group.

risdiplam in SMA 2-3: significantly improved motor function and stabilisation

Combination Therapies

Onasemnogene abeparvovec + nusinersen (n=13, SMA 1)

Seven patients received nusinersen concomitantly. 80% achieved stabilisation and 2 patients (on monotherapy) achieved walking.

Risdiplam + nusinersen (n=6, SMA 2)

Two patients had previously received nusinersen. MCID RULM was achieved by 33%, and quality of life improved- ALSFRS-R and EK2 MCID were achieved by 50%, and 83%, respectively.

Risdiplam and RG7800, olexosime, nusinersen or onasemnogene apebarvovec (n=174, SMA 1 to 3)

The primary objective of this study was the safety of risdiplam in non-treatment-naïve patients. No other endpoints were reported. Risdiplam was considered safe.

none of the studies investigated the effect of combination on outcomes

In all patient cohorts, irrespective of SMA type or therapy used, no significant improvements were recorded for respiratory and nutritional function with the majority of studies reporting no change or an increase in the need for ventilation and nutritional support at follow-up.

Adverse events were common in all studies that reported it but seldom classified as treatment-related. Post-lumbar puncture syndrome was frequently reported across nusinersen studies, and overall, disease-related respiratory complications were common.

all studies: no significant improvements in respiratory or nutritional function, adverse events frequent but treatment-unrelated

Conclusion:

evidence for improved motor function, no improvment to respiratory and nutritional function, adverse events frequent but mostly treatment-unrelated

"disease-modifying" therapies rather than curative

Both trial data and real-world evidence exists for the safety and efficacy of all therapies on the motor function in all SMA-type patients with clear indications that early treatment initiation leads to better outcomes, showcasing the importance of newborn screening. Improvements and stabilisation in older, later-onset SMA patients were also evident, suggesting an increase in overall functionality in patients with milder disease variations.

No clear evidence exists for any improvement in respiratory and nutritional function regardless of SMA type or therapy. Important questions remain on lifetime permanence or regression of gains, impact on Qol, the timeframe for therapy maintenance as well as clear indicators for discontinuation, and the changing medical needs of treated SMA patients.

In any case there is no compelling evidence to support the notion of "curative" therapy, but rather "disease-modifying" treatment.

1 Introduction

SMA: autosomal-rezessiv vererbte genetische Erkrankung, verringertes SMN-Protein führt zu Muskelatrophie

Spinal muscular atrophy is one of the most common autosomal recessive inherited diseases with an estimated frequency of 1: 6000 live births and carrier status and a carrier frequency of 1 in 50 in Europeans [1, 2].

The most frequent form is caused by a homozygous mutation or deletion on the SMN1 (SMN=survival motor neuron) gene on chromosome 5q13 leading to the production of reduced levels of SMN protein. This causes the loss of alpha motor neurons and leads to progressive proximal and axial muscle atrophy with respiratory muscle weakness playing a dominant role in morbidity and mortality of patients [3, 4].

Humans possess an alternative SMN gene which also encodes the production of SMN protein but due to a single nucleotide difference, the translation of this gene results predominantly in short, non-functional variants instead of the full-length version [5]. It has been suggested that 5-10% of SMN produced by SMN2 translation is functional. This is not enough to compensate for the loss of SMN1 but explains the role of SMN2 copy numbers as disease modifiers.

Anzahl der SMN2 Genkopien beeinflusst den Krankheitsverlauf, mehr Kopien= milderer Verlauf mit besserer Motorfunktion und höherer Lebenserwartung

An inverse relationship between disease severity and high SMN copy number can be observed but there are exceptions and other factors are likely to influence phenotypic expression, so that SMN2 copy alone cannot be reliably used as a prognostic indicator [1, 6].

Nevertheless, the majority of type 1 SMA patients carry two SMN2 copies, type 2 SMA patients three SMN2 copies, type 3a SMA patients (age of onset before 3 years) three SMN2 copies, type 3b SMA patients (age of onset after 3 years) four SMN2 copies, and type 4 four to six SMN2 copies (Table 1-1 and Figure 1-1).

SMA has traditionally been divided into four groups dependent on the age of onset and maximum achieved motor ability (Table 1-1):

- SMA 1: onset <6 months, never able to sit.
- SMA 2: onset <6-18 months, never able to walk.
- SMA 3: onset 1.5-10 years, able to walk but regresses.
- SMA 4: adult onset with slow decline.

SMA 1: schwerste Form Lebenserwartung unbehandelt 12-24 Monate

The most severe form of SMA 1 leads to rapid deterioration of muscle function, requiring respiratory and nutritional support, with an average life expectancy of 24 months prior to the advent of disease-modifying therapies (DMT), whilst patients with later onset forms (SMA 2 to 4) can achieve higher motor function and have a longer to normal life expectancy. Regression of motor skills and respiratory complications still dominate the disease progress. Table 1-1 and Figure 1-1 demonstrate the relationship of SMA type, age, and motor skills in the natural disease history.

Table 1-1: SMA classification. Adjusted from Table 1 in [1] .

Type	Age at onset	Incidence	Prevalence	Maximummotor function	SMN2 copy number	Life expectancy
SMA 0	Fetal	<1	0	-	1	Days-weeks
SMA 1	<6m 1a: birth- 2weeks 1b: <3 months 1c: >3 months	60	15	Never Sits	1, **2**, 3	<2 years
SMA 2	6-18m	25	70	Never walks	2,**3**,4	2-40 years
SMA 3	3a: <3years 3b: >3 years	15	15	Walks but regression likely	**3,4**,5	Normal
SMA 4	>35 years	<1	1	Slow decline	**4,5**	Normal

Bold numbers indicate the most frequent SMN2 copy number.

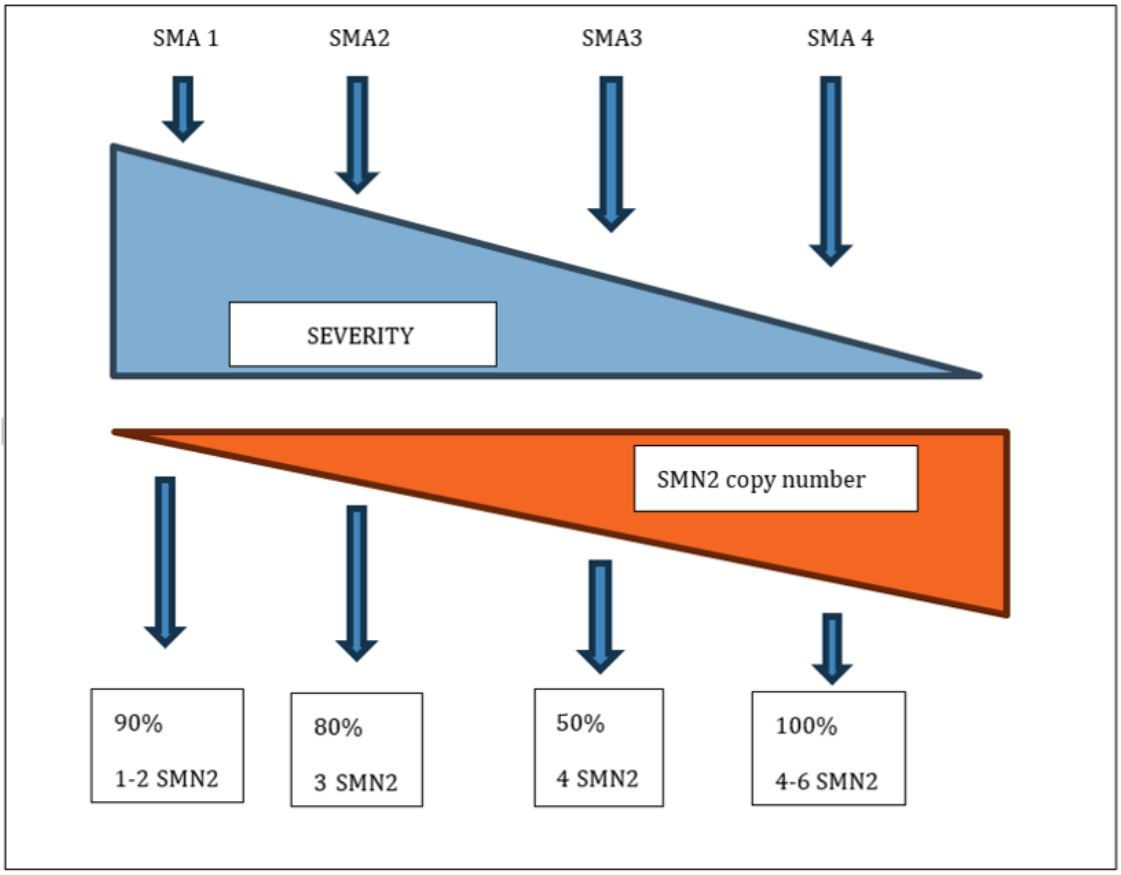

Figure 1-1: Correlation between SMA subtypes and SMN2 copy nummer Adjusted from Figure 1 in [1]

1.1 Currently approved therapies for SMA

seit dem letzten Review keine weitere Neuzulassung für SMA-Therapie

Since our last review [7] in 2021 was conducted, no new treatments have been approved for the treatment of SMA.

Nusinersen (Spinraza ®) by Biogen has been licenced since 2017 for the use in any patient with 5q SMA type 1 to 4, without limitations, based on 2 pivotal trials [8, 9].

Spinraza®, Mai 2017 SMA 1-4

Nusinersen is an antisense oligonucleotide which increases the proportion of exon 7 inclusion in SMN2 messenger ribonucleic acid (mRNA) transcripts. Displacement of splicing factors leads to retention of exon 7 in the SMN2 mRNA and hence when SMN2 mRNA is produced, it can be translated into the functional full-length SMN protein.

Because of the inability of antisense oligonucleotide (ASO) to cross the brain-blood barrier, nusinersen must be administered intrathecally and only increases SMN protein in the central nervous system (CNS), but not in peripheral nerve and organ tissue. Treatment should be initiated as early as possible after diagnosis with four loading doses on days 0, 14, 28 and 63. A maintenance dose should be administered once every four months thereafter. There is currently no consensus on the duration of treatment. The most commonly reported side effects are related to administration of treatment through lumbar puncture and include headache, back pain and vomiting. Some cases of hydrocephalus have been reported. Scoliosis and associated spinal fusion surgery complicate intrathecal delivery [10, 11].

Zolgensma®, Mai 2020, SMA 1

Onasemnogene abeparvovec (Zolgensma®) by Novartis has been approved since 2020 for use in patients with 5q SMA, bi-allelic mutation in the SMN1 gene and a clinical diagnosis of SMA type 1, or patients with 5q SMA, bi-allelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene.

Onasemnogene abeparvovec is a gene therapy and works by the systemic intravenous application of a non-replicating self-complementary adeno-associated virus 9 (scAAV9) that introduces intact SMN1 cDNA into infected cells. This leads to the expression of functional SMN protein in both peripheral muscle and organ tissues as well as spinal and CNS motor neurons.

Treatment is delivered as a one-time single-dose infusion and needs to be accompanied by steroid treatment to reduce the risk of side effects. Hepatotoxicity has been established as a potentially fatal, but rare severe adverse event. Other common side effects are raised liver enzymes, thrombocytopenia, raised levels of troponin (indicating damage to the heart muscle), fever and vomiting [11, 12]

Evrysdi®, Mai 2021, SMA 1-3

Risdiplam (Evrysdi®) by Roche is the latest and only orally administered medication approved since 2021 for the treatment of patients with 5q SMA aged 2 months and older, with a clinical diagnosis of SMA type 1, 2 or 3, or patients with 1 to 4 copies of SMN2 [13]

Risdiplam is a small molecule that increases exon 7 inclusion during SMN2 pre-mRNA splicing resulting in increased functional SMN protein in peripheral muscle tissue and CNS system. The ability to cross the blood-brain barrier reduces the need for intrathecal administration and allows systemic distribution. This increases functional SMN protein, not only in the central nervous but also in the peripheral nervous system and non-neuronal organs and tissues.

Safety profile has been favourable during the pivotal trials FIREFISH NCT02913482 [14] and SUNFISH NCT02908685 [15] with fever, rash and diarrhoea as the most common side effects reported. Results for the ongoing RAINBOWFISH trial NCT03779334 of risdiplam in pre-symptomatic infants from birth to 6 weeks are still outstanding.

1.2 Costs of therapies and cost of illness

sehr hohe Kosten für Therapien, wenig Information zu direkten und indirekten Kosten von SMA

The cost of annual nusinersen and risdiplam treatment is €300.000 and €85.000 respectively [16, 17]. The one-time treatment with onasemnogene abeparvovec is €1.9 million [18]. Evidence on the cost of illness of SMA is limited and complicated due to variability across disease phenotypes and differences in scope and cost of medical resources across different geographic areas. A recent systematic review [19] conducted by authors of the Karolinska Institute in Sweden evaluating studies on eight countries (Australia, France, Germany, Italy, Sweden, the UK and the US) estimated the mean per-patient annual medical cost between $3320 for SMA type 3 in Italy and $324410 for SMA type 1 in the US. They also estimated mean per-patient annual non-medical and indirect costs with the highest indirect medical cost being estimated at $136800 in a study on SMA type 1 in Sweden, and the highest mean per-patient indirect cost being estimated at $74910 for SMA type 2 in Australia.

1.3 Updated HTA assessments and recommendations

nur 3 (große) HTA-Institutionen angesehen:

IQWiG, CADTH, NICE

provide context we reviewed results of several HTA institutions (Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Germany, Canada's Agency for Drugs and Health Techologies (CADTH) /Canada and National Institute for Care Excellenc (NICE)/UK) for updates since our last review. IQWiG has not provided any updates since our last review, NICE has updated its recommendation for To onasemnogene abeparvovec and has now released its recommendation for risdiplam, and CADTH has updated its recommendation for nusinersen in SMA 2 and 3 patients.

IQWiG [17, 20, 21]

keine Änderung Nusinersen: Zusatznutzen (ZN) für SMA 1, kein ZN für SMA 2+3

Onasemnogene abeparvovec kein ZN, Mangel and Daten

Nusinersen: Indication of a major added benefit in comparison with best supportive care (BSC) in children with early onset of disease (in the first 6 months of life, but an added benefit in comparison with BSC in later onset SMA types is not proven due to lack of any relevant data for the assessment. For infants who are not yet symptomatic but are expected to have early onset of disease due to a certain genetic predisposition (no more than two SMN2 gene copies), a hint of a non-quantifiable added benefit of nusinersen in comparison with BSC can be derived from the study data.

Onasemnogene abeparvovec: No added benefit proven for any of the 3 forms of SMA ((presymptomatic)SMA 1, SMA 2 and SMA 3)due to lack of data.

Risdiplam: Suggestion of a non-quantifiable added benefit in SMA1 children with early onset of disease and no added benefit proven for any of the other three types of SMA patients (pre-symptomatic, SMA 2 and SMA 3).

Risdiplam: ZN für SMA 1 kein ZN für SMA 2+3

CADTH [22-24]

Nusinersen remains recommended for pre-symptomatic patients with two to three SMN2 copies or patients with disease duration of less than six months, two copies of SMN2, and symptom onset after the first week after birth and on or before seven months of age, or are patients who are 12 years of age or younger with symptom onset after six months of age, and never achieved the ability to walk independently under the condition that the patient is not currently requiring permanent invasive ventilation.

Nusinersen: (prä)symptomatisch SMA 1 (2-3 SMN2 Kopien) < 7 Monate oder SMA 2 <12 Jahre

Recently a recommendation was made against reimbursement of the treatment of patients with type 2 and type 3 5q spinal muscular atrophy (SMA) regardless of ambulatory status if initiated in patients older than 18 years of age.

SMA 2+3 (≥ 18 J): keine Empfehlung

Onasemnogene abeparvovec remains recommended for patients who are symptomatic or pre-symptomatic with one to three copies of SMN2, six months of age or younger and are not currently requiring permanent feeding or ventilatory support (either invasive or non-invasive) - only under specialist care.

Onasemnogene abeparvovec: SMA 1 (prä)symptomatisch (1-3 SMN2 Kopien) ≤ 6 Monate

Risdiplam remains recommended for patients symptomatic and either aged between two and seven months or non-ambulatory patients eight months to 25 years with 2 or 3 SMN2 copies and who are not currently requiring invasive ventilatory support.

Risdiplam: symptomatische, nicht ambulante Pts. 2-7 Monate (2 SMN2 Kopien) 7 Monate -25 Jahre (2-3 SMN2 Kopien)

NICE [25-27]

Nusinersen remains recommended as a treatment option for pre-symptomatic SMA, or SMA type 1, 2 or 3, and the conditions in the managed access agreement (which includes being free from permanent invasive ventilation) are followed.

Nusinersen: SMA 1 präsymptomatisch oder SMA 1-3

Onasmenogene abeparvovec is now also recommended for treating presymptomatic 5q SMA with a biallelic mutation in the SMN1 gene and up to 3 copies of the SMN2 gene in babies aged up to 12 months old under consideration of the commercial agreements specified and also remains recommended for SMA 1 in patients under 6 months of age, and if they are aged 7 to 12 months old, only if their treatment is agreed by the national multidisciplinary team.

Onasemnogene abeparvovec: SMA 1 präsymptomatisch (bis 3 SMN 2 Kopien) <12 Monate und SMA 1 <6 Monate

It is recommended for these groups only if the patients are not on permanent ventilation for more than 16 hours a day or a tracheostomy is not needed and the company provides it according to the commercial arrangement (which includes being free from permanent invasive ventilation).

Risdiplam: SMA 1-3 >2 Monate oder präsymptomatisch SMA 1-4 < 7 Monate (bis 4 SMN2 Kopien)

Risdiplam is recommended since April 2023 as an option to treat 5q spinal muscular atrophy (SMA) in people older than 2 months and a clinical diagnosis of SMA 1, 2 or 3 or with pre-symptomatic SMA and 1 to 4 SMN2 copies, and the conditions of the managed access agreement (which includes being free from permanent invasive ventilation) are followed.

1.4 Objectives and scope of this report

Ziel des Updates:

In 2021, the Austrian Institute for Health Technology Assessment (AIHTA) published a systematic review [7] on the evidence of ≥ 12-month follow-up of patients with spinal muscular atrophy (SMA) treated with nusinersen, onasemnogene abeparvovec or combination therapies . No data was available for risdiplam at that time.

Aktualisierung der Evidenz zu mittel- bis langfristigen Effektivität und Sicherheit von allen zugelassenen SMA Therapien in SMA 1-4

In our last review, we assessed the mid-term outcomes (≥12 months) of SMA 1 patients treated with nusinersen or onasemnogene abeparvovec, and SMA type 2 to 4 patients treated with nusinersen. Of 225 SMA type 1 patients treated with nusinersen, nine died, six withdrew due to lack of efficacy, and 35 patients were lost to follow-up. In terms of motor outcomes, 100% of patients reached the minimal clinically important difference (MCID) for CHOP INTEND and 67-100% for HINE-2. In 12 SMA type 1 patients treated with onasemnogene abeparvovec, 75% achieved sitting for ≥30 seconds and 17% achieved standing unsupported, both motor milestones not normally observed during the natural disease history of SMA type 1 patients. In one study of 18 patients treated with a combination of onasemnogene abeparvovec and nusinersen, 100% reached the MCID for CHOP-INTEND, but only 40% for HINE-2.

In patients with SMA type 2 to 4, of 341 patients treated with nusinersen, one patient died and nine withdrew due to lack of improvement. Small improvements (below the MCID) and stabilisation as well as deterioration were observed.

Whilst motor outcomes improvement was consistently observed, in all patient groups, regardless of SMA type or treatment used, no significant improvements were observed in the need for respiratory and nutritional support measures.

Adverse events were reported in almost 100% of patients.

Nachbeobachtung: Nusinersen und Onasemnogen abeparvovec: ≥24 m Risdiplam ≥12 m

This review aims to update the evidence on longer-term safety and efficacy outcomes of SMA type 1 to 4 patients treated with nusinersen, onasmenogene abeparvovec, risdiplam or combination therapies. Given the later approval of risdiplam, compared to nusinersen and onasemnogene abeparvovec, we include studies with a follow-up time of ≥12 month and ≥24 month, respectively.

Questions regarding stabilisation or further improvement of motor skills over time, persistence of gained abilities, effect on respiratory and nutritional function and overall quality of life (QoL) will be discussed utilising the most up-to-date evidence.

2 Methods

2.1 Research question

What mid- to longer-term (≥ 24 months for nusinersen and onasemnogene abeparvovec and ≥ 12 months for risdiplam or a combination of these therapies) clinical benefit on motor function, respiratory function, nutritional needs as well as quality of life and safety are observed in paediatric and adult patients suffering from SMA type 1 to 4 treated with any of the three currently approved SMA-therapies?

Forschungsfrage: mittel- bis längerfristige Wirksamkeit und Sicherheit der 3 zugelassenen SMA Therapien

2.2 Inclusion criteria

The inclusion criteria of the previous systematic review from 2021 have been slightly adapted regarding the follow-up periods. Details are summarized in Table 2-1.

Table 2-1: PICO framework

Population	Patients with SMA type 1 to 4
Interventions	Nusinersen, onasemnogene abeparvovec, risidiplam or combination therapies
Comparator	Best supportive care
Outcome	Motoric function ((HINE (-2), CHOP INTEND, HFSME, RULM, 6MWT) Respiratory function- invasive and non-invasive ventilation support Nutritional status- need for feeding support Quality of life (QoL) Adverse events/Serious adverse events
Study design	Randomized controlled trials, observational studies (prospective/retrospective case series) Systematic reviews and meta-analyses for safety outcomes
Publication period	May 2021-July 2023
Language	German, English

2.3 Literature search and Study selection

A systematic literature search was performed in July 2023 using the Cochrane library, Medline, Embase and International Network of Agencies for Health Technology Assessment database (INAHTA). Details on the search strategy can be found in Appendix.

systematische Literatursuche Juli 2023

323 Zitate identifiziert, + 1 durch Handsuche, + 9 Zitate aus der letzten Review: 21 Studien in 29 Publikationen eingeschlossen

After the removal of duplicates, the abstracts of 323 records were screened independently by two researchers (CW, DG) and 61 full texts were evaluated for inclusion eligibility. In case of discrepancies, mutual discussion or consultation with a third reviewer was utilized to resolve the issue. We also screened the publications of our previous review in order to include all existing data matching the updated search criteria to maximise the relatively scarce body of evidence. In the end, 21 studies in 29 publications were included.

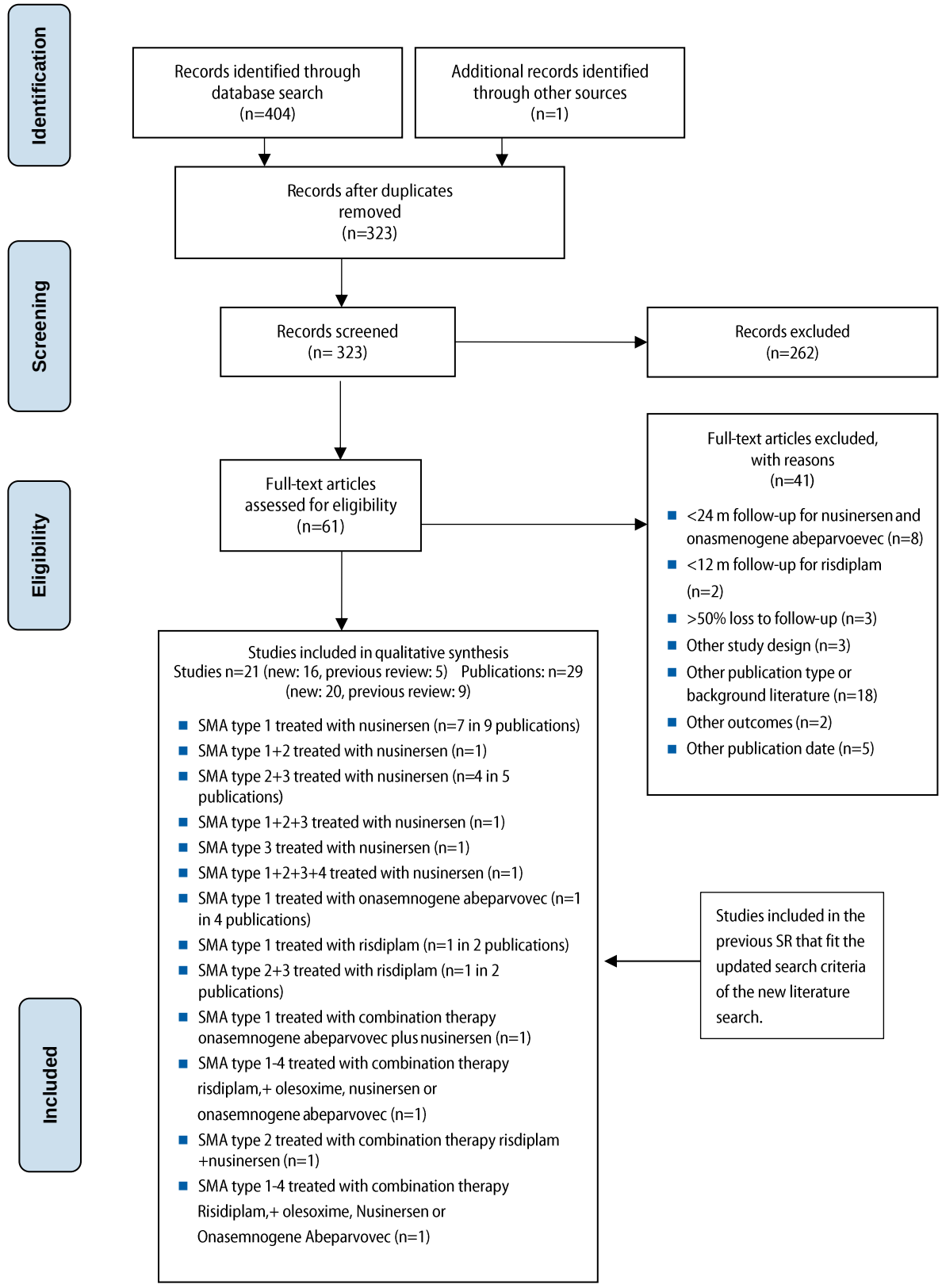

Figure 2-1: PRISMA flowchart

2.4 Data extraction

4-Augen Prinzip in allen Arbeitsschritten

One researcher (DG) extracted all relevant data systematically into extraction tables which were reviewed by a second researcher (JE) for accuracy.

2.5 Quality assessment of the studies

IHE checklist

Bewertung der Studienqualität: IHE checklist and Cochrane ROB 2.0

Both researchers independently evaluated the risk of bias (ROB) in the included studies applying the Institute of Health Economics (IHE) Risk of Bias checklist for case series [28] and the Cochrane ROB tool for randomized controlled trials [29]. Results are presented in the Appendix RoB Assessment tables.

Overall RoB was assessed using a predefined point score (range: 0 – 20, Table 2-2): a high score indicates a low RoB and a low score indicates a higher RoB. Detailed thresholds are presented in Table 2-3.

Table 2-2: Overall risk of bias (RoB) point scores for RoB assessment of case series

Answers to specific questions of the IHE-20 checklist	Points
No	**0**
Partial	**0.5**
Unclear	**0.5**
Yes	**1**

Table 2-3: Cut-off criteria for the risk of bias (RoB) assessment of overall RoB of case series

Criteria	Points
Low risk	**> 18**
Moderate risk	**14.5 to 18**
High risk	**≤ 14**

2.6 Synthesis and presentation of findings

qualitative Synthese

Due to the included studies' heterogeneity, we were unable to perform quantitative statistical analysis.

A narrative review of the results for different SMA types and treatments under consideration of MCID, where applicable, are presented in plain text. Results were summarised in Table A- 10 to Table A- 21.

3 Results

3.1 Study Characteristics

Our review includes 21 studies in 29 publications on the mid- to long-term effectiveness and safety of nusinersen, onasemnogene abeparvovec, risdiplam or a combination of therapies.

21 Studien eingeschlossen:

Five studies in nine publications were already included in our last review but were included again as they describe longer-term follow-up and add to the body of evidence which is still of limited quantity.

Fifteen studies evaluated treatment with nusinersen, one with onasemnogene abeparvovec and two with risdiplam. Three studies included patients receiving a combination of therapies.

15 zu Nusinersen, 1 zu Onasemnogen abeparvovec, 2 zu Risdiplam und 3 zu Kombinations-therapie

Nusinersen was assessed for treatment in SMA type 1 patients in seven studies (in nine publications), in SMA type 1 and 2 patients in one study, in SMA type 2 and 3 patients in four studies, for ambulant SMA type 3 patients in one study and for SMA type 1 to 3 and 1 to 4 in one study, respectively.

The onasemnogene abeparvovec study exclusively enrolled SMA type 1 patients. One risdiplam study evaluated treatment in SMA1 type patients, and one evaluated treatment in both SMA type 2 and 3.

1.374 Patient*innen

SMA1: 293
SMA2: 569
SMA3: 510
SMA4: 2

Three studies included a combination of therapies although the effect of the combination was not the primary investigation objective, rather patients included in the treatment for one drug had previously or concomitantly received another without this being considered in the methods or results evaluation. One study evaluated onasemnogene abeparvovec and nusinersen in SMA type 1 patients, one study evaluated risdiplam and any other DMT in SMA type 1 to 4 patients, and one study evaluated risdiplam and nusinersen in SMA type 2 patients.

The total number of patients enrolled in all studies was 1374 patients.

Nusinersen: 948 Ptn. (SMA 1: 212, SMA 2: 327, SMA 3: 407, SMA 4: 2)

The total number of patients enrolled in all nusinersen studies was 948 and included 212 patients with SMA type 1, 327 with SMA type, 2, 407 with SMA type 3 and two with SMA type 4.

The total number of SMA type 1 patients enrolled in the onasemnogene abeparvovec study was 12.

Onasemnogen abeparvovec: 12 SMA 1

The total number of patients enrolled in the two risdiplam trials was 221: 41 SMA-type 1 patients and in type 2 and 3 SMA trials 128 and 52 patients, respectively.

Risdiplam: 221 Ptn. (SMA 1: 41, SMA 2: 128 SMA 3: 52)

The combination therapies enrolled a total of 193 patients, with one study enrolling 13 SMA type 1 patients, one study enrolling six SMA type 2 patients and a third study enrolling 15 SMA type 1, 108 SMA type 2 and 51 SMA type 3 patients.

Kombinations-therapien: 193 Ptn. (SMA 1: 28, SMA 2: 112, SMA 3: 51)

7 Studien mit Kindern, 8 Studien mit Erwachsenen und 7 Studien mit gemischter Studienpopulation

Thirteen studies enrolled only paediatric patients [14, 30-48] one study investigated only adult SMA patients [49] and the rest assessed a mix of age ranges. This raises the question of the clinical validity of their diagnosis and highlights issues with the genotype-phenotype correlation of the disease and balancing this in trials and studies.

Nachbeobachtung: Nusinersen: 24-48 M Risdiplam: 12-24 M Onasemnogen abeparvovec: 24 M Kombinationstherapie: 12 Monate - 5 Jahre

In terms of follow-up, the mean follow-up periods of the nusinersen studies ranged from 24 months to 48 months, whilst the onasemnogene abeparvovec study only reports 24-month follow-up findings to date. For risdiplam, we included studies with a minimum follow-up of 12 months due to this treatment only being approved in June 2020 and no studies having been available for our last review. The included studies for risdiplam in SMA type 1 and 2 reports on the same cohorts, for 12-, and 24 -month follow-up time, respectively. The combination therapy study on onasemnogene abeparvovec with nusinersen in SMA1 has the longest follow-up time, with 5.2 years. The other two combination therapy studies include risdiplam in combination and only have 12 months of follow-up data.

“Loss to FU“ häufig berichtet

Loss to follow–up was reported in 14 studies, while in five studies all patients could be followed up until the pre–defined study end [37, 41-43, 46, 47, 50]. One [49] was unclear in their description.

20 Beobachtungsstudien, davon 2 mit historischen Kontrollgruppen, 1 RCT

Concerning study design, all studies were of an observational, non-comparative design except for the risdiplam study in SMA 1 patients, which was a randomized controlled trial (RCT). Two observational studies used historical controls. Eleven studies were conducted prospectively, six retrospectively and the rest were unclear about this in their publication.

The majority of studies (14/21) were multicentre studies conducted in a variety of countries.

Endpunkte: Wirksamkeit und Sicherheit

nur 6/21 Studien berichten auch über Lebensqualität

Most publications reported on efficacy outcomes as well as safety, with five focusing mainly on adverse events. Most reported efficacy endpoints were motor skills. The assessment tools Children’s Hospital of Philadelphia Infant Test of Neuromuscular Disease (CHOP-INTEND), Hammersmith Infant Neurological Examination- section 2 (HINE-2) and Bayley Scales of Infant Development-III (BSID-III) were mostly used for infantile-onset SMA types and Hammersmith Functional Motor Scale- Expanded (HFSME), (Revised) Upper Limb Module (RULM), 6-Meter-Walk Test (6MWT), Motor Function Measure (MFM) and Manual Muscle Test (MMT) using the Medical Research Council Scales (MRC) for patients with less severe forms and older onset forms.

Respiratory outcome was assessed by evaluating the need for invasive and non-invasive ventilation, and in some studies also by lung function tests. Bulbar function was mainly assessed by describing the need for nutritional support.

Quality of life outcomes were only assessed by six studies using the Amyotrophic Lateral Sclerosis Functional Scale -Revised (ALSFRS), Egen Klassifaktion (EG), Clinician/Patient described Global Impression of Change (C-GIC, P-GI), Fatigue Severity Scale (FSS), Short Form Survey SF36 , SMA Independence Scale-Upper Limb Self Report Module (SMAIS-ULM) and Global Attainment Scale (GAS).

15/21 Studien vom Hersteller finanziert. In 23/29 Publikationen Autor*innen mit Interessenskonflikten

Fifteen studies under investigation were funded by the manufacturer and four were funded by a research institute, non-profit organisation, or research grant. In 23/29 publications, authors declared a conflict of interest. One study reported conflict of interest without specifying details and one study declared no conflict of interest. Table 3-1 to Table 3-4 include details on study characteristics

Mehrfachpublikatonen über gleiche Patient*innenkohorten

Multiple publications on the same study cohort occurred in five instances: Two publications [34, 39] reported the 24-month and 48-month follow-up findings on the same cohort of patients. The NCT02122952 study population was reported on in three publications Lowes et. Al 2019 [47] and two publications by Al-Zaidy et.al. [42, 46] and part of the CS2 study cohort (NCT01703988, NCT02052791) was reported on in two publications (Darras et.al. and Montes et.al [45, 48]. Data from the FIREFISH trial NCT02913482 was analysed at 12 and 24 months by Mercuri et al. and Oskoui et al. [15, 51].

RoB meist moderat, RCT niedrig

Our risk of bias analysis evaluated the majority of studies at moderate risk of bias, mainly because of single-arm and unblinded designs, funding and conflict of interest concerns, retrospective data collection and lack of details on loss to follow-up or adverse events. Only three studies were considered at high risk and three at low risk. The RCT evaluated with the Cochrane ROB tool was assessed to be at low risk of bias.

Details on the risk of bias assessment can be found in the Appendix RoB Assessment tables.

Table 3-1: Included studies on nusinersen

SMA 1					
Authors/country	**Number of pts**	**Age range**	**FU period**	**Funding/Conflict of Interest**	**Endpoints**
Acsadi et al. 2021 [30] USA, Germany	21	crossover group: 28.7m (24.5–65.3) nusinersen group 16.7 m (7.3–48.6)	28m	Funding: **Biogen, Ionis Pharmaceuticals** All authors declared conflict of interest authors -Avexis, Biogen, Genentech, Novartis, Roche, Sarepta	Respiratory support HINE-2 CGI-C AEs and SAEs
Finkel et al. 2021 [36] USA/Canada	20	3w-7m	36m	Funding: **Biogen**	HINE-2 CHOP INTEND SAE
Lavie et al. 2022 [35] Israel	20	1m-6m	24m	Funding: **Biogen** provided SMA registry only	Respiratory support Ventilation support
Lavie et al. 2021 [40] Israel	20	1m-6m	36m	Funding: **Biogen** provided SMA registry only	Facial deformity Spinal deformity Nutritional support
Menard et al. 2023 [41] France	18	4 m (median)	2m – 64m 38m (median)	**No funding** 3/11 authors declare conflict of interest: Avexis, Roche, Biogen,Scholar Rock	CHOP INTEND Respiratory Management
Modrzejewska et al. 2022 [32] Poland	26	4.79 y (2 y - 15 y)	18-26m	**No funding** 1/13 author declared conflict of interest- Biogen	CHOP INTEND Respiratory support Nutritional support AEs
Pane et al. 2021 [39] Italy	68	2m-15.9y	24m	Funding: **Famiglia SMA** 9 authors declare conflict of interest - Biogen	CHOP INTEND HINE-2 Respiratory support Nutritional support
Pane et al. 2023 [34] Italy	48	7d -12 y	48m	Funding: **Biogen, Ministry of Health Universita Catolica del S.C.** 15/33 of authors declare conflict of interest: Biogen, Avexis, Novartis, Genesis Pharma and Biologix	CHOP INTEND HINE-2 HFSME 6MWT Respiratory support Nutritional support
Westtrate et al. 2021 [37] United Kingdom	24	1m - 7.6y	24m	Funding: **Biogen, NIHR Great Ormond Street Biomedical Research Centre** 5/9 authors declare conflict of interest- Biogen, Avexis, Roche, Novartis	CHOP INTEND P-FOIS (bulbar function) Respiratory support Nutritional support

SMA 1+2					
Authors/country	**Number of pts**	**Age range**	**FU period**	**Funding/Conflict of Interest**	**Endpoints**
Iwayama et al. 2023 [50] Japan	7 SMA 1: 4 SMA 2: 6(3) 3 got diagnosis changed to SMA 1C after review because of limited motor function	2 y - 40y	3.55 y (1.78 y – 4.53 y)	**No funding** Authors declare conflict of interest for lectures/manuscript writing but do not mention which pharmaceutical company.	CHOP INTEND HFSME RULM
SMA 2+3					
Authors/country	**Number of pts**	**Age range**	**FU period**	**Funding/Conflict of Interest**	**Endpoints**
Darras et al 2019 [44] USA	28 SMA 2: 11 SMA 3: 17	2y –15 y	32 m	Funding: **Biogen, Ionis Pharmaceuticals** Most authors declare conflict of interest-- AveXis, Biogen, Bristol-Myers Squibb, Cytokinetics, Marathon, PTC, Roche, Santhera, Sarepta; National Institute of Neurologic Disorders and Stroke, Slaney Family Fund for SMA, SMA Foundation, Working on Walking Fund; Summit, Genentech, Muscular Dystrophy	AEs, SAEs
Fainmesser et al 2022 [52] Israel	37 SMA2:15 SMA3: 22	38 y (21-61y) 38 y (28-49y) 34 y(21-64y)	26-30 m	Funding: **Biogen** funds Israel SMA registry 3/7 authors declare conflict of interest- Biogen, Roche	MMT RHS ALSFRS-R FEV 1
Montes et.al. 2019 [45] USA	14 SMA 2: 1 SMA 3: 14	2-15 y	35 m	Funding: **Biogen** 14/15 authors declare conflict of interest- Astellas, Biogen, Cytokinetics, Roche, Scholar Rock, Ionis Pharmaceuticals, Cure SMA, AveXis, Children's Hospital of Philadelphia, ATOM International, Mallinckrodt, Novartis, Cure SMA, SMA Europe, SMA Foundation, SMA Reach (UK), Dynacure, PTC, Sarepta, NIH, Slaney Family Fund for SMA, Santhera, Fibrogen, Summit, Wave, Pfizer, Famiglie SMA Italy, Italian Telethon, Metafora, Department of Defense, Glut1 Deficiency Foundation, Hope for Children Research Foundation, Ultragenyx, Otonomy, Myotonic Dystrophy Foundation	6MWT
Pane et al 2022 [53] Italy	113 SMA2:46 SMA3:65	2.64 y- 47.8 y 3.21y -68.27y	≥24 m (2.56 y)	Funding: **Famiglia SMA, Biogen SMA registry,Ministry of Health** 12/27 authors declare conflict of interest- Biogen	HFSME RULM

Pechman et al 2022 [54] Germany, Austria, Switzerland	256 young sitter: 107 older sitter: 73 lost sitter: 37 lost walker: 39	young sitter (<5 y): 30.8±13.2m older sitter:(>5 y): 120±39.1m lost sitter: 98.5m± 61.6m lost walker: 134m± 54.6m	max 38m	Funding: **Biogen, Novartis** More than 50% of authors declare conflict of interest -Biogen, Avexis, Novartis, Roche,Sanofi, Pfizer, etc.	HFSME RULM Respiratory support Nutritional support
SMA 3					
Authors/country	**Number of pts**	**Age range**	**FU period**	**Funding/Conflict of Interest**	**Endpoints**
Pechman et al 2023 [55] Germany	231 Paediatric walkers: 114 Adult walkers: 117	89m-117.6m 405m-481.9m	max 38m 28m: Paed. Walkers n=84 Adult Walkers n=81 38m: Paed. Walkers n=55 Adult Walkers n=55	Funding: **Biogen, Novartis** More than 50% of authors declare conflict of interest -Biogen, Avexis, Novartis,Roche ,Sanofi, Pfizer, etc.	6MWT HFSEM RULM Respiratory support Bulbar function Fatigue AEs
SMA 1+2+3					
Authors/country	**Number of pts**	**Age range**	**FU period**	**Funding/Conflict of Interest**	**Endpoints**
Tscherter et al 2022 [56] Switzerland	44 SMA1: 11 SMA2: 21 SMA3 n=12	(0.1y-44.6y) 0.1y-16.1y 1.2y-31.4y 2.5y-44.6y	6m-41m 2.1 y 1.8y 1.8y (Mean treatment time)	**No funding** 6/12 authors declare conflict of interest-Avexis, Novartis, Biogen, Roche, etc.	CHOP INTEND HINE HFSME RULM 6MWT Respiratory support Nutritional support Speech development

SMA 1-4					
Authors/country	**Number of pts**	**Age range**	**FU period**	**Funding/Conflict of Interest**	**Endpoints**
Bjelica et al 2023 [49] Germany	38 SMA1: 1 SMA2: 14 SMA3: 21 SMA4: 2	38.4±14.1 y	30m	Funding: **Project DEAL** 3/5 authors declare conflict of interest -Biogen, Roche, Deutsche Gesellschaft fuer Muskelerkrankte and others	HFSE RULM SF-36 FSS Pulmonary function

Table 3-2: Included studies on onasemnogene abeparvovec

SMA 1					
Authors/Country	**Number of pts**	**Age range**	**FU period**	**Funding/Conflict of Interest**	**Endpoints**
Al –Zaidy et al. 2019a [46] **USA**	12	3.4 m (0.9 m - 7.9 m)	24	Funding: **AveXis,** No conflict of interest declared	Respiratory support Nutritional support Motor milestones
Al-Zaidy et al 2019b [42] USA	12	0.9m-7.9m	24m	Funding: **Avexis** No conflict of interest declared	Respiratory support Nutritional support Swallow function Speech Motor milestones Hospitalisations
Lowes et. al. 2019 [47] (USA)	12	1.8 m - 5.1 m	24	Funding: **AveXis** 12/16 authors declare conflict of interest-- AveXis, Roche, F. Hoffmann-LaRoche AG, Sarepta Therapeutics, Exonics Therapeutics	Respiratory support Nutritional support CHOP INTEND
McGrattan et al 2023 [38] US/EU only START trial data with long enough follow up	65 START: 11	25.4-48m	24m	Funding: **Novartis** All authors declare conflict of interest -Biogen, Novartis, Roche, Pfizer, involvement in other SMA trials	BULBAR FUNCTION: Communication Swallow Full oral nutrition Airway protection

Table 3-3: Included studies on risdiplam

SMA1					
Authors/country	**Number of pts**	**Age range**	**FU period**	**Funding/Conflict of Interest**	**Endpoints**
Darras et al. 2021 [14, 48] multiple countries NCT02913482 FIREFISH PART 2	41	1-7m	12m	Funding: **Hoffmann LaRoche** >50% of authors declare conflict of interest. Hoffman LaRoche, Biogen, Novartis,Sanofi, Sarepta, Scholar Rock, Ionis Pharmaceutices etc.	Sitting > 5 secs (Item 22 Bayley III) CHOP INTEND HINE-2 Event-free SURVIVAL AE
Masson et al. 2022 [14] multiple countries NCT02913482 FIREFISH PART2	41	1-7m	24m	Funding: **Hoffman LaRoche**	Sitting > 5 secs (Item 22 Bayley III) CHOP INTEND HINE-2 Event-free SURVIVAL AE
SMA 2+3					
Authors	**Number of pts**	**Age range**	**FU period**	**Funding/Conflict of Interest**	**Endpoints**
Mercuri et al. 2022 [15] multiple countries NCT02908685 SUNFISH TRIAL	180 Risisidiplam: 120 SMA2:84 SMA3: 36 Placebo: 60 SMA2: 44 SMA3:16	A2-25 y	12m	Funding: **Hoffman -LaRoche** All authors declare conflict of interest: Biogen, LaRoche, Novartis, Avexis etc	MFM32 RULM HFSME SMAIS-ULM C-GIC AEs Respiratory support
Oskoui et al 2023 [51] multiple countries NCT02908685 SUNFISH TRIAL (38)	180 Risidiplam: 120 Cross-over: 60	2-25 y	12-24m	Funding**: Hoffman- La Roche** All authors declare conflict of interest – Biogen, Novartis, LaRoche, Avexis etc	MFM32 RULM HFSME SMAIS-ULM AEs Respiratory support

Table 3-4: Included studies on combination therapies

+					
Authors/country	**Number of pts**	**Age range**	**FU period**	**Funding/Conflict of Interest**	**Endpoints**
Mendell et al. 2021 [43] USA	n=13	28.4-48 m	5.2 y (4.6-6.2) y	Funding: **Novartis** 7/12 authors declare conflict of interest: Novartis, Milo Biotech, Catalyst, Avexis, Sarepta, , ATOM International, Casimir	AEs/SAEs RESPIRATORY support Motor Milestones
risidiplam + RG7800, olesoxime, nusinersn or onasemnogene abeparvovec in SMA 1-4					
Authors/country	**Number of pts**	**Age range**	**FU period**	**Funding/Conflict of Interest**	**Endpoints**
Chiriboga et al. 2023 [33]	174 RG7800:13 olesoxime: 71 nusinersen: 76 onasemngene abeparvovec: 14	1-60 y	12m	Funding: **Hoffmann–La Roche** All authors declare conflict of interest- Roche, Biogen, CS Genetics, Avexis, Novartix, Sarepta, Scholar Rock, Pfizer	AEs/SAEs Pharmacokinetics (SMA protein in blood)
risidiplam + nusinersen in SMA2					
Authors/country	**Number of pts**	**Age range**	**FU period**	**Funding/Conflict of Interest**	**Endpoints**
Nungo Garćon et al. 2023 [31] Spain	6	17-16y	12m	Funding: **CUIDAME, Intitut de Salud Carlos III, Generalitat de Valencia** 2/5 authors declare conflict of interest: Biogen,Roche,Avexis	BMI FVC% RULM EK2 ALSFRS-R C-GIC P=GIC GAS

3.2 Outcomes

Motor skills

validierte Instrumente zur Messung motorischer Endpunkte

Most studies used validated instruments to assess the effect of the therapies on the motor skills of patients and depending on the age of the patient and the SMA type, the following instruments were commonly used:

For *SMA type 1* patients, the **CHOP INTEND** scale and the **HINE-2** score were evaluated frequently. One RCT assessed infants with the **BSID-III**.

CHOP INTEND: motorische Entwicklung in Kindern (< 4 Jahre) max 64 Punkte, MCID: ≥ 4 Punkte

CHOP INTEND is a 64-point scale developed specifically for children with SMA type 1 aged 3 months up to age 4 years, and includes items such as spontaneous movement, head control, rolling over, and hand grip which can easily be observed by the investigator [57]. Children affected by SMA 1 score much lower than unaffected children (median 20 vs 50 points) [58]. The minimal clinically important difference (MCID) is ≥ 4 points.

HINE-2: motorische Entwicklung in Kindern (≤ 2 Jahre) max 26 Punkte MCID: ≥ 2 Punkte

Section 2 of HINE examines the motor skills of children up to 2 years of age and evaluates eight key functions: Voluntary grasp (reaching out and grasping an object), head control (controlling the muscles of the head and neck), kicking while lying on the back, rolling over, sitting up, crawling, standing and walking. A maximum of 26 points is possible [57]. The MCID is ≥2 points.

BSID-III: Entwicklung von Kleinkindern (1-42 Monate) Sektion 2: Motorik

BSID-III assesses development of children aged one to 42 months and covers 5 domains- cognition, motor, language, socio-emotional and adaptive behaviour [59]. Only section 2- the motor section was used to evaluate SMA type 1 patients.

For patients suffering from *later-onset* SMA form *SMA type 2 to 4*, **HFSM(E)**, **(R)ULM**, **6MWT, MFM** and the **MRC scales** were used to assess motor skills.

HFSME: Motorfunktion in Kindern max 66 Punkte MCID ≥3 Punkte

The HFSM(E) measure has been developed to assess the physical abilities of children with non-ambulatory SMA and can be applied to patients of all ages who have type 2 or 3 SMA, however a significant floor effect affects use in adults [60]. The expanded version has extra items adjusted for type 3 SMA patients who can walk. The maximum score is 66 points. The MCID is ≥3 points.

6MWT: Leistungsfähigkeit beim Gehen MCID >30m

The 6MWT is used for the clinical evaluation of fatigue, muscle strength, and walking ability in ambulatory SMA patients. Although the test was traditionally developed for patients with cardiac or respiratory disease, it has been validated for assessment of SMA patients [60]. Patients have to walk a 30-metre course for six minutes with the aim of walking as far as possible and the MCID is >30 metres.

RULM: Funktionalität der oberen Extremitäten, max 37 Punkte MCID ≥ 2 Punkte

The RULM is a tool developed to assess the upper limb function in SMA patients with a maximum score of 37 points and a MCID of ≥ 2 points. It evaluates motor skills with consideration of daily living functionality (close ziplock bag, writing, picking up tokens, lifting weight above shoulders) and is a useful addition to HFSME. It shows a ceiling effect in ambulant patients with SMA type 3 (without upper limb weakness) and a floor effect in a proportion of non-sitters [60] .

MMT: Muskelstärke max 5 Grade keine MCID

The MMT was used in one study for SMA types 2 and 3 and is an alternative approach to assessing SMA patients. Manual muscle testing measures muscle strength according to the six-point Medical Research Council (MRC) score.

A score of zero defines a plegic muscle, and five indicates normal muscle strength [61].

MFM32 is a validated tool to assess motor skills in patients with SMA types 2-3. A change of ≥3 points is a considered a clinically meaningful improvement, whilst a score change of ≥0 points indicates stabilisation [62].

MFM: Motorfunktion in Kindern und Erwachsenen MCID ≥3 Punkte

Quality of life (QoL)/ Daily functioning

These outcomes were assessed by **ALFRS**, **EK**, **SF-36**, **FSS**, **SMAIS-ULM, CGI-C and GAS.**

ALFRS-R has been adapted for use in SMA patients and has recently been validated [63]. It assesses daily functioning by assessing 12 items covering four domains (bulbar, upper limbs, lower limbs, respiratory) with a maximum score of 48.

Lebensqualität mit zum Teil validierten Instrumenten bewertet, die die tägliche soziale und körperliche Funktionsfähigkeit sowie Müdigkeit bewerten

EK is a validated tool for SMA patients that assesses 17 items for eight daily-life categories (wheelchair use, wheelchair transfers, trunk mobility, eating, swallowing, breathing, coughing, fatigue).

The SF-36 survey is a questionnaire on health-related quality of life assessing eight different dimensions of health-related quality of life (HRQoL): physical functioning, role-limitations due to physical health, bodily pain, perception of general health, vitality, social functioning, role-limitations due to emotional status and mental health [64].

keine validierte MCID

The FSS is a validated scale evaluating physical, social, and cognitive effects of fatigue experienced during the past week.

The SMAIS-ULM is a tool to assess the degree of assistance required for an SMA type 2 or non-ambulant type 3 patient to perform typical daily activities. A change of ≥3 points has been suggested as clinically meaningful [63].

The CGI-C is a tool initially developed for psychiatric patients with the observer rated scale ranging from very much worse (1 point) to very much improved (7 points) and can be completed by clinicians, caregivers or patients themselves [65].

The GAS is a tool where personalized functional goals are established at baseline during discussion with the patient and re-evaluated at the end of the study period. Each goal is rated on a 5-point scale, with the degree of attainment captured for each goal area [66].

Respiratory and nutritional outcomes

Evaluated as separate outcomes in many studies, these outcomes are inextricably to a patient's quality of life. They are important indicators for disease management as respiratory complications (often related to aspiration) are the main cause of death in SMA patients [67]. Most studies reported on the number of patients receiving respiratory support, either invasive ventilation (IV) or non-invasive ventilation (NIV) and most report details on number of hours/day or number of tracheostomies. However, not all studies report baseline and follow-up findings, making conclusions difficult.

die meisten Studien berichten über den Bedarf an Beatmungsunterstützung und Ernährungsstatus, aber mit weniger Detail als Motorik-Endpunkte

Adverse events

unerwünschte (schwere) Ereignisse meist berichtet

When (severe) adverse events (S)AE were evaluated, drug- and procedure-related, as well as disease-related adverse outcomes were reported.

3.2.1 Nusinersen in SMA type 1

7 Studien, 9 Publikationen 196 Patient*innen Nachbeobachtung: max 48 Monate

Safety and efficacy of nusinersen in type 1 SMA patients was evaluated in seven studies (in 9 publications) with a total of 196 patients enrolled. Three studies enrolled patients aged older than 4 years of age, prompting inquiries into the accuracy of their SMA 1 diagnosis of since life expectancy in this most severe form of SMA has been shown to be significantly shortened with the majority of children affected dying by age 2 [2, 68]. Five studies were conducted prospectively, two retrospectively and for two this was not clearly explained. The follow-up period varied between 24 months and 48 months. Loss to follow-up was discussed in all studies, with only two studies reporting data for all patients until the pre-defined last visit.

Mortality and discontinuation

10 Patient*innen starben, Details nur zu 3 Ptn Therapieabbruch häufig

In the five studies reporting loss to follow-up, a total of 10 patients died. Only one study described details on cause of death. In Lavie et al. [40] two patients reportedly died of respiratory failure and one due to hypoxic brain injury after an aspiration incident. In Acsadi et al. [30],one patient in the control group died during the placebo phase, but all other patients both from the intervention group and the cross-over group continued until the study end. In Finkel et al.[36], five patients died, two withdrew with no explanation given, and 11 discontinued to enter a new trial (SHINE NCT02594124). During the first 24 months in Pane et al. [39], there was no loss to follow up. However, during the 24-48-month observation period, one patient died, five patients changed treatment and seven discontinued, three because of perceived lack of benefit and four because of side effects. Menard et al. [41] report the death of one patient.

Motor outcomes

6/7 Studien berichten Motorikendpunkte

Of the seven studies, one did not collect any information on motor outcomes [35, 40]. Three studies reported CHOP INTEND at baseline and follow up, one study reported HINE-2 results at baseline and follow-up and two studies reported on both.

CHOP INTEND MCID wurde in allen Studien angegeben, die dieses Ergebnis berichteten

statistisch signifikante Veränderungen für alle Altersgruppen außer 5–12 Jahren nach 48 M

Mean CHOP INTEND scores were reported as improved above the MCID threshold in all studies that reported this outcome. From 30±10.5 to 48 ±12.7 (+17.3±12.2) at a median follow-up of 36 months [36], from 19.11 ±14.28 to 26.5 ±18.04 (+7.38, $p<0.001$) at a mean follow-up of 26 months [32], from 18.09±14.22 to 26.75±19.35 (+8.66±9.35) at 24 months, and with improvement of +10.6±12.1in the same cohort after 48 months follow-up [34, 39]. Two studies- (43) (44)reported median and interquartile ranges (IQR) rather than mean findings. Baseline was recorded as 27 (19.5-28.4) and 32, with median scores at follow-up being 46 (31-55.5) and 42.

Pane et al. [34, 39]conducted subgroup analysis for age at treatment initiation and found statistically significant changes across the whole cohort after 24 months of treatment. After 48 months only the changes in the 5-12 years old cohort were non-significant. Overall, the positive trajectory persisted, 37

patients improved (77.1%) and 33 (68.8%) achieved the MCID threshold. This was the only study that investigated the influence of SMN2 copy number on outcomes and this was not found to be a predictive variable for change, whilst age at treatment initiation being <210 days resulted in a significant difference in the magnitude of changes at any time point.

früher Behandlungsbeginn jedoch nicht Anzahl der SMN2 Kopien prädiktiv für Verbesserung

Influence of disease severity on outcome was also investigated showing statistically significant CHOP INTEND changes only in Dubowitz score 1.5 and 1.9 patients, but not in the worst affected 1.1 patients. The Dubowitz score is an infrequently used scale to distinguish variations of disease severity within the specific SMA types [69].

gemischte Ergebnisse zum Einfluss des Erkrankungsgrades auf Ergebnisse

The other study reporting on SMA type 1 subgroups (type 1a, b and c) [37] reported an equal percentage of each group to show improvement but follow-up data was missing on one 1a patient, one 1b patient and three type c patients.

HINE-2 MCID wurde vom Großteil der Ptn. in allen Studien erreicht.
Responder: 63–80%

In the study with crossover design [30], HINE-2 scores in the nusinersen group improved from baseline 7.6±5.4 to 15±2 at 33-months follow up, whilst the crossover group improved from baseline 6.7±5.0 to 9±2 at 21 months, with the 33-month scores not recorded. Eighty percent of the nusinersen group were motor milestone responders.

Another study [36] evaluating low and high-dose nusinersen treatment in patients with either 2 or 3 SMN2 copies, reported the scores for the total cohort only at baseline (2 ±2.4). Two patients from the low-dose cohort (all had 2 SMN2 copies) achieved MCID threshold, as well as both patients from the high-dose cohort with 3 SMN2 copies.In the remaining seven patients from the high-dose cohorts with 2 SMN2 copies, the mean improvement was +10.43± 6.18. 63% of the per-protocol efficacy evaluable population achieved motor milestones.

Verbesserungen in der gesamten Kohorte Ø+2,62 (p<0,001) (1 Studie)
früher Behandlungsbeginn prädiktiv für Verbesserungen, SMN2 Kopien Anzahl nicht

In the study evaluating the same cohort at 24 and 48 months [34, 39], the HINE-2 score improved from 0.88±1.33 by +2.62±4.39 (p<0.001) at 24 months and +4.3±5.7 (p<0.001) at 48 months. Subgroup analysis for HINE-2 scores revealed no relationship between SMN2 copy number and score change. Age at treatment initiation was influential, with statistically significant changes at 24 and 48 months only reported for patients that commenced treatment <210days and <2 years of age. After 24 months, 31 % of children achieved sitting, 100 % of the children that initiated treatment <210years of age, 55% of patients that initiated treatment <2years of age, but only 17.6% of children that were older at treatment start.

nach 48 Monaten: 4.6 % stabil, 58 % Verbesserung in HINE-2

After 48 months, 41.6% of patients had stable motor scores, and 58% achieved improvement on at least one item of the HINE scale.

Respiratory support

großteils erhöhter Bedarf an Beatmungsunterstützung

The need for respiratory support, both non-invasive (NIV) and invasive (IV), was recorded by all studies at baseline and follow-up apart from one study [36] which did not record need for invasive ventilation support at baseline. Three studies [30, 37, 41] reported no need for IV at baseline or follow up. It is of note that in Finkel et al. [36] only the cohort of two patients with 3 SMN2 copy numbers did not require any respiratory support at baseline or follow-up.

The majority of studies reported increased percentage of patients needing respiratory support as well as increased time on ventilator. One study [34]

reported stabilisation of IV at follow-up. Two studies [32, 40] reported a minimal reduction of the percentage of patients requiring of NIV or IV >16h/day.

Nutritional support

The need for nutritional support was recorded at baseline and follow-up for 5/7 studies, one did not record this outcome at all and one recorded only follow-up findings.

Verschlechterung des Ernährungsstatus im Großteil der Studien

The need for tube feeding (gastrostomy or nasogastric tube) increased in all patient cohorts apart from Modrzejewska et al. 2021 [32], where two patients had discontinued at follow-up. In Finkel et al. [36], 50% of patients with 3 SMN2 copies required tube feeding as opposed to 100% in the cohort with 2 SMN2 copies. In one study with subgroup analysis for SMA type 1 severity types [37] 100 % of patients with SMA type 1a and 1b required tube feeding, but only 67% of patients with SMA type 1c.

Quality of life endpoints

100% der Ärzt*innen und Betreuer*innen beobachten „keine Verschlechterung“ oder „moderate Verbesserung“

eine „große Verbesserung“ nur zu 43% resp.64%

No studies looked in detail at QoL assessment, but one study reported on caregiver and investigator evaluation of the CGI-C [30]. Clinicians evaluated both the nusinersen and crossover group as “having no worsening” or “showing at least any improvement” at 100%, and control group at only 74% and 14 %. “Much improvement “was described in nusinersen, crossover and control group as 43%, 17% and 0%, respectively. The caregiver evaluation also rated both the nusinersen and crossover group as having “no worsening” or “showing at least any improvement” at 100%, with the control group at 71% and 43%. “Much improvement “was described in nusinersen, crossover and control group as 64%, 83% and 14%, respectively.

Adverse events

Two studies did not report on AE. Of two publications that reported on the same cohort, but with different follow-up times, only one reported AE.

unerwünschte Ereignisse häufig (100%) aber nur 10% therapiebedingt. Lumbalpunktion-assoziiertes Syndrom typisch

Of the studies that reported AE from an open-label extension one [30] reported 100% events and 50% (SAE) in the intervention and crossover group. However, only two (10%) were judged to be possibly related to treatment. The most common AE was post-lumbar puncture headache and vomiting in the treated group. In the control group that never received nusinersen, 86% and 43 % AE and SAE occurred, respectively. Another study [36] reported 100% AE and 80% SAE respectively, whilst reported that no patients suffered from any treatment related AE. Two studies reported on specifics of AE with one [32] reporting post lumbar headache, respiratory infection, cerebrospinal fluid (CSF) leakage and liver enzyme rises and another reporting 20% of patients suffering from headaches, pain and nausea [34].

3.2.2 Nusinersen in type 1 and 2 SMA

1 Studie, 7 Ptn.

We identified one publication evaluating nusinersen in a mixed cohort of type 1 and type 2 SMA patients [50]

This was a retrospective study from Japan, with no loss to follow-up, that included seven patients aged 12 -40 years based on their genetic and clinical diagnosis, but as discussed earlier, the clinical diagnosis of SMA type 1 (infantile onset) is at odds with the age range of these patients. Median follow-up time was 3.5 years.

keine statistisch signifikante Verbesserung der Motorfunktion, andere Endpunkte nicht gemessen

They evaluated motor outcomes with CHOP INTEND, HFSME and RULM but no statistically significant changes were observed. **CHOP INTEND** improved from a mean of 5 to a mean of 21 points, mean **HFSME** scores were 0 at baseline and follow-up and median **RULM** score improved from 0 to 3 points. Respiratory and nutritional outcomes were only recorded at baseline. Seventy-five percent of patients required non-invasive respiratory support, with a higher percentage of SMA type 1 patients compared to SMA type 2 (75% vs 33%). Quality of life outcomes or adverse events were not recorded at all.

3.2.3 Nusinersen in type 2-3 SMA

Four studies in five publications reported on SMA in older onset type 2 and 3 SMA patients. One was a prospective case series [52], one a retrospective analysis [45] and for the other two the data collection methods are not clearly described. Montes et al. [45] retrospectively analysed data from the same trial as Darras et al. [44], hence their findings will be considered together.

4 Studien, 432 Patient*innen

In total, 432 patients were enrolled, 289 with type 2 and 156 with type 3 SMA. Two studies did not record SMN2 copy numbers, but one study [54] stratified patients according to age and motor ability and recorded SMN2 numbers. They differentiated SMA type 2 patients into younger and older sitters, patients who had lost the ability to sit ("lost sitters") and SMA type 3 patients who all had lost the ability to walk ("lost walkers"). The majority of all patients in all groups had 3 SMN2 copy numbers and all of the lost walkers had more than 2 copies.

289 SMA 2
156 SMA 3
(die Mehrheit mit 3 SMN2-Kopien)

By definition SMA type 2 patients are expected to be able to sit. Pane et al. [53] included nine non-sitters and it is unclear if these patients lost their ability to sit or if they were wrongly labelled as SMA type 2 patients.

Follow-up time varied between 24 months and 48 months across the studies. Loss to follow-up was reported in all five publications.

Nachbeobachtung: 24-48 Monate

Mortality and discontinuation

Two studies report only one patient each as lost to follow-up [52, 53]. In both cases, patients discontinued due post-lumbar puncture headaches. The third study [54] reported 13 discontinuations, seven patients changed treatment and for six of the patients, no details are given. Additionally, 15 patients were lost to follow-up with no further explanation given. Only 129 of 256 patients had data at 38 months- the last pre-defined study point. During the trial (ISIS-396443-CS2, NCT01703988, NCT02052791) informing two publications, four patients discontinued unrelated to treatment.

alle Studien berichten „Loss to FU": keine Erklärung (21), Behandlungswechsel (7), Nebenwirkungen (2)

No deaths were reported in any of the studies.

keine Todesfälle

Motor outcomes

A variety of motor outcomes were evaluated in the studies, with three studies reporting results for **HFSME** or revised **HFSME (RHS).**

steter Anstieg der HFSME-Punkte 1 Studie: signifikante Verbesserung in SMA2 Ptn, die sitzen konnten und SMA 3 Ptn, die gehen konnten

One study [52] reported a baseline RHS score of 14 (5-30 IQR), while the total score at 26 months follow-up was reported as 23.5 (11.5-48.5 IQR).

For SMA 2 patients, the score improved from 5 (2-10 IQR) to 9.5 (2.7-31.2) and for SMA 3 patients from 28.5 (16.44-44.2 IQR) to 32.5 (13.24-49.7 IQR). None of the findings were statistically significant although the authors argue that RHS assessment in SMA patients is limited by floor effect which has been discussed by others [60].

Pane et al. [53] describe a statistically significant score improvement at 24 months follow-up across the cohort of SMA 2 patients of +1.9±4.6 from a baseline of 10.6±9 (p=0.019). When stratified in subgroups, the findings only showed statistical significance in sitters (+ 2.2±5, p=0.020), but not in non-sitters (+1.8±4, p=0.577).

Across the SMA 3 cohort, there was also a statistically significant improvement of +1.5±4.8 from 39.5±17 (p=0.017) When stratified, the improvements were only statistically significant in ambulatory patients (+2.5±5, p=0.004) but not in non-ambulatory patients (-0.3±2.8, p>0.05).

34,6% der „young sitters“ und 25,6% der „lost walkers“ erreichten den MCID

The third study [54] described improvements of +7 points from 20.7±11.4 in young sitters, +0.1 from 15.7±12.4 in older sitters, and + 2.9 from 29.9±9.1 in “lost sitters”. Authors reported clinically meaningful improvements of >3 points in a total of 63/254 patients (24.6%). Follow-up data from 38 months was not available for “lost sitters.” When stratified into subgroups, the highest percentage of clinically meaningful changes occurred in young sitters at 34.6%, followed by patients “lost walkers” (25.6%), older sitters (15.1%) and “lost sitters” (13.5%). Inferential analysis showed SMN2 copy number influencing the HFSME score. Lower baseline scores were associated with smaller improvements overall. In younger sitters, only 8.4% of children gained >3 points between 26- and 38-month follow-up. Most of the gains were observed earlier.

SMA 2: 78% erreichen den MCID

SMA 3: 36% erreichen den MCID

Darras et al. [44] reported an increase of mean HFSME scores by +10.08±2.9 at follow-up from a baseline of 21.3±2.9. Among SMA 2 patients, 7/9 (78%) reached clinically meaningful improvements (>3 points) at the last predefined study visit day 1050 (38 months). In SMA 3 patients, the improvement was +1.8 ±0.9 from 48.9±3 with clinically meaningful improvements (>3 points) in 4/11 (36%) patients at follow-up. In the 13 patients who were able to walk the score improved by +2.6± 0.8 from 54.8±1.5 with clinically meaningful improvements (>3 points) observed in 4/9 (44%) patients. No p-values were reported.

RULM was reported by three studies.

RULM erreichte nur bei SMA 2-“Sitters” statistisch signifikante Veränderungen

One study [53]reported stratified results for SMA 2 and 3 patients. In SMA 2 patients overall, the baseline score of 14.2 ± 7.3 improved with statistical significance (p=0.018) by +1.6± 3.1 at 24 months follow-up. When stratified into sitters and non-sitters, significance could only be found for the sitters (+1.7±3.5, p=0.036) but not for non-sitters (+1.3±2.5, p=0.276).

In SMA 3 patients, no statistically significant improvement was detected in total cohorts or any age-, functionality- or severity-stratified groups at 24 months follow-up.

A second study reporting on RULM in non-ambulant patients (49) found clinically meaningful improvements (> 2 points) in 32.4 % of patients. The highest percentage of patients with clinically meaningful improvements were observed in older sitters (41.1%), followed by "lost walkers" (38.5%), and younger sitters (28%), and "lost sitters (21.6%). Young sitters had a mean improvement of +9.1 from a baseline of 16.2±7.1, older sitters +2.2 from a baseline of 19.0±7.5. "Lost sitters" had a mean improvement of +7.3 points from a baseline of 12.8±7.1, while "lost walkers" had an improvement of +3.3 from 26±6.1. Lower baseline RULM scores were associated with smaller gains and improvements were observed continuously during the follow-up period, in contrast to HFSME scores. This study reported no loss of motor milestones in any patients and six (14.9%) of young sitters and one (1.3%) of older sitters achieved walking independently. Four lost sitters (10.8%) and one lost walker (2.6%) regained the ability to sit independently.

32,4% der "young sitters" erreichten den MCID, gefolgt von „lost walkers"

Darras et al. [44] also reported on ULM only in non-ambulant patients and found an overall improvement of +4±2.4 from the baselines of 11.9±0.9 and 11.9±0.9 for SMA 2 and 3 patients, respectively. Clinically meaningful improvements (> 2 points) were observed in 5/9 (56%) patients at follow-up.

56% von Ptn die nicht gehen konnten, erreichen den MCID

One study [52] reported on **MMT** presenting median and IQR scores. MMT score was 66 (44.5-80.50) at baseline and 75 (62.5-84) at 26-month follow-up across the cohort. For SMA 2 patients, the scores changed from a baseline of 45 (38-59) to 63 (42-77.2) and for SMA3 the score stayed nearly the same from 80 (68-85) to 80 (68.2-84.7) None of the changes were statistically significant.

keine Verbesserung des MMT

The two publications describing data from the same cohort [44, 45] also reported on **6MWT** in walkers. Darras et al. [44] found a mean increase in walking distance (metres) of +92 ±21.5 from a baseline of 253.3±50.7 at the 38-month follow-up. Clinically meaningful improvements (>30 metres increase from baseline) were observed in 100% of patients (8/8). Data was not available for seven of the SMA 3 patients at follow-up. Two of the four children who lost the ability to walk before the study start regained it and one SMA 2 patient unable to walk before the study gained the ability to walk.

6MWT 100% Verbesserungen > MCID (92-98m)

Montes et al. [45] utilized data from the same trial to do a post- hoc analysis of 14 patients, 13 of them SMA 3, and stratified into ages below and above 11 years old. They found that older patients achieved less improvements in distances compared to baseline (<11y: 259.8±155.5, >11y: 190.0±250.9) than younger children. The total median walking distance increase was 98 metres at follow-up and median fatigue associated with the 6MWT reduced by 3.87% across the cohort end of the follow-up time.

größere Erfolge bei jungen Ptn

Respiratory support

Only one of the four studies reported on respiratory support [54]. None of the patients required invasive support during the observation period. At baseline, 39 of all patients (15.2%) required < 16h/day of NIV, compared to 61/256 (23.8%) after 38 months of follow-up.

Stratified by motor ability, NIV requirement increased in all patient groups from baseline: among young sitters from 11.2 % to 13%, older sitters from 21.9% to 38.3%, in "lost sitters" from 24.3% to 40.5% and in "lost walkers" from 5.1% to 12.8%. One older sitter was able to discontinue respiratory support during the treatment period.

Atemfunktion, Ernährung und Lebensqualität nur in 1 von 4 Studien berichtet

steigender Bedarf an nicht-invasiver Beatmung trotz Therapie

Nutritional support

Only one study reported on nutritional support [54].

steigender Bedarf an Unterstützung der Ernährung trotz Therapie

Compared to baseline, four more patients additionally required feeding support during follow-up, two patients in the "lost sitters" group, one in the older sitters group and one in the younger sitters group, but this patient could discontinue again after 4 months.

Quality of life endpoints

keine Verbesserung von Lebensqualität

One study reported ALSFRS-R [52] mean score improvement in all patients but did not detect statistically significant changes between baseline and follow-up in the total cohort, nor when stratified into SMA 2 or SMA 3 patients. It should be noted that follow-up data was only available for half of all patients, and only in 4/15 of SMA 2 and 12/19 of SMA 3 patients.

Adverse events

unerwünschte Ereignisse häufig,

aber nicht als therapiebedingt bestätigt

Three of the studies reported AE. One only reported post lumbar headache in three patients (8%) and some weight gain, a case of Crohn's disease and diabetes 2, all considered unrelated to treatment [52].

The other study reported 144 AE in 64 patients, of which none were confirmed drug-related but 31 (25.4%) were considered as possibly drug-related events [54]. Respiratory infection (45.8%), gastroenteritis (20.8%) and post-lumbar puncture (LP) syndrome (headache, 9%) were most commonly reported.

The third study described side effects in more detail with all 28 patients (100%) experiencing more than one AE and 5/28 patients (18%) experiencing an SAE. The most common AE described were LP syndrome in 16/28 (57%), headache in 13/28 (46%), nasopharyngitis in 12/28 (43%) and upper respiratory tract infection (URTI) in 12/28 (43%) of patients. Less common were puncture site pain, rhinorrhoea, vomiting, pyrexia, joint contracture and scoliosis. The most common severe events listed were post-lumbar puncture (LP) syndrome in two patients, lower respiratory tract infection (LRTI), respiratory distress, and viral pneumonia in one patient, acute respiratory failure from pneumonia due to respiratory syncytial virus in one patient and vesicoureteral reflux and pyelonephritis in one patient.

3.2.4 Nusinersen in SMA type 3 ambulant patients

1 Studie: 114 pädiatrische und 117 erwachsene SMA 3 Ptn, meist 3 oder 4 SMN2 Kopien Nachbeobachtung 38 M

One SMA registry study evaluated 114 paediatric and 117 adult patients suffering from SMA 3 who were able to walk and with the majority having 3 or 4 copies of SMN2 [55].

Follow-up time was 38 months.

Mortality and discontinuation

keine Todesfälle. 3 Ptn beenden Therapie (2 keine Details, 1 alternative Therapie)

No patients died during the follow-up period. Three patients discontinued, two of them changed to risdiplam, for the other one no details were given.

Fourteen patients were lost to follow-up after 12 months again without any further description of details.

Motor outcomes

This study assessed **RULM**, **HFSME** and **6MWT.**

Mean **RULM** scores improved in the paediatric population from a baseline of 32.4 to 35.1 (+2.8) at 38 months. In the adult population, the scores reduced by a mean of 0.5 from a baseline of 34.7 to 34.1. However, clinically meaningful changes (> 2 points) were observed during the follow-up period in 23.7% of paediatric and 14.5% of adult patients.

23,7% der Kinder und 14,5% der Erwachsenen erreichten RULM MCID

Mean **HFSME** scores improved by 5.3 points in the paediatric population and reduced by -1.4 points in the adult population. Clinically meaningful improvements (>3 points) were observed in the paediatric and adult populations in 33.3% and 35.9%, respectively.

33,3% der Kinder und 35,9% der Erwachs. erreichten HFSME MCID

During the **6MWT**, paediatric patients improved their mean walking distance by 39.3 metres and adult patients by 24.4 metres, with clinically meaningful improvements (>30 metres) detected in 27.2 % and 26.5%, respectively. The improvements occurred at the 28- and 36-month follow-up in 13.1% and 12.7% of paediatric patients, and 9.9% and 5.5% of adult patients, respectively.

27,2% der Kinder und 26,5% der Erwachs. erreichen 6MWT MCID

Inferential analysis showed higher SMN2 copy number having statistically significant influence on score improvement.

höhere SMN2-Kopienzahl beeinflusste die Verbesserung

Respiratory support

No patients required IV at baseline or follow-up. NIV increased from a baseline of zero to three adult patients (2.56%) requiring support at follow-up.

trotz Therapie bei 3 Erwachsenen NIV Beatmung notwendig

Nutritional support

No patients required permanent tube feeding at baseline or follow-up.

kein Bedarf an perman.parenteraler Ernährung

Quality of life endpoints

Fatigue was recorded in patients at baseline and follow-up. Overall, fatigue decreased from 29.8% of patients to 9.1% in the remaining cohort - almost half were lost to follow-up in both paediatric and adult patients. In children, fatigue reports decreased from 23.7% to 3.6% of patients and in adults, from 35.9% to 14.5% at the end of the follow-up period.

weniger Müdigkeit bei Kindern und Erwachsenen

Adverse events

Fifty AE were recorded in 40 patients, with 32 (64%) requiring hospitalisation. Sixteen events (32%) were considered possibly related to the treatment. The most frequent issues were post-LP syndrome (26%), fractures/accidents (36%) and infectious diseases (16%). 14% of events were not specified.

häufige unerwünschte Ereignisse: Post- Lumbalsyndrom

3.2.5 Nusinersen in SMA type 1-3 and 1-4

2 Studien mit 88 Patient*innen 12 mit SMA 1 35 mit SMA 2 33 mit SMA 2 2 mit SMA 4

Two studies evaluated treatment with nusinersen in patients with all types of SMA. One [56] included 44 patients with SMA 1 to 3: 11 with SMA 1, 21 with SMA 2 and 12 with SMA 3. Six patients were ambulant. Median follow-up was longest for the SMA type 1 patients at 2.1 years, and 1.8 and 1.9 years for SMA 2 and 3, respectively. The second study [49] included patients with SMA1 to 4: one with SMA 1, 14 with SMA 2, 21 with SMA 3 (seven with SMA 3a and 14 with SMA 3b) and two with SMA 4. Of all patients, 28.9% were ambulant. Follow-up time was 30 months.

Mortality and discontinuation

keine Todesfälle 3 Ptn beendeten Therapie

No patients died in either study. In Tscherter et al. [56], three patients discontinued due to inclusion in another trial and difficulties during the LP procedure. In Bjelica et al [49] data is missing for several outcomes at various timepoints, and lack of willingness of patients and short hospital stays due to Covid were named causes for incomplete data.

Motor outcomes

RULM and **HFSME** were recorded in both studies, Tscherter et al. [56] recorded RULM and HFSME for SMA 2 and 3 separately and recorded **6MWT** for SMA3 and **CHOP-INTEND** for SMA 1 patients. Bjelica et al. [49] reported RULM and HFSME across the cohort.

SMA 2/3: Verbesserungen, Stabilisation, aber auch Verschlechterungen in RULM und HFSME

In Tscherter et al. [56] in SMA 2 patients, from a median baseline of 14, **RULM** scores increased between 1 and 5 points in five patients, between 1 and 3 points in further five patients and showed no change in two patients at follow-up. Among SMA 3 patients, two patients achieved 4 to 6 points higher, in two patients the score remained unchanged, and one patient had lost 2 points at follow-up. Across the whole cohort in Bjelica et al. [49] mean score improvement was +2.0 points by month 22 and +0.2 points by month 30, suggesting stabilisation of the gains.

HFSME scores also showed a mix of improvement and stabilisation in Tscherter et al. [56] where in SMA 2 patients, five achieved score improvements between 1 and 15 points, four patients achieved score improvements from 1 to 5 points and seven patient's scores remained unchanged. In SMA 3 patients the median score changed from baseline of 41 to 53 at follow-up with eight patients achieving higher total scores at follow-up, six patients achieving >2 points and three patients achieving lower scores than at baseline.

In Bjelica et al. [49], a mean score reduction of 0.2 (±5.6) from baseline 24.7 was recorded at follow-up. No significant differences in HFSME scores were detected at any time point during the treatment period ($p>0.05$).

SMA 1: CHOP INTEND Verbesserungen vor allem in Kindern mit frühem Therapiebeginn

Tscherter et al. [56] also recorded **CHOP INTEND** scores at baseline and follow-up for the SMA 1 patients and found that mean scores improved by 25 points in a range of 2 to 42 points with children receiving treatment under 18 months of age achieving higher score improvements (+29.5, 25-42) compared to children who were older at treatment initiation (+5, 2-8).

SMA 3: im 6MWT Verbesserung der erreichten Distanz bei allen Ptn

For SMA 3 patients, the **6MWT** was also assessed in five patients, with all of them achieving longer distances at follow-up. Median distance walked improved from 387 to 466 metres with the increases ranging from 72 to 146 metres.

Respiratory support

Atemfunktion unverändert oder Verschlechterung unter Therapie

The need for respiratory support was reported at baseline and follow-up only for SMA 1 patients in Tscherter et al. [56]. For patients commencing treatment under 18 months of age, no patients required NIV at baseline, and three required nocturnal support >16h/day at follow up. In the patients commencing treatment at older than 18 months, four patients required NIV support both at baseline and follow-up. Changes in CHOP INTEND scores were not found to be statistically significantly different in patient with or without ventilation support. No patients required IV support at baseline or follow-up.

SMA 2 and SMA 3 patients were not described. In Bjelica et al. only baseline but no follow up was reported. Seven patients required NIV at baseline, and none required IV support.

Nutritional support

trotz Therapie erhöhter Bedarf an parenteraler Ernährung

The need for nutritional support was reported at baseline and follow-up only for SMA 1 patients in Tscherter et al. [56]. In patients commencing treatment under 18 months of age, no patients required tube feeding at baseline, but four patients required a percutaneous endoscopic gastrostomy (PEG) at follow-up. In patients commencing treatment older than 18 months of age, four patients required support whilst follow-up was not recorded. In Bjelica et al. [49], two patients required PEG feeding at baseline, again with no records described at follow-up.

Quality of life endpoints

Verbesserung bei Müdigkeit, aber Verschlechterung der Lebensqualität

One study [49] reported on QoL endpoints: FSS and SF36.

FSS was reported on all patients with no loss of follow-up. The baseline mean of 40.1±11.9 improved by a mean of 3.4±8.3 points. The SF36 score reduced by a mean of -4.8±15.3 points from a baseline mean of 58.6±12.

Adverse events

unerwünschte Ereignisse häufig

Lumbalpunktions-syndrom, etc.

Adverse events were only recorded by Tscherter et al. [56] with 15 of 44 (34%) patients suffering from at least one side effect other than effects related to LP procedure, which 14% of patients experienced. Thrombocytosis, thrombocytopenia, proteinuria, coagulation disorders and electrocardiogram changes were reported in 16%, 14%, 2%, 5% and 5% of patients, respectively.

3.2.6 Onasemnogene abeparvovec in SMA 1

4 Publikationen über NCT02122952 START Trial

Four publications evaluated data from the same open label clinical trial, the START trial (NCT02122952) assessing onasemnogene abeparvovec in 12 SMA 1 patients, all with 2 SMN2 copies. Follow-up time was 24 months. Three publications were already included in our last review [42, 46, 47].

One of these three publications compared the outcomes of the treated cohort with a group of untreated SMA1 patients and a cohort of healthy children [46].

The publication [38] found in the updated search assessed bulbar function in a post hoc analysis of pooled data from various trials (START NCT02122952, STRIVE-US NCT03306277 and STRIVE-EU NCT03461289), but only patients from the START trial had a long enough follow-up time to match our

updated inclusion criteria thus we only include findings from this cohort in our assessment.

Mortality and discontinuation

keine Todesfälle. kein "Loss to FU"

No patient died during follow up and all patients completed the study but only 11 patient's data was analysed in the post-hoc analysis without any explanation on the reasons [38]. In the study that compared the treated cohort with untreated SMA 1 patients, ten children died and five were lost to follow-up.

Survival

nach 24 Monaten FU leben 100% der Kinder vom START Trial, aber nur 50% der aus Kontrollgruppe

All children treated with onasemnogene abeparvovec were alive at 24-month follow-up. In the untreated cohort of SMA 1 children used as a historical control group (35), only 8/16 (50%) children were alive at 24-month follow-up.

Motor outcomes

signifikante Verbesserung in CHOP-INTEND bei allen therapierten Ptn

CHOP INTEND scores therapiert Ø 56,4 unbehandelt: Ø 5,3

Motor function was assessed by CHOP INTEND in two publications [46, 47], reporting significant improvements. Al-Zaidy et al. [46] report varying mean baseline scores in the group treated with onasemnogene abeparvovec compared to the untreated group and healthy individuals (28±12.3, 20.3±7.3 and 51±8.9, respectively.) No follow-up data was recorded for healthy children. The untreated SMA 1 patients from the comparison cohort had a progressive decline with a mean score of 5.3 at follow-up as opposed to the patients treated with onasemogene abeparvovec who had a mean score of 56.5. No standard deviation was available for follow-up data. All 12 infants achieved and maintained more ≥ 4 points improvement. Eleven achieved more than 40 points on the CHOP-INTEND scale, in contrast to none of the infants in the untreated cohort.

Subgruppenanalyse: größte Verbesserungen bei Ptn mit niedrigen Ausgangswerten und frühem Behandlungsbeginn

Lowes et al. [47] evaluated the impact of age at treatment start and motor function on outcomes by stratifying into subgroups (early dosing/low motor group, early dosing/ high motor group and late dosing group). The mean change of the whole treatment group was +28.3 points. The early dosing/low motor group had a baseline score of 15.7± 1.53 and achieved a follow-up score of 50.7± 5.77 with a mean improvement of 35 points. The late dosing group had a baseline of 26.5±7.66 and achieved a follow-up score of 49.8± 16.48 with a mean improvement of 23.3. The early dosing/ high motor group started from a baseline of 44±7.94 and rapidly achieved a mean score of 60.3±6.35 with a lower mean improvement of 15.6.

Motor milestones

92%: Sitzen > 5s 75%: Sitzen >30s 2 Ptn lernen Gehen

Lowes et al. [47] report 11/12 patients (92%) achieving head control and sitting independently for more than five seconds, including all three patients from the low motor/ early treatment group. Nine patients (75%) achieved sitting for more than 30 seconds. Two patients (from the high motor early dosing group) achieved standing unassisted and walking.

weitere Verbesserungen nach 24 Monaten

Al- Zaidy et al. [42] claim that further motor improvements were observed beyond the 24-months observation period, two more patients achieved sitting for >30 seconds bringing the total to 11/12 (92%) patients, 9/12 (75%) achieved rolling, 4/12 (33%) achieved standing with support and 2/12 (17%) achieved crawling, pull and stand and walking.

Although motor milestones were not formally assessed in the comparison group of untreated SMA 1 patients, deduction of function from CHOP INTEND scores suggests no infants in the untreated group achieved any of them.

Respiratory support

erhöhter Bedarf an NIV-Beatmung trotz Therapie

The documentation of respiratory outcomes in the publication lacks comprehensive detail. Two patients from the late dosing group required NIV at baseline, increasing to five patients at follow-up. (41.6%) The additional patients are from the low motor/early dosing group as described in [47].

No patients required IV support.

Nutritional support

keine Verbesserung des Ernährungsstatus

Five out of 12 (41%) patients required tube feeding at baseline with only one more patient requiring support at follow-up. Half of the patients continued to be fed exclusively orally (34). All three patients in the early treatment/low motor group, and two (33%) of the patients in the late dosing group but none of the patients in the early treatment/high motor group required support at baseline [47]. Follow-up data is limited, with no information on the additional patient that required nutritional support.

However, the three patients that required support in the early treatment/low motor group, were also able to be safely fed orally at follow-up.

Bulbar function

11/12 Ptn erreichten adäquate Schluckfunktion

One study [38] evaluated bulbar function by analysing four endpoints representing adequate bulbar function: absence of physician-confirmed physiological swallowing impairment, receiving full oral nutrition, absence of adverse events that indicate pulmonary compromise and the ability to communicate by being able to vocalize at least two different vowel sounds.

6/12 (50%) mit ausschließlich oraler Ernährung

It was found that 75% of evaluable patients achieved all components of bulbar function but the majority of patients were only followed for 18 months. We only present findings from 11 of the 12 patients in the START trial which were integrated in this post-hoc analysis. Four out of 11 patients displayed normal swallowing at baseline which increased to 11/11 (100%) after 24 months of treatment. All patients could receive oral feeding, even if receiving support to optimize nutrition. Full oral nutrition was possible in 7/11 patients at baseline and only one patient lost this ability by the end of follow-up. No patient had aspiration events or pneumonia at baseline, and at follow up 8/11 (72%) patients maintained their pulmonary stability.

Communication was not recorded at baseline. At follow-up, only 4/11 patients had communication recorded, and all 4 (100%) were able to form vowels as required.

Adverse events

unerwünschte und schwere unerwünschte Ereignisse häufig (100%/ 83%), aber nur 4 therapiebedingt

Only one publication reported safety endpoints with 100% of patients experiencing an AE and 83% of patients experiencing a SAE. In total, 274 AE and 53 SAE were recorded. Only four events in three patients were considered related to treatment with no further details given.

3.2.7 Risdiplam in SMA 1

2 Publikationen über FIREFISH NCT02913482 41 Patient*innen, 12 und 24 Monate Nachbeobachtung

Two publications describe the same trial FIREFISH NCT02913482. One publication [48] describes findings after 12 months, and the second publication [14] describes findings after 24 months of 41 SMA 1 patients treated with risdiplam. All patients had 2 SMN2 copies. In both studies outcomes in treated patients were compared with an untreated historical control group, using the upper boundary of the 90% confidence intervals in untreated SMA1 patients to create a performance criterion threshold.

Mortality and discontinuation

3 Ptn starben durch krankheitsbedingte respiratorische Komplikationen

Three patients died during the first 12 months of treatment due to treatment-unrelated respiratory complications attributed to disease progression. All others completed the 24-month follow-up period.

Motor milestones

nach 12 Monaten: 29% lernten sitzen ≥5s

nach 24 Monate: 44% lernten sitzen ≥30s

kein Kind konnte gehen oder stehen nach 24 M

The primary endpoint of the first part of the trial was the ability to sit without support for ≥ 5 seconds according to item 22 of the **BSID III**. No children achieved this at baseline. After 12 months of treatment, 12 of 41 patients (29%) (CI 95%16-14) had achieved this milestone, a finding statistically significantly different to the performance criterion of 5% from natural history data ($p<0.001$). During the second part of the trial further items from the BSID-III motor scale were assessed: sitting for ≥ 30 seconds (item 26), standing alone (item 40) and walking independently (item 42). No patients could sit for ≥ 30 seconds at baseline. After 12 and 24 months of follow-up, 7/41 patients (17%, 90% CI 8-30) and 18/41 patients (44%, 90%CI 31-58) had achieved this milestone, respectively. This finding was statistically significantly different to the natural history performance criterion ($p<0.001$).

No infants could stand or walk independently, at baseline and after 24 months of treatment (0%, 90% CI 0-7) ($p<0.001$).

Motor outcomes

CHOP INTED Ø von 22 auf 42 Punkte >40 Punkte 56% nach 12 Monaten 76% nach 24 M

stat. signifikanter Unterschied zur historischen Kontrollgruppe

CHOP INTEND scores were prespecified for analysis only at month 12. The hypothesis testing was hierarchical and outcomes not in the hierarchy at month 24 were presented without a p-value.Total cohort scores (mean and range) improved from a baseline of 22 (8-37) to 42 (13.05-57) at 12 months, with 23/41 patients (56%) achieving more than 40 points in total and 37/41 patients (90%) improving more than four points. Both findings were statistically significantly different to the 17% performance criterion from the natural history data ($p<0.001$): After 24 months, 31/41 patients (76%) achieved a total of more than 40 points and 37/41 patients had improved more than four points- no change to the 12 months' findings.

nach 12 Monaten Verbesserung von HINE-2 in 78% der Ptn

Improvement - defined as an increase of at least two points in the ability to kick (or maximum score), or an increase of at least one point in head control, rolling, sitting, crawling or standing - was assessed with **HINE-2**. Investigators recorded the percentage of patients showing improvement as defined above, with 32/41 patients (78%) (CI 95%, 77-97) ($p<0.001$) and 35/41 patients (85%) (CI 95%,73-93) showing a response to treatment. Worsening was defined as a decrease of at least two points in the ability to kick (or lowest score) or a decrease of at least 1 point in head control, rolling, sitting, crawling, standing or walking. Baseline mean (95% CI) was recorded as 1 (0.5-5.0). HINE-2 absolute values were not recorded at any follow-up point.

Respiratory support

At baseline 12 patients (29%) required some kind of ventilation (NIV or IV was not specified). After 12 months and 24 months of treatment, 31 (75%) and 33 (80%) required respiratory support, respectively.

trotz Behandlung: Bedarf an NIV und IV, Anstieg von 29% auf 80%

Nutritional support

Baseline was not recorded, but at 12 and 24 month-follow up, 6 and 7 patients respectively, required support (15% and 17%)

keine Information zur Ausganssituation, nach 24 M brauchen 17% Unterstützung

Survival

Event-free survival was defined as being alive without the use of permanent ventilation. Three patients died during the first 12 months, but no more reached either of the endpoint by the end of the 24-month observation period.

Adverse events

During the 24-month treatment period, 356 AE were recorded with 100% of patients experiencing at least one event. Seven events were listed as treatment-related with no further details given. The most frequent AE were URTI (54%), pneumonia (46%), pyrexia (44%) and constipation (29%). Sixty-eight SAE were recorded in 28 patients with the most frequent issues listed as pneumonia (39%) and respiratory distress (7%). No AE led to treatment discontinuation or dose modifications.

min. 1 unerwünschtes Ereignis in 100% der Ptn

Pneumonie und Atemnot häufig

3.2.8 Risdiplam in SMA 2 and non-ambulant SMA 3 patients

Two publications [15, 51] reported on the same study, a phase 3 RCT- (SUNFISH trial, NCT 02908685), describing the 12- and 24-month follow-up findings of part 2), respectively.

2 Publikationen über RCT SUNFISH NCT02908685

In total, 180 patients were enrolled. In the first, double-blind phase of the trial, 120 patients were randomized to receive risdiplam and 60 were randomized to receive placebo for 12 months. For the second, open-label extension phase, all patients received risdiplam, with blinding maintained for patients, investigators and all individuals in direct contact with the patients until the final 24-month assessments had been completed.

180 Patient*innen: 120 Risdiplam 24 M 60 Placebo 12 M, dann Crossover (Verblindung ist aufrecht)

All patients were SMA type 2 or non-ambulant type 3 patients. In the risdiplam group, 84 (70%) SMA 2 and 36 (30%) SMA 3 patients were included and in the placebo group, 44 (73%) and 16 (27%), respectively. The majority of patients in both groups had 3 SMN2 copies (89 and 83%, respectively).

SMA 2: 128 SMA 3 (ohne Gehfunktion): 52 (großteils 3 SMN3 Kopien)

The 12-month analysis (14) compared the findings of the risdiplam and placebo groups. For the 24-months analysis [51] for patients on risdiplam from baseline, findings at 12, 18, and 24 months were described, and an external comparator group was utilized to contextualise results at the end of the observation period. This group consisted of patients from a natural history study (NCT02391831) and from the placebo arm of a phase 2 RCT (NCT01302600) on olexosime, a compound which never achieved regulatory approval. For the crossover group, an adjusted baseline was used and results after 12 months of risdiplam treatment were described.

5 Patient*innen „Lost to FU“

During the first 12 months of treatment, three patients from the treatment group and one from the placebo group discontinued to start already approved treatments. During the crossover phase of the study, two patients discontinued. Data from 164/180 (91%) patients is available from the 24-month final study visit as Covid restrictions complicated follow-up.

Motor outcomes

Motor outcomes were assessed with **MFM32**, **RULM** and **HFSME.**

MFM 32: stat. signifikanter Unterschied zwischen den 2 Gruppen nach 12 Monaten

≥3 Punkte (38%) vs (24%), Stabilisation (80%) vs (24%)

At baseline the mean (SD) **MFM32** scores of the risdiplam and placebo group were 45.48 ±12.09 and 47.35±10.12 respectively. At 12-month follow-up, the least mean (95% CI) square changes were 1.36 (0.61-2.11) and 0.19 (-1.22-0.84) with mixed model repeated measure analysis estimating a statistically significant treatment difference: 1.55 (0.30-2.81)(p=0.016) (14). No clinically meaningful change estimate has been established so far, but the authors used >3 points of improvement as the threshold. In the risdiplam group, the percentage of patients who achieved this threshold was 44/115 (38%) compared to 12/59 (24%) in the placebo group, with an odds ratio of 2.35. A score change of 0 (no deterioration) or more is considered stabilisation and this was achieved in 80/115 (80%) of patients in the treatment group compared to 32/59 (24%) in the placebo group.

nach 24 Monaten Ø +1,8 (Risdiplam) vs Ø +1,3 (Crossover)

After 24 months of treatment the mean change from baseline scores (95% CI) in the risdiplam group was +1.8 (0.7-2.9) and +0.3 (-0.7-1.3) in the crossover group (from an adjusted baseline of 47.14 (±10.87) [51]. Of the three dimensions, the distal aspects of the MFM test had the highest score improvements, +6.3 (4.2-8.3) and +2.0 (0.4-3.5) in the risdiplam and crossover group, respectively.

nach 24 Monaten stat. signifikanter Unterschied in Verbesserung MFM32 zwischen externer Vergleichsgruppe and Risdiplam-Gruppe

When comparing the risdiplam group to the external comparator, total mean (SD) baseline scores were relatively similar at 47.2 (±12.3) and 47.1(±12.9), respectively. Younger patients (<6 years of age) had relatively higher scores in either group. After 24 months of treatment, the least square mean change (95% CI) was +1.4 (-0.2-3.1) in the risdiplam group, whilst the external comparator scores reduced by-1.7 (-3.4-0), a statistically significant treatment difference (p<0.0001).

MCID: 32% (Risdiplam), 16% (Crossover)

The percentage (95% CI) of patients improving ≥ 3 points was 32% (23.8-41.5) in the initial risdiplam group, and 16% (7.4-27.4) in the crossover group. The percentage (95% CI) of patients with remaining stable (≥ 0 points) was 58% (48.7-67.4) and 59% (44.9-71.4), respectively. When comparing the initial risdiplam group with the external comparator, 34 versus 16 patients achieved ≥3 points, an odds ratio (95%CI) of 2.5 (1.1-5.6) (p=0.0253). Stabilisation (≥0 points) was observed in 63 compared to 40 patients, with an odds ratio of 2.7 (1.4-5.1) which was statistically significant (= 0.0029).

RULM: nach 12 Monaten stat. sign. Unterschied Ø +1,6 (Risdiplam) vs Ø +0,02 (Crossover)

At baseline, **RULM** score was 19.65±7.22 in the risdiplam group and 20.9±6.41 in the placebo group. After 12 months of treatment, differences between the groups were found to be statistically significant with a least squares mean change (95% CI) of +1.6 (1.00-2.22) and +0.02 (-0.83-0.87) respectively, with an odds ratio of 1.61 (p=0.047) [14].

nach 24 Monaten Behandlung Ø +2,8 vs 0,9

After 24 months the mean change (95%CI) in the initial risdiplam group was 2.8 (1.9-3.6) and 0.9 (0.1-1.6) from an adjusted baseline (20.41±6.4) in the crossover group [51].

The comparison between the initial risdiplam group and the external comparator was not recorded.

At baseline the mean (SD) HFSME scores were similar at 16.10 (±12.46) and 16.62 (±12.09) in the treatment and placebo group, respectively. The least mean square change (95% CI) was 0.95 (0.29-1.610) in the risdiplam group and 0.37 (0.54-1.28) in the placebo group (p=0.39) [15]. After 24 months of treatment the risdiplam group had a mean change (95% CI) of +2.2 (1.1-3.1) whilst the crossover group had a change of 0.09 (-1.0-1.1). It must be noted that only nine patient's data were available for analysis [51].

kein Unterschied in HFSME nach 12 M nach 24 M Behandlung Ø +2,2 vs +0.09

The comparison between the initial risdiplam group and the external comparator was not reported.

Respiratory support and nutritional support

The need for respiratory care was only recorded at baseline, but not at follow-up and includes cough assist or bilevel positive airway pressure (BiPAP). At baseline 40 (33%) patients in the risdiplam group required support, and 30 (50%) in the placebo group. No patient had a tracheostomy. Nutritional support was also only recorded at baseline, with two patients in the treatment group and none in the placebo group requiring tube feeding [14].

Atmungsfunktion und Ernährungsstatus nur am Studienbeginn beschrieben

Quality of life endpoints

Quality of life was assessed with SMAIS-ULM and GCI-C.

Baseline for SMAIS-ULM and GCI-C was not reported.

At 12-month follow-up [14], the least square mean (95%CI) caregiver-reported SMAIS-ULM score was +1.65 (0.66-2.63) in the risdiplam group and -0.91 (-2.23-0.42) in the placebo group, but differences were not statistically significant (p=0.39). The patient-reported score changed by +1.04 (-0.26-2.5) and by -0.40 (-2.13-1.32) in the risdiplam and placebo group, respectively. After 24 months of treatment [51] (in the risdiplam group, the caregiver-reported SMAIS-ULM, changed by a mean of 2.7 (1.7-3.7) compared to the crossover group, which showed a mean change of 1.6 (0.4-2.8). No p-values were reported. The patient-reported SMAIS mean score change was 0.8 (-0.8-2.4) and 0.6 (-1.0-2.2) in the respective groups. GCI-C was only reported at follow-up by Mercuri et al. [15] and the percentage of patients recorded by clinicians as improved was 57/120 (48%) in the risdiplam group and 24/60 (40%) in the placebo group. Findings were not statistically significant (p=0.39).

nach 12 M und 24 M kein stat. signifik. Unterschied zwischen den Gruppen Lebensqualität

Betreuer bewerten Verbesserungen höher als Patient*innen

Adverse events

No deaths occurred in either group at any time point during the study period and no AE led to dose modification or interruption in any patient of any group.

keine Todesfälle, keine Therapieabbrüche oder Dosis-Modifikationen

More AE occurred in the first 12 months compared to the second phase of the study. During the first 12 months, 789 events in total were recorded in the treatment group and 354 in the placebo group, with one or more events reported in 111 (93%) and 55 (92%), respectively. One or more SAE were reported in 24 (20%) and 11 (18%), respectively.

unerwünschte Ereignisse häufig Therapiebedingt: 13% (risdiplam) 10% (Placebo)

In the risdiplam group, 16 events (13%) were considered to be treatment-related, and 6 events (10%) in the placebo group. AE that occurred more frequently in the treatment group (>5% difference) were pyrexia, diarrhoea, rash, mouth ulcers, UTI and arthralgia. Pneumonia was the most common severe adverse event that only occurred more frequently in the risdiplam group.

in 12-24 M FU, schwere unerwünschte Ereignisse häufiger in der Risdiplam Gruppe

Pneumonie häufig

During the 12-24-month follow-up period, 506 AE occurred in the risdiplam group versus 242 in the crossover group, with one or more events recorded in 110 (91%) and 48 (80%) of patients, respectively. One or more SAE occurred more frequently in the risdiplam group (25 patients, 20.8%) than in the crossover group (three patients, 5%).The most common AE during the second phase of the study remained similar with URTIs, nasopharyngitis, pyrexia, headache, diarrhoea and vomiting being frequently recorded and pneumonia again being listed as the most common severe adverse event which only occurred in the risdiplam but not in the crossover group during the 12-24-month observation period.

3.2.9 Combination therapies

3 Studien, primäre Intention aber nicht die Prüfung der Wirksamkeit der Kombinationstherapie

In three studies patients had been treated with a combination of therapeutic agents, but only one of them considered the impact of the combination of treatments in their analysis.

One study, which has the longest follow-up time of all studies included, describes the long-term safety and efficacy of SMA1 infants treated with onasemnogene abeparvovec, and seven of the 13 patients received concomitant nusinersen [43].

The second study evaluates risdiplam in SMA 2 non-sitter patients older than 16 years of age and two of the six patients enrolled had previously received nusinersen [31].

The third study included 174 patients who had previously received either RG7800, olexosime, nusinersen or onasmenogene abeparvovec to assess the safety, tolerability and pharmacokinetics of risdiplam in these patients [33].

Onasemnogen abeparvovec and nusinersen

13 Ptn mit niedriger oder therapeutischer Dosis von onasmenogene abeparvovec, 7 erhielten zeitgleich nusinersen

Nachbeobachtungszeit: 5,2 Jahre

In Mendell et.al. [43], which describes findings from a long-term follow-up study called START LTFU, patients from the START study who received onasemnogene abeparvovec were eligible to enter. Three patients received a low dose and ten patients received the therapeutic dose. All three patients from the low-dose onasemmogene cohort and four of the high dose cohort received concomitant nusinersen. Seven of the 13 participants received concomitant nusinersen treatment and six patients were treated only with onasemnogene abeparvovec. The primary objective was not to analyse combination therapies but to report long-term safety outcomes of onasemnogene abeparvovec. The authors did not report results separately for the subgroup who received nusinersen as concomitant therapy thus no conclusions can be drawn on the effect of the combination. This study has the longest follow-up period in this review, with a mean of 5.2 years.

Motor outcomes

This study's primary endpoint was safety, but the authors also reported on motor milestone achievements for the therapeutic dose cohort. Eight of 10 patients (80%) maintained the milestones already achieved and two (20%) achieved standing with support. These two patients had not received nusinersen concomitantly.

Stabilisierung der Motorfunktion in 80%. 2 Ptn (Monotherapie) Stehen mit Hilfe

Respiratory support

The need for ventilation support was also not a primary endpoint in this study, but the authors report the need for non-invasive support remaining stable at 4/10 (40%) of patients in the therapeutic dose cohort, with the low-dose findings not recorded. Invasive support was not required by any patient in either dose cohort at baseline or follow-up, and only one of the three patients (33%) in the low-dose cohort required IV support at follow-up.

keine Änderung oder Verschlechterung des Bedarfs an Beatmungs-unterstützung

Nutritional support

The need for nutritional support was not discussed in this publication but in phase 1 of the START trial preceding this extension, all patients in the low treatment group (100%) and 5/10 patients (50%) in the therapeutic dose group required tube feeding.

keine Information zu Einfluss auf Ernährungsstatus

Adverse events

The total number of AE was not recorded but the total number of SAE was eight (62%). None of the events were considered to be related to therapy and none led to discontinuation. The most frequent SAEs recorded were acute respiratory failure in 4/13 (31%), pneumonia in 4/13 (31%) and dehydration in 3/13 (23%) patients, respectively.

62% schwerwiegende unerwünschte Ereignisse, aber nicht therapiebedingt

Risdiplam and nusinersen

One study [31] investigated six adolescent and adult SMA 2 patients (non-sitters) who received risdiplam as part of an expanded access program NCT04256265.

A range of outcomes were prospectively recorded evaluating nutritional status, pulmonary function, motor skills and QoL and these were compared with the retrospectively recorded baseline values. Follow-up time was 12 months. Two of the six patients had previously received nusinersen, but no subgroup analysis was performed.

2/6 SMA 2 Patient*innen erhielten Nusinersen vor Risdiplam in

Mortality and discontinuation

No patient died or left the study.

keine Todesfälle

Motor outcomes

Mean total **RULM** score was 3.16 at baseline. At follow-up, 2/6 (33%) patients improved by two points or more, which is the minimal clinically important difference.

RULM MCID in 2/6 pts (33%)

Respiratory support

Respiratory outcome did not change from baseline with 4/6 (67%) patients requiring non-invasive support and no patient requiring invasive ventilation.

keine Verbesserung der Atemfunktion

Nutritional support

keine Verbesserung des Ernährungsstatus

No changes occurred during the follow-up period with 3/6 (50%) of patients requiring nutritional support at baseline and follow-up.

Quality of life endpoints

Quality of life was assessed with **ALSFRS_R, EK2, C-GIC**, and GAS.

ALSFRS: 3/6 (50%) erreichen MCID

On the **ALSFRS** scale, the mean changed from a baseline of 18.6 to 22, with a mean improvement of 3.5. The MCID of ≥ 2 points was achieved by 3/6 patients (50%) after 12 months of treatment. Two of these three patients had been on nusinersen previously.

EK2: 5/6% (83%) erreichen MCID

On the **EK2** scale, the mean changed from 31.5 to 27.5 with a mean improvement of 4 points. The MCID threshold of ≥ 2 points was achieved 5/6 (83%) of patients. Two of these five patients had been on nusinersen previously.

C-GIC +1/ leichte Verbesserung in allen Ptn, P-GIC positive und negative Bewertungen

In the clinician-assessed **GIC**, mild improvements were found for all patients (+1), in the patient-assessed GIC, four patients showed mild (+1), one moderate improvement (+2) and one no change at all.

GAS ≥ 1 Ziel erreicht: 4/6 pts (67%)

Personalized goals were established in discussion with the patients at baseline and re-evaluated with the **GAS** scale at follow-up. Two patients did not achieve any of the set goals, and four patients achieved at least one.

Adverse events

Kopfschmerzen und GI-Symptomatik in 1/6

One patient reported mild AE that led to temporary withdrawal, and after restarting they experienced the same- headaches and gastrointestinal symptoms. No other AE or SAE are reported.

Risdiplam and RG7800, olexosime, nusinersen or onasemnogen abeparvovec

Risdiplam in 174 Patient*innen, die davor schon andere Therapien erhalten hatten

This trial NCT 03032172 [33] assessing the safety, tolerability and pharmacokinetics of risdiplam in non-treatment naïve patients enrolled 174 paediatric and adult SMA 1 to 3 patients. Of all patients, 15 had SMA 1 (9%), 108 had SMA 2 (62%) and 51 had SMA3 (29%). The majority had 3 SMN2 copies (78%).

Prior to enrollment, 71 patients (41%) had received olexosime, and 13 patients had been enrolled in the MOONFISH trial with 10 of them receiving RG7800 and three receiving a placebo. Seventy-six patients had received nusinersen, and in this group, three also had received olexosime previously. Onasemnogene abeparvovec had been administered to 14 patients, with one of these patients also having received nusinersen previously.

Sicherheit, Verträglichkeit und Pharmakokinetik primäre Endpunkte

Efficacy was not evaluated, and no subgroup analysis was performed. No patients died. One patient withdrew due to issues with blood access prior to receiving treatment. Eight patients chose to withdraw during follow-up. Five of them in the first 12 months; one due to lack of improvement, one suffered from irritable bowel syndrome/panic attacks and for three the cause was not recorded. After 12 months, three more patients withdrew, one due to Covid safety concerns for two the reason was not recorded.

Motor outcomes

Motor outcomes were not assessed. At baseline, 105/168 patients (63%) for which data was available, had an HFME score <10, but no follow-up data was recorded.

Motorik-Endpunkte,

Respiratory support

The need for ventilation support was only assessed at baseline with 93/174 patients (53%) requiring either NIV, IV or BiPAP.

Atmungs- und

Nutritional support

This outcome was only recorded at baseline with 11/174 (7%) of patients requiring tube feeding support.

Ernährungs-unterstützung,

Lebensqualität

nicht berichtet

Scoliosis

Despite previous treatments, at baseline, 83% of patients had scoliosis, and 39% had a curvature of >40%.

No follow-up data was recorded.

Adverse events

No deaths occurred during the study period.

The total recorded number of AE was 923, with 159 patients (92%) experiencing at least one event. Thirty-three patients (19%) experienced one or more treatment-related side effects. The most frequent AE unrelated to the treatment were upper respiratory tract infection, pyrexia, headaches and nausea. The total number of SAE was not recorded, but 24 patients (14%) experienced at least one. Six events led to treatment interruption or dose modification but only one patient was considered to have a treatment-related side effect- tachycardia. The most common SAE were pneumonia, L/URTI, UTI and respiratory failure.

keine Todesfälle unerwünschte Ereignisse in 92% der Ptn, 19% therapiebedingt, schwere unerwünschte Ereignisse: 14%

4 Discussion

Our systematic review identified 21 studies in 29 publications. The available evidence for nusinersen has increased since our last review [7] but remains limited for onasemnogene abeparvovec and risdiplam. Overall, the evidence stems from heterogenous, open-label, single-arm studies employing observational descriptive study design, thus invalidating internal validity and restricting our ability to perform statistical analysis.

Zusammenfassung der Ergebnisse
21 Studien in 29 Publikationen
1374 Patient*innen

The majority of studies was manufacturer-funded with most publications declaring author conflict of interests.

A total of 1374 patients were analysed. Fifteen studies investigated nusinersen in 948 patients, one study investigated onasemnogene abeparvovec in 12 patients, two studies investigated risdiplam in 221 patients and a combination of therapies was received by 193 patients.

Nusinersen in SMA 1

In total, 212 SMA 1 patients were treated with nusinersen. 10 patients died despite treatment.

100% of SMA 1 patients reached the MCID of ≥ 4 points with subgroup analysis confirming statistically significant changes in the majority of age groups. HINE-2 MCID threshold (>2 points) was achieved by 63-80%. Younger age at treatment initiation but not SMN2 copy number was predictive for change [34, 39]. The influence of disease severity on motor outcomes was inconclusive.

früherer Behandlungsbeginn führt zu besseren Ergebnissen
Anzahl SMN2 Kopien nicht prädiktiv für Verbesserung

Sitting, a milestone normally never achieved by untreated SMA 1 patients was achieved by 100% of infants who initiated treatment before 210 days of age but only by 17.5% of children who were older than 2 years.

Verchlechterung Atmungs- und Ernährungsfunktion

The majority of studies reported an increased need in respiratory and nutritional support.

Nusinersen in later-onset SMA-type patients

Nusinersen in SMA 2 and non-ambulant SMA 3 patients and in SMA 1 to 4.

A total of 432 patients (289 SMA 2 and 156 SMA 3) received nusinersen. No patients died.

HFSME scores and RULM scores increased steadily in all patients. HFSME MCID thresholds were reached in 78% of SMA2 and 34% of SMA 3 patients and RULM MCID thresholds were achieved between 32.4 and 56% of patients. 6MWT also increased above MCID in all studies reporting this outcome.

HFSME- und RULM-Punkte kontinuierlich erhöht
MCID erreichen zwischen ~¼ bis ~¾ der Ptn. bis 26 m FU, höchste Verbesserungen in Ptn. mit frühem Therapiebeginn oder höherer Motorfunktion

In the stratified cohort, the highest improvements occurred in children with early treatment initiation and/or high baseline motor function. Only 8.4 % of children gained above the MCID threshold beyond the 26-month follow-up period. All patients in the stratified study maintained their milestones and 15% of SMA2 sitters learned to walk.

Verschlechterung Atmungs- und Ernährungfunktion

One study reported on respiratory and nutritional support, and found an increase in the need for NIV across all stratified groups with the smallest increase in the group that was able to sit and had initiated treatment early. No patients required IV.

Nusinersen in SMA ambulant patients

~ 1/3 erreichten MCID for RULM, HFSME and 6MWT

One-hundred and seventeen pediatric and 114 adult patients received nusinersen. No patients died.

Atmung und Ernährung stabil bis Verschlechterung

Motor outcomes were assessed with RULM, HFSME and 6MWT. For RULM, 23.7% of paediatric patients and 14.5% of adult patients reached the MCID, for HFSME 33.9% and 35.9%, and for the 6MWT 27.2% and 26.5%, respectively. SMN2 copy number did influence score improvement.

geringere Müdigkeit in Kindern und Erwachsenen

The need for NIV respiratory support increased slightly but no patients required IV respiratory support or permanent parenteral feeding at baseline or follow-up. Fatigue scores improved in all patients.

Onasemogene abeparvovec in SMA 1 patients

nur 12 Patient*innen

12 patients received onasemnogene abeparvovec. No patients died.

100% erreichten CHOP INTEND MCID 92% >40 Punkte

All patients reached the CHOP INTEND MCID of ≥ 4 points and 92% achieved and maintained more than 40 points during the 24-month follow-up period. Early treatment initiation lead to higher improvements regardless of baseline motor function.

92% lernen sitzen (weitere Verbesserung nach 24 Monaten)

After 24 months, 75% of children achieved sitting for at least 30 seconds and 2 more achieved this milestone beyond the 24-month observation period (92%). Two patients (17%) achieved standing without support.

Verschlechterung der Atmungsfunktion aber Stabilisation der Ernährung

The requirement for respiratory support more than doubled from baseline but only one more patient required nutritional support. Swallow function improved in patients allowing 100% of patients able to safely swallow [38].

Risdiplam in SMA 1 patients

3 Patient*innen starben trotz Behandlung

Fourty-one patients received risdiplam. Three patients died during treatment (7%). 90 % of patients achieved the CHOP INTEND MCID threshold of ≥ 4 points at the 12- and 24-month assessments and the percentage of patients achieving more than 40 points was 76% and 56%, respectively. 17% of patients able to sit for at least 30 seconds after 12 months, and 44% after 24 months of treatment. However, no patients learned to stand or walk independently. When assessed against natural history data, all improvements were statistically significant.

90% erreichen CHOP INTEND MCID 56% > 40 Punkte 44% lernen sitzen

Atemfunktion extreme Verschlechterung, Ernährung stabil

The need for respiratory support increased substantially from 29% of patients at baseline to 80% of patients after 24 months of treatment and one more patient required nutritional support compared to the baseline.

Risdiplam in later-onset SMA 2 and 3 patients

180 patients were enrolled in this RCT. No patients died.

RCT mit 180 Ptn keine Todesfälle

Despite only moderate overall improvements, higher mean score differences across motor scores were observed for the risdiplam group compared to the placebo group after 12 months. After 24 months, the initial risdiplam group reached significantly higher mean MFM 32 scores than the external comparator group. After 24 months, a higher percentage of risdiplam patients achieved the MCID(≥ 3 points) compared to the untreated external comparator group after 24 months (p= 0.0253).

moderate Verbesserungen der Motorfunktionen aber signifikanter Unterschied zu Placebo nach 12 M und zur unbehandelten Vergleichsgruppe nach 24 M

Stabilisation in the MFM was achieved in 80% of risdiplam patients compared to 32% in the placebo group after 12 months and was similar between risdiplam and crossover group by 24 months. Compared to the untreated external comparator group, the difference in stabilisation was statistically significant after 24 months.

MCID und Stabilisation häufiger erreicht

No respiratory or nutritional outcomes were recorded at follow-up.

keine Information zu Atmungs- und Ernährungsfunktion

No significant changes in QoL measured with SMAIS-ULM and GAS between risdiplam and placebo groups.

keine Verbesserung der Lebensqualität

Combination therapies

None of the studies had the effect of the combination on outcomes other than safety as their main objective.

3 Studien mit Kombination: Effekt der Kombination nicht primäres Studienziel

Onasemnogene abeparvovec and nusinersen

Seven patients received nusinersen concomitantly. 80% achieved stabilisation and 2 patients (on monotherapy) achieved walking.

Risdiplam and nusinersen

Two patients had previously received nusinersen RULM MCID was achieved by 33% of patients but no change in the need for respiratory or nutritional support could be observed. QoL improved with -ALFRS-R and EK2 MCID were achieved by 50% and 83%, respectively.

Risdiplam and RG7800, olexosime, nusinersen or onasemnogene abeparvovec

This study assessed the safety, tolerability and pharmacokinetics of risdiplam in 174 non-treatment-naïve SMA 1 to 3 patients and did not report other outcomes. Outcomes on safety were favourable.

Adverse events

Adverse events were common in all studies that reported on this outcome but were rarely classified as treatment- related. Associated with the intrathecal administration, post-lumbar puncture syndrome was frequently reported across nusinersen studies, and overall, disease related respiratory complications were common.

Interpretation

Substantial heterogeneity and inconsistencies across the studies make interpretation difficult.

The majority of studies report losses to follow-up and details on discontinuation but questions regarding lost patient's individual demographic, baseline and disease progression remain. These factors as well as the lack of blinding could introduce bias in the results, possibly in favour of the intervention. Patients who don't do well are more likely to withdraw and if patient outcomes whose disease progression was not favourable are not recorded this will affect results. Unblinded studies tend to suffer from performance bias, when patients and researchers are aware of the intervention, their trust in the effect might consciously or subconsciously influence the perception and detection of a positive outcome [70].

korrekte SMA 1 Diagnose fraglich in 4/6 nusinersen Studien, weil viele Ptn > 4 Jahre

In four of the six studies [30, 37, 41, 50] on nusinersen in SMA 1, patients over the age of 4 were included which prompts questions about an accurate diagnosis of the subtype, as life expectancy in this most severe form of SMA is traditionally considered to be significantly shorter, with the majority of children affected dying by age 2 [68, 71].

Einfluss der SMN2 Kopien Anzahl noch unklar

In all studies on nusinersen different percentages of respective SMN2 copy numbers were recorded across different cohorts but only three studies investigated the influence on outcomes, with one [39] reporting no influence and two others [54, 55] reporting statistically significant influence on motor score improvement.

wenige Studien beobachten Patient*innen >36 Monate

Follow-up times were variable with only a few studies observing patients beyond 36 months. Loss to follow-up was acceptable as we excluded any publication with more than 50% of patients lost.

Whilst most studies used validated tools for endpoint measurement, there was variability and inconsistency in reporting the same endpoints limiting comparability between studies.

eindeutige Verbesserung der Motorfunktion in SMA 1 Patient*innen mit allen Therapien - viele lernen Sitzen

Despite the heterogeneity, evidence is apparent for improvement of motor outcomes beyond the MCID in a large percentage of SMA 1 patients treated with any of the therapeutic agents with many achieving sitting- a milestone historically not observed during the natural disease progress. Walking remained inaccessible for SMA 1 patients. The variations in positive outcomes between the different SMA 1 study cohorts could be due to baseline heterogeneity, selection bias or natural variations in disease progress, rather than the superiority of one therapeutic over another but these would be important research questions to address, especially given their price differences and the still largely unknown entity of what influences disease phenotypes beyond SMN2 copy number.

In later-onset SMA patients, more patients received nusinersen and across all studies, between approximately ¼ to ¾ of patients achieved improvement of motor outcomes beyond the MCID, and at least stabilisation and maintenance of motor milestones. One study reports SMA 2 patients learning to walk when treated early [54]. In the study on patients receiving risdiplam [9, 51], improvement beyond MCID threshold was also observed more frequently in treated patients and 80% of patients achieved stabilisation. It is of note that more patients receiving risdiplam had SMN 2 copies, whilst across the majority of nusinersen studies, a higher percentage of patients had SMN 3 copies. Knowing the influence of SMN copy number on disease severity, this heterogeneity between patients receiving different therapeutics could have influenced the outcome, but the comparing the efficacy of treatments is beyond the scope of this review. Whilst stabilisation might be interpreted as less valuable than some of the results in younger-onset patients, maintaining motor function in a patient with milder disease phenotype, and no need for ventilation or nutritional support, will have a significant positive impact on the overall QoL over their disease trajectory.

auch in SMA 2-4 Ptn, ¼ - ¾ erreichen Verbesserung (MCID) in Motorfunktion, oder zumindest Stabilisierung

weiterhin Unklarheit zu Erhaltung oder Regression der Motorfunktion

Uncertainty regarding the continuity of progress or regression of gained motor function over time remains since very few studies have observed patients long enough to this date.

Evidence suggests that early treatment results in better outcomes in both SMA1 and later-onset SMA types. Stratified analyses report that 100% of SMA 1 infants treated with nusinersen before 210 days of age achieved sitting, compared to only 17.5% of those that were treated after their second birthday and 15% of SMA 2 children that were able to sit and treated with nusinersen under 5 years of age learned to walk, compared to none in the group of children who were able to sit, but were older than 5 years at treatment initiation. Screening programs are in place in a number of countries to identify affected children early [72]. A study on survival in patients diagnosed with SMA younger than 2 years of age comparing different time points before, during and after the introduction of the screening program, did not find conclusive evidence that survival differed between these periods, but overall, treatment with nusinersen was associated with increased survival [73].

ausreichende Evidenz, dass früher Therapiebeginn zu besseren Erfolgen führt, in SMA1 und later–onset Formen

Whilst other outcomes were frequently not assessed and reported on with the same rigour as motor outcomes, findings point to a lack of effect on respiratory and nutritional status with the majority of studies reporting an increase in the need for respiratory and nutritional support despite treatment, particularly in the more severe forms of SMA, with worsening or no change in the milder forms of SMA. This is significant as respiratory impairment is considered the most frequent non-neurological complication and the leading cause of mortality in SMA [67]. A recent review on changes in ventilatory support requirements of SMA patients after receiving nusinersen or onasemnogene abeparvovec treatment is in line with our findings, reporting that regardless of non-invasive or invasive ventilation support, very little change was observed post-treatment [74]. In a discrete choice experiment survey of 100 SMA type 1 to 4 patients, a change in pulmonary function was the highest valued treatment attribute again highlighting the importance of this outcome which so far has failed to respond as well to treatment as motor function.

ABER:
keine Verbesserung von Atem- und Ernährungsfunktion, wenige Studien untersuchen diese Endpunkte im Detail

Therapien verändern den Krankheits-phenotyp und bringen neue klinische Herausforderungen mit sich

The new therapies are changing the disease phenotype, but patients continue to require proactive multidisciplinary management of comorbidities [72] and long-term disease progress is uncertain. In any case there is no compelling

„Disease-modifying“ Therapien, aber nicht kurativ

evidence to support the notion of "curative" therapy, but rather "disease-modifying" treatment.

Research into the changing healthcare needs of patients with the new disease phenotypes is needed in order to address the complex medical needs post-treatment. A very recent study [75] on SMA 1 children who had received a variety of therapeutic agents reports that "treated SMA 1" behaves as a completely separate entity to untreated SMA 1 or milder forms of SMA previously encountered with children exhibiting significant alterations on respiratory, nutritional and in particular, orthopaedic needs.

Langzeitprognosen sehr unsicher

The fact that currently the treatments appear at most to change the disease trajectory (particularly in SMA type 1 patients) from certain death to severe chronic illness with unknown long-term prognosis, opens up a difficult ethical debate around the rescue narrative particularly dominant in paediatric medicine and the high costs related to these treatments add a layer of complexity for decision-makers in countries with government-funded health care coverage [76].

kaum Evidenz zu Krankheitskosten von SMA und wenige methodisch wertvolle ökonomische Analysen

A recent systematic review on the cost of illness in SMA [19] identified a lack of evidence on the cost of illness in SMA patients particularly in the context of new and highly-priced therapies and an expert review on recommendations for economic evaluations of cell and gene therapies [77] found a lack of consensus on the correct methodology for economic evaluations of such novel treatments and a tendency for any available recommendations not to be followed. The authors discuss the need for consideration of novel payment mechanisms and suggest the inclusion of HRQoL outcomes of patients and caregivers– an outcome strikingly absent from most of the studies included in our review.

4.1.1 Limitations

Literatursuche limitiert auf englische und deutsche Texte

Limitations of the systematic review:

We limited our search to publications in English or German which might have led to the non-inclusion of some relevant findings of real-life evidence.

oft Zeitverzögerung von Studienende bis zur Publikation: regelmäßige Updates notwendig

There is often a substantial time lag between study completion and time of publication thus the body of evidence presented in our review only represents the findings published in the narrow time frame specified. Regular updates are necessary to inform policy accurately as more time passes since the first approval of the therapies. In particular for risdiplam, given its later approval, more data is required for more conclusive evidence generation.

Limitation of the evidence published:

unverblindete Beobachtungsstudien, vom Hersteller finanziert, Autoren mit Interessenskonflikten Outcomes nicht einheitlich berichtet

As discussed earlier, the majority of all studies were observational, single-arm, unblinded studies, often including only a moderate number of patients, and manufacturer funding and conflict of interest of authors compromise validity. Substantial study heterogeneity restricts the performance of a meta-analysis. Frequently, important outcomes for long-term prognoses, such as the effect on respiratory function or HRQoL, were not reported in sufficient detail and motor function was reported with different tools in different studies and not consistently recorded at baseline and follow-up, prompting questions of cherry-picking data to present positive outcomes.

5 Conclusion

The available evidence stems predominantly from heterogeneous, industry-funded studies at moderate risk of bias and the majority of authors declared a conflict of interest.

There is evidence for the effectiveness of all three approved treatments in all SMA types for motor function and better results were generally observed with earlier treatment initiation and higher baseline function. It must be noted that the body of available evidence is much greater for treatment with nusinersen than with risdiplam and onasemnogene abeparvovec, for which we only identified two and one long-term study, respectively.

There is no evidence of any improvement in respiratory and nutritional needs for any SMA type treated with any of the therapies.

For infantile onset SMA 1 patients, findings still point to the suggestion that the treatment of pre-symptomatic or early symptomatic children with at least 2 SMN 2 copies and not requiring respiratory support will lead to the best outcomes, but evidence on the influence of SMN2 copy number was not conclusive across the few studies that investigated this. Thus, newborn screening is of great importance.

Mean motor function improvements might be smaller in later-onset SMA patients, but these patients generally have a much higher baseline function and smaller improvements or even stabilisation in an already milder disease phenotype is clinically relevant.

Many questions remain, in particular on the permanence or possible regression of achieved motor functions over the course of a patient's lifetime, on the impact on general QoL and social functioning of patients and their families beyond the narrow endpoints assessed in clinical trials, on the timeframe for therapy maintenance and clinical indicators for discontinuation and the changing disease phenotypes in treated SMA patients with evolving medical needs.

Our literature search failed to detect studies where the effect of the combination on outcomes other than safety was the primary study endpoint. Comparison between different therapeutic options is beyond the scope of our review but remains an important research question to answer.

Evidenz für Effektivität aller Therapieformen auf motorische Funktion in allen SMA Patient*innen

bessere Ergebnisse bei früherem Therapiebeginn

keine Verbesserung der Atem- / Ernährungfunktion

Neugeborenen-Screening ist wichtig

viele offene Fragen bleiben:

***Erhalt der motorischen Fähigkeiten oder Regression?**

***Lebensqualität kaum untersucht?**
***Einfluss der Anzahl der SMN2 Kopien unschlüssig?**

***Dauer der Therapien?**
Veränderung von Phenotyp neue Bedarfe?

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7 Appendix

7.1 RoB Assessment tables

Table A- 1: Risk of bias assessment of included studies on nusinersen in SMA 1

Study reference/ID	Acsadi et al. 2021 [30]	Finkel et al. 2021 [36]	Lavie et al. 2021 [40]	Lavie et al. 2022 [35]	Modrzejewska et. al. 2021 [32]	Menard et al. 2023 [41]
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes
Study design						
2. Was the study conducted prospectively?	Yes	Yes	Yes	Yes	Yes	No
3. Were the cases collected in more than one centre?	Yes	Yes	No	No	Yes	Yes
4. Were patients recruited consecutively?	Yes	Unclear	Unclear	Unclear	No	Unclear
Study population						
5. Were the characteristics of the patients included in the study described?	Yes	Yes	Yes	Yes	Yes	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes	Yes	Partial	Partial	Yes	Partial
7. Did patients enter the study at a similar point in the disease?	No	Yes	No	No	No	Unclear
Intervention and co-intervention						
8. Was the intervention of interest clearly described?	Yes	Yes	Yes	Yes	Yes	No
9. Were additional interventions (co-interventions) clearly described?	Yes	Yes	Yes	Yes	Yes	No
Outcome measures						
10. Were relevant outcome measures established a priori?	Yes	Yes	Yes	Yes	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	No	No	No	No	No	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes	Yes	Yes	Yes	Yes
13. Were the relevant outcome measures made before and after the intervention?	Yes	Yes	Yes	Yes	Yes	No
Statistical analysis						
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Yes	Yes	Yes	Yes
Results and conclusions						
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes	Yes	Yes	Yes	Yes
16. Were losses to follow-up reported?	Yes	Yes	Yes	Yes	Yes	Yes
17. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Yes	Yes	No	No	Yes	Yes
18. Were the adverse events reported?	Yes	Yes	Yes	Yes	Yes	Partial
19. Were the conclusions of the study supported by results?	Yes	Yes	Yes	Yes	Yes	Yes
Competing interests and sources of support						

Study reference/ID	Acsadi et al. 2021 [30]	Finkel et al. 2021 [36]	Lavie et al. 2021 [40]	Lavie et al. 2022 [35]	Modrzejewska et. al. 2021 [32]	Menard et al. 2023 [41]
20. Were both competing interests and sources of support for the study reported?	Yes	Yes	Yes	Yes	Partial	Yes
Overall Risk of bias	Moderate risk	Low risk	Moderate risk	Moderate risk	Moderate risk	Moderate risk

Table A- 2: Risk of bias assessment of studies on nusinersen in SMA 1 continued

Study reference/ID	Pane et al. 2021 [39]	Pane et al. 2023 [34]	Weststrate et al. 2021 [37]
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes
Study design			
2. Was the study conducted prospectively?	Unclear	Unclear	No
3. Were the cases collected in more than one centre?	Yes	Yes	No
4. Were patients recruited consecutively?	Unclear	Unclear	Unclear
Study population			
5. Were the characteristics of the patients included in the study described?	Yes	Yes	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	No	No	Yes
7. Did patients enter the study at a similar point in the disease?	No	No	No
Intervention and co-intervention			
8. Was the intervention of interest clearly described?	No	No	No
9. Were additional interventions (co-interventions) clearly described?	No	No	No
Outcome measures			
10. Were relevant outcome measures established a priori?	Yes	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	No	No	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes	Yes
13. Were the relevant outcome measures made before and after the intervention?	Yes	Yes	Yes
Statistical analysis			
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Yes
Results and conclusions			
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes	Yes
16. Were losses to follow-up reported?	Yes	Yes	Yes
17. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Yes	Yes	No
18. Were the adverse events reported?	No	Yes	No
19. Were the conclusions of the study supported by results?	Yes	Yes	Yes
Competing interests and sources of support			

Study reference/ID	Pane et al. 2021 [39]	Pane et al. 2023 [34]	Weststrate et al. 2021 [37]
20. Were both competing interests and sources of support for the study reported?	Yes	Yes	Partial
Overall Risk of bias	Moderate risk	Moderate risk	High Risk

** Pane et al 21 and 23 describe the same cohort. Pane 23 does include description of AE.*

Table A- 3: Risk of Bias assessment of included studies on Nusinersen in SMA 1+2

Study reference/ID	**Iwayama et al. 2023 [50]**
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes
Study design	
2. Was the study conducted prospectively?	No
3. Were the cases collected in more than one centre?	No
4. Were patients recruited consecutively?	Yes
Study Population	
5. Were the characteristics of the patients included in the study described?	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Partial
7. Did patients enter the study at a similar point in the disease?	No
Intervention and co-intervention	
8. Was the intervention of interest clearly described?	Yes
9. Were additional interventions (co-interventions) clearly described?	Yes
Outcome measures	
10. Were relevant outcome measures established a priori?	Yes
11. Were outcome assessors blinded to the intervention that patients received?	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes
13. Were the relevant outcome measures made before and after the intervention?	Yes
Statistical analysis	
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes
Results and conclusions	
15. Was follow-up long enough for important events and outcomes to occur?	Yes
16. Were losses to follow-up reported?	Yes
17. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Yes
18. Were the adverse events reported?	No
19. Were the conclusions of the study supported by results?	Yes
Competing interests and sources of support	
20. Were both competing interests and sources of support for the study reported?	Yes
Overall Risk of bias	High risk

Table A- 4: Risk of bias assessment of included studies on nusinersen in SMA 2+3

Study reference/ID	Fainmesser et al 2022 [52]	Darras et al. 2019 [44]	Montes et al. 2019 [45]	Pane et al. 2022 [53]	Pechmann et al. 2022 [54]	Pechman et al. 2023 (SMA3 walkers) [55]
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes
Study design						
2. Was the study conducted prospectively?	Yes	Yes	No	Unclear	Unclear	Unclear
3. Were the cases collected in more than one centre?	No	Yes	Yes	Yes	Yes	Yes
4. Were patients recruited consecutively?	Unclear	Unclear	Unclear	Yes	No	No
Study population						
5. Were the characteristics of the patients included in the study described?	Yes	Yes	Yes	No	Yes	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Partial	Yes	Yes	Partial	Partial	Yes
7. Did patients enter the study at a similar point in the disease?	No	Yes	Yes	No	No	Yes
Intervention and Co-Intervention						
8. Was the intervention of interest clearly described?	Yes	Yes	Yes	Yes	No	No
9. Were additional interventions (co-interventions) clearly described?	Yes	Yes	Yes	Yes	No	No
Outcome measures						
10. Were relevant outcome measures established a priori?	Yes	Yes	Yes	Yes	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	No	No	No	No	No	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes	Yes	Yes	Yes	Yes
13. Were the relevant outcome measures made before and after the intervention?	Yes	Yes	Yes	Yes	Yes	Yes
Statistical Analysis						
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Unclear	Yes	Yes	Yes
Results and Conclusions						
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes	Yes	Yes	Yes	Yes
16. Were losses to follow-up reported?	Unclear	Yes	No	No	Yes	Yes
17. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Yes	Yes	Partial	Yes	Yes	Yes
18. Were the adverse events reported?	Yes	Yes	No	No	Yes	Yes
19. Were the conclusions of the study supported by results?	Yes	Yes	Yes	Yes	Yes	Yes
Competing interests and sources of support						
20. Were both competing interests and sources of support for the study reported?	Yes	Yes	Partial	Yes	Yes	Yes
Overall Risk of bias	Moderate risk	Low risk	High Risk	Moderate risk	Moderate risk	Moderate risk

Table A- 5: Risk of bias assessment of included studies on nusinersen in SMA 1-3 and 1-4

Study reference/ID	Tscherter et al. 2022 [56]	Bjelica et al. 2023 [49]
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes
Study design		
2. Was the study conducted prospectively?	No	Yes
3. Were the cases collected in more than one centre?	Yes	No
4. Were patients recruited consecutively?	Yes	Yes
Study population		
5. Were the characteristics of the patients included in the study described?	Yes	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes	Partial
7. Did patients enter the study at a similar point in the disease?	No	No
Intervention and Co-Intervention		
8. Was the intervention of interest clearly described?	No	Yes
9. Were additional interventions (co-interventions) clearly described?	No	Yes
Outcome measures		
10. Were relevant outcome measures established a priori?	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	No	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes
Statistical Analysis		
13. Were the relevant outcome measures made before and after the intervention?	Yes	Yes
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes
Results and Conclusions		
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes
16. Were losses to follow-up reported?	Yes	Yes
17. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Yes	Yes
18. Were the adverse events reported?	Yes	No
19. Were the conclusions of the study supported by results?	Yes	Yes
Competing interests and sources of support		
20. Were both competing interests and sources of support for the study reported?	Yes	Yes
Overall Risk of bias	Moderate risk	Moderate risk

Table A- 6: Risk of bias assessment for included studies on onasemnogene abeparvovec in SMA 1

Study reference/ID	McGrattan et al. 2023 [38]	Al-Zaidy et. al.a 2020 [42]	Al Zaidy et al b. 2020 [46]	Lowes et al. 2020 [47]
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Yes	Yes
Study design				
2. Was the study conducted prospectively?	No	Yes	Yes	Yes
3. Were the cases collected in more than one centre?	Yes	No	No	No
4. Were patients recruited consecutively?	Unclear	Unclear	Unclear	Unclear
Study population				
5. Were the characteristics of the patients included in the study described?	Partial	Partial	Yes	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Partial	Yes	Yes	Yes
7. Did patients enter the study at a similar point in the disease?	Unclear	No	No	No
Intervention and Co-Intervention				
8. Was the intervention of interest clearly described?	Yes	Yes	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	Yes	Yes	Yes	Yes
Outcome measures				
10. Were relevant outcome measures established a priori?	Yes	Yes	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	No	No	No	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes	Yes	Yes
13. Were the relevant outcome measures made before and after the intervention?	Yes	Yes	Yes	Yes
Statistical Analysis				
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Unclear	Yes	Yes?	No?/unclear
Results and Conclusions				
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes	Yes	Yes
16. Were losses to follow-up reported?	Yes	Yes	Yes	Yes
17. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	No	No	No	No
18. Were the adverse events reported?	Yes	Partial	Yes	No
19. Were the conclusions of the study supported by results?	Yes	Yes	Yes	Yes
Competing interests and sources of support				
20. Were both competing interests and sources of support for the study reported?	Yes	Partial	Yes	Yes
Overall Risk of bias	Moderate risk	Moderate risk	Moderate risk	Moderate risk

Table A- 7: Risk of bias assessment for included studies on risdiplam in SMA 1

Study reference/ID	**Darras et al. 2021 [48]**	**Masson et al. 2021 [14]**
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes
Study design		
2. Was the study conducted prospectively?	Yes	Yes
3. Were the cases collected in more than one centre?	Yes	Yes
4. Were patients recruited consecutively?	Unclear	Unclear
Study population		
5. Were the characteristics of the patients included in the study described?	Yes	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes	Yes
7. Did patients enter the study at a similar point in the disease?	No	No
Intervention and co-intervention		
8. Was the intervention of interest clearly described?	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	Yes	Yes
Outcome measures		
10. Were relevant outcome measures established a priori?	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	No-	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes
13. Were the relevant outcome measures made before and after the intervention?	Yes	Yes
Statistical analysis		
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes
Results and conclusions		
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes
16. Were losses to follow-up reported?	Yes	Yes
17. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Yes	Yes
18. Were the adverse events reported?	Yes	Yes
19. Were the conclusions of the study supported by results?	Yes	Yes
Competing interests and sources of support		
20. Were both competing interests and sources of support for the study reported?	Yes	Yes
Overall Risk of bias	Moderate risk	Moderate risk

Table A- 8: Risk of bias assessment on included studies on risdiplam in SMA 2 and 2+3

Study reference/ID	Mercuri et al. 2022 [15]	Oskoui et al. 2022 [51]
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes
Study design		
2. Was the study conducted prospectively?	Yes	Yes
3. Were the cases collected in more than one centre?	Yes	Yes
4. Were patients recruited consecutively?	Unclear	Unclear
Study population		
5. Were the characteristics of the patients included in the study described?	Yes	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes	Yes
7. Did patients enterthe study at a similar point in the disease?	No	No
Intervention and co-intervention		
8. Was the intervention of interest clearly described?	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	Yes	Yes
Outcome measures		
10. Were relevant outcome measures established a priori?	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	Yes	Yes
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes
13. Were the relevant outcome measures made before and after the intervention?	Yes	Yes
Statistical analysis		
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes
Results and conclusions		
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes
16. Were losses to follow-up reported?	Yes	Yes
17. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	Yes	Yes
18. Were the adverse events reported?	Yes	Yes
19. Were the conclusions of the study supported by results?	Yes	Yes
Competing interests and sources of support		
20. Were both competing interests and sources of support for the study reported?	Yes	Yes
Overall Risk of bias	Low risk	Low risk

Table A- 9: Risk of bias assessment of included studies on combination therapies

Study reference/ID	Chiriboga et al. 2022 [33]	Mendell et al. 2021 [43]	Nungo Garzon et al 2023 [31]
1. Was the hypothesis/aim/objective of the study clearly stated?	Yes	Yes	Partial
Study design			
2. Was the study conducted prospectively?	Yes	Yes	Unclear
3. Were the cases collected in more than one centre?	Yes	No	No
4. Were patients recruited consecutively?	Unclear	Unclear	Yes
Study population			
5. Were the characteristics of the patients included in the study described?	Yes	Yes	Yes
6. Were the eligibility criteria (i.e. inclusion and exclusion criteria) for entry into the study clearly stated?	Yes	Yes	Yes
7. Did patients enter the study at a similar point in the disease?	No	Unclear	No
Intervention and co-intervention			
8. Was the intervention of interest clearly described?	Yes	Yes	Yes
9. Were additional interventions (co-interventions) clearly described?	Yes	Yes	Yes
Outcome measures			
10. Were relevant outcome measures established a priori?	Yes	Yes	Yes
11. Were outcome assessors blinded to the intervention that patients received?	No	No	No
12. Were the relevant outcomes measured using appropriate objective/subjective methods?	Yes	Yes	Yes
13. Were the relevant outcome measures made before and after the intervention?	Yes	Yes	Yes
Statistical analysis			
14. Were the statistical tests used to assess the relevant outcomes appropriate?	Yes	Yes	Yes
Results and conclusions			
15. Was follow-up long enough for important events and outcomes to occur?	Yes	Yes	Yes
16. Were losses to follow-up reported?	Yes	Yes	Yes
17. Did the study provide estimates of random variability in the data analysis of relevant outcomes?	No	No	Yes
18. Were the adverse events reported?	Yes	Yes	Yes
19. Were the conclusions of the study supported by results?	Yes	Yes	Yes
Competing interests and sources of support			
20. Were both competing interests and sources of support for the study reported?	Yes	Yes	Yes
Overall Risk of bias	Moderate risk	Moderate risk	Moderate risk

Revised Cochrane risk-of-bias tool for randomized trials (RoB 2)

Edited by Julian PT Higgins, Jelena Savović, Matthew J Page, Jonathan AC Sterne
on behalf of the RoB2 Development Group

Version of 22 August 2019

The development of the RoB 2 tool was supported by the MRC Network of Hubs for Trials Methodology Research (MR/L004933/2- N61), with the support of the host MRC ConDuCT-II Hub (Collaboration and innovation for Difficult and Complex randomised controlled Trials In Invasive procedures - MR/K025643/1), by MRC research grant MR/M025209/1, and by a grant from The Cochrane Collaboration.

Study details

Reference	Mercuri et al. Safety and efficacy of once-daily risdiplam in type 2 and non-ambulant type 3 spinal muscular atrophy (SUNFISH p a phase 3, double-blind, randomised, placebo-controlled trial. The Lancet Neurol 2022; 21: 42-52.

Study design

- [X] Individually-randomized parallel-group trial
- [ ] Cluster-randomized parallel-group trial
- [ ] Individually randomized cross-over (or other matched) trial

For the purposes of this assessment, the interventions being compared are defined as

Experimental: risdiplam Comparator: placebo

Specify which outcome is being assessed for risk of bias	clinical efficacy and safety

	Primary endpoint: Change from baseline in MFM32 total score at 12 m FU Key Secondary endpoints - % of patients with >3pts change from baseline MFM32 total - Change from baseline RULM total score - Change from baseline HFMSE total score - Change from baseline in best percentage-predicted value in FEV1 - Change from baseline in SMAIS reported by caregivers % of patients graded as improved on CGIC scale
Specify the numerical result being assessed. In case of multiple alternative analyses being presented, specify the numeric result (e.g. RR = 1.52 (95% CI 0.83 to 2.77) and/or a reference (e.g. to a table, figure or paragraph) that uniquely defines the result being assessed.	Table 2, Table 3

Is the review team's aim for this result…?

x to assess the effect of *assignment to intervention* (the 'intention-to-treat' effect)

☐ to assess the effect of *adhering to intervention* (the 'per-protocol' effect)

If the aim is to assess the effect of *adhering to intervention*, select the deviations from intended intervention that should be addressed (at least one must be checked):

☐ occurrence of non-protocol interventions

☐ failures in implementing the intervention that could have affected the outcome

☐ non-adherence to their assigned intervention by trial participants

Which of the following sources were <u>obtained</u> to help inform the risk-of-bias assessment? (tick as many as apply)

x Journal article(s) with results of the trial

x Trial protocol

x Statistical analysis plan (SAP)

x Non-commercial trial registry record (e.g. ClinicalTrials.gov record)

☐ Company-owned trial registry record (e.g. GSK Clinical Study Register record)

☐	"Grey literature" (e.g. unpublished thesis)
☐	Conference abstract(s) about the trial
☐	Regulatory document (e.g. Clinical Study Report, Drug Approval Package)
☐	Research ethics application
☐	Grant database summary (e.g. NIH RePORTER or Research Councils UK Gateway to Research)
☐	Personal communication with trialist
☐	Personal communication with the sponsor

Responses underlined in green are potential markers for low risk of bias, and responses in red are potential markers for a risk of bias. Where questions relate only to sign posts to other questions, no formatting is used.

Domain 1: Risk of bias arising from the randomization process

Signalling questions	Comments	Response options
1.1 Was the allocation sequence random?	"Participants were randomly assigned to receive either risdiplam or placebo (":1) and stratified by age with permuted block randomisation by use of a computerised interactive response system, outsourced to an external party. The randomisation list was maintained and concealed by the external party."	Y
1.2 Was the allocation sequence concealed until participants were enrolled and assigned to interventions?		Y
1.3 Did baseline differences between intervention groups suggest a problem with the randomization process?	Table 1- baseline characteristics	N
Risk-of-bias judgement		Low

Optional: What is the predicted direction of bias arising from the randomization process?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 2: Risk of bias due to deviations from the intended interventions (effect of assignment to intervention)

Signalling questions	Comments	Response options
2.1. Were participants aware of their assigned intervention during the trial?	"Employees of the sponsor who were involved in study management and data analysis were masked to treatment assignment until the primary analysis. Patients, investigators, and all individuals in direct contact with patients at each site (except for unblinded pharmacists handling study medication) were masked to treatment assignment until the final patient completed 24-month assessments."	N
2.2. Were carers and people delivering the interventions aware of participants' assigned intervention during the trial?		N
2.3. If Y/PY/NI to 2.1 or 2.2: Were there deviations from the intended intervention that arose because of the trial context?		NA
2.4 If Y/PY to 2.3: Were these deviations likely to have affected the outcome?		NA
2.5. If Y/PY/NI to 2.4: Were these deviations from intended intervention balanced between groups?		NA
2.6 Was an appropriate analysis used to estimate the effect of assignment to intervention?	"for efficacy analyses, all individuals who were randomly assigned to a group were included; for each endpoint, individuals who fulfilled the corresponding missing item rules were excluded, as predefined in the statistical analysis plan"	Y
2.7 If N/PN/NI to 2.6: Was there potential for a substantial impact (on the result) of the failure to analyse participants in the group to which they were randomized?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to deviations from intended interventions?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 3: Missing outcome data

Signalling questions	Comments	Response options
3.1 Were data for this outcome available for all, or nearly all, participants randomized?	Data available for over 95% of patients for all outcomes except for the "mean change from baseline in the best percentage-predicted forced vital capacity" (which it is available for 70% of patients)	PY
3.2 If N/PN/NI to 3.1: Is there evidence that the result was not biased by missing outcome data?		NA
3.3 If N/PN to 3.2: Could missingness in the outcome depend on its true value?		NA
3.4 If Y/PY/NI to 3.3: Is it likely that missingness in the outcome depended on its true value?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to missing outcome data?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 4: Risk of bias in measurement of the outcome

Signalling questions	Comments	Response options
4.1 Was the method of measuring the outcome inappropriate?		N
4.2 Could measurement or ascertainment of the outcome have differed between intervention groups?		N
4.3 If N/PN/NI to 4.1 and 4.2: Were outcome assessors aware of the intervention received by study participants?	"Employees of the sponsor who were involved in study management and data analysis were masked to treatment assignment until the primary analysis."	Y
4.4 If Y/PY/NI to 4.3: Could assessment of the outcome have been influenced by knowledge of intervention received?		PN
4.5 If Y/PY/NI to 4.4: Is it likely that assessment of the outcome was influenced by knowledge of intervention received?		NA
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias in measurement of the outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Domain 5: Risk of bias in selection of the reported result

Signalling questions	Comments	Response options
5.1 Were the data that produced this result analysed in accordance with a pre-specified analysis plan that was finalized before un-blinded outcome data were available for analysis?		PY
Is the numerical result being assessed likely to have been selected, on the basis of the results, from...		
5.2. ... multiple eligible outcome measurements (e.g. scales, definitions, time points) within the outcome domain?		PN
5.3…. multiple eligible analyses of the data?		PN
Risk-of-bias judgement		Low
Optional: What is the predicted direction of bias due to selection of the reported result?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Overall risk of bias

Risk-of-bias judgement		Low
Optional: What is the overall predicted direction of bias for this outcome?		NA / Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Table A- 10: Nusinersen in SMA 1

	Acsadi et al.2021 [30]	Finkel et al.2021 [36]	Lavie et al. 2021 [35, 40]	Menard et al.2022 [41]	Modrzejewska et al. 2021 [41]
Patients n **SMN2 copy n=2/3**	**21** **Nusinersen group:** 14 3/11 **Crossover** group: 7 3/3	**20** **Cohort 1:** 4 (6-12mg Nusinersen) 4/0 **Cohort 2:** 16 (12mg Nusinersen) 13/2+1unkown	**20** 13/1 (unknown 6)	**17** no detailed description of SMAN2 copy numbers	**26** 16/9 (n=1 with 4)
FU m	**24**	Median **36.2** (IQR 20.6-41.3)	**24** for respiratory outcome **36** for non-respiratory outcomes	Median **38** (IQR 22-44)	**18-26** Mean 26±18.04
Loss to FU n	1 patient in control group died during placebo phase	**Cohort 1** 1 patient died 1withdrawal (no explanation) **Cohort 2:** 4 died 1 withdrawal (no explanation) 11 discontinued (to enter SHINE trial)	2 patients died 1 discontinued due to hypoxic episode after aspiration	1 patient died	0
CHOP-INTEND mean±SD (range) or median (IQR)	n.r	**Baseline:** 30±10.5(17-64) (n=20) **at FU:** 48.3 ±12.7 (n=13) +17.3±12.2 **Cohort 1 (**2 SMN2 copies) **Baseline:** 27±5.1(22-34) (n=4) **at FU:** pt 1 score change= 22 (n=2) pt 2 score change=-8**	n.r	**Baseline:** 27 (IQR 19.5-28.5) **(n=8)** **at FU:** 46 (IQR 31-55.5) **(n=8)**	**Baseline:** 19.11± 14.28 **at FU:** 26.5 ± 18.04 +7.38, p<0.001

		Cohort 2 (2 SMN2 copies) **Baseline: v**27±69(17-38) (n=13) **at FU:** total mean score =46** (n=7) **Cohort 2** (3 SMN2 copies) **Baseline:** 53±15.6(42-64) (n=2) **at FU:** n.r			
HINE-2 mean±SD (range)	**Nusinersen group** **Baseline:** 7.6±5.4 21m FU: 13±2 >33m FU: 15±2 **Crossover group** **Baseline:** 6.7±5.0 21m FU: 9±2 >33mFU: n.r **Proportion of milestone responders:** **Nusinersen group:**0.79 **Crossover group:** 0.29	**Total Baseline:** 2 ±2.4 (1-12) **Total at FU:** n.r **Cohort 1**(2 SMN2 copies) **Baseline:** 2 ±0.8 (1-3) (n=4) **at FU:** pt 1 +20 (n=2) pt 2 +2** **Cohort 2** (2 SMN2copies) **Baseline:** 1±0.5(1-2) (n=13) **FU day 1135 :** 11.86±6 (n=7) +10.43± 6.18 **Cohort 2** (3 SMN2 copies) **Baseline:** 8± 5.7(4-12) (=2) **at FU:** pt 1 +20 pt 2 +15**	n.r	n.r	n.r

Motor Milestone criteria response n (%)	**HINE-2 responders:** **Nusinersen group** 13/14 (93) **Cross-over group:** 5/6 (83)	**ENDEAR response criteria met** 11/20 (55) **Cohort 2**(2SMN2 copies): 8/13 (62) **Cohort 2**(3xSMN2copies): n.r **Cohort 1:** n.r. **Meeting Finkel et al. response criteria** Per-protocol efficacy evaluable population: 12/19 (63) Safety population :12/20 (60) Cohort 2 (2xSMN2 copies): 4/8 Cohort 2 (3xSMN copies): n.r Cohort 1: n.r	n.r	n.r	n.r
Respiratory support noninvasive n (%)	**Nusinersen group** **Baseline ventilator use:** 3/14 (21) **at FU mean percentage time on ventilator:** 11.3% **Control+Crossover group** **Baseline ventilator use:** 4/7 (57)	**Cohort 2 (**2 SMN2 copies) **Baseline:** 0/13 (0) **at FU:** 4/13 requiring BIPAP **Baseline time on ventilator:** 0/day **at day 1072 FU:** 10.6h/day	**Total Baseline:** 8/20 (40) **<16h/ day:** 4/20 (20) **>16h /day:** 4/20 (20) **none:** 4/20(20) **Total at FU :**10/17(59) **<16h/ day:** 7/17 (41) **>16h /day:** 3/17 (17.6) **none:** 0/17 (0)	**Baseline:** 2/17(12) **at FU:** 13/17(76) no improvement/ reduction in any respiratory management	**Baseline:** 5/26 (19.2) **>16h/day:** 13/26 (50) **at FU:** 5/26 (19.2) **>16h/day:** 11/26 (42.3)

	at FU **mean *percentage time* on ventilator:** 29.8	**Cohort 2** (3 SMN2 copies) **Baseline**: 0/2(0) **at FU**: 0/2(0) **Cohort 1:** n.r	*{percentages are author's own calculations from Tables 2 in and Table 2 in (41,42)		
Respiratory Support invasive n (%)	**Nusinersen group** **Baseline:** 0 **at FU:** 0 **Crossover group:** **Baseline:** 0 **at FU:** 0	**Total Baseline:** n.r **Total at FU:** n.r **Cohort 2 (2 SMN2 copies):** **Baseline**: n.r (n=13) **at FU:** 4/13 (31) requiring IV 2/13 (15) Tracheostomy **Cohort 2** (3SMN2 copies) **Baseline:** n.r (n=2) **at FU:** 0/2(0) requiring IV 0/2(0) Tracheostomy **Cohort 1:** n.r	**>16h/day** **Baseline:** 8/20 (40) **at FU:** 7/17 (41) {percentages are author's own calculations from Table 2 in (41,42)	**Baseline:** 0/17(0) **at FU** 0/17(0)	**Baseline:** 13/26(50) **at FU:** 16/26 (61.54)
Nutritional support n (%)	n.r	**Cohort 2** (2 SMN2 copies) **Baseline:** 1/13 (8) **at FU:** 13/13 (100) **Cohort 2**(3 SMN2 copies) **Baseline:** 0/2 **at FU:** 1/2 (50)	**Baseline:** 13/20 (65) PG 12/20 (60) NGT 1/20 (5) **at FU:** 16/17(94) PG 15/17 (88) NGT 1/17(5)	**Baseline** n.r **at FU:** **PG**11/17(65) **NG**9/17 (53)	**Baseline:** 15/26 (57.7) **at FU:** 13 (50)

		Cohort 1: n.r	{percentages are author's own calculations from Tables 1, 2 and Table 2 in (41,42)		
CGI-C score *** **(%)**	**<u>Investigator Evaluation</u>** **Control group:** No worsening:71% Any improvement:14% Much improvement: 0 **Crossover group:** No worsening:100% Any improvement:100% Much improvement:17% **Nusinersen group:** No worsening:100% Any improvement: 100% Much improvement: 43% **<u>Cargiver evaluation</u>** **Control group:** No worsening: 71% Any improvement:43% Much improvement: 14% **Crossover group:** No worsening:100% Any improvement:100% Much improvement:83% **Nusinersen group:** No worsening:100% Any improvement: 100% Much improvement: 64%	n.r	n.r	n.r	n.r
Facial Hypo-plasia and Scoli-osis n (%)	n.r	n.r	**Facial hypoplasia** **Baseline:** 4/20 (20) **at FU:** 15/17 (88) **Scoliosis** **Baseline:** 5/20 (25) **at FU:** 13/17 (76)	n.r	n.r

AEs/SAEs n (%)	**Nusinersen group:** 14/14 (100) **Cross-over group :** 6/6 (100) **Control group** 6/7 (86) No disconinuation or withdrawal due to study treatment **SAE** **Nusinersen** group 9/14 (64) **Crossover group** 4/6 (67) **Control (Sham period)** 3/7 (43)	**Any AE:** 20/20 (100%) **Cohort 2:** 16/16 (100) **Cohort 1:** n.r **Any SAE:** 16/20 (80) **Cohort 2:** 13/16 (86) **Cohort 1:** nr.	**0 treatment related side effects reported.** 3patients died: 2 acute respiratory failure 1 hypoxic brain injury 4 patients had chronic atelectasis	**significant decrease** in the total number of **hospitalisations** between the first and second year of treatment. **p= 0.04**	**Post-lumbar puncture syndrome** 4/26 (15.4) **Respiratory tract infection:** 4/26 (15.4) **Increased liver enzymes** 2/26 (7.7) **CSF leakage** 2/26 (7.7)

**Since exact numbers are not reported in Acsadi et.al. 2021, the numbers are based on estimations from Figure 2, C in* (39)

***Since exact numbers are not reported in Finkel et al.2021, the numbers are based on estimations from Figure 2, B and S2, B and D in* (40)

**** Change of ≤2 on the CGI-I scale defined as much improvement, ≤3 as any improvement, ≤4 as no worsening.*

Abbreviations: (S)AE=(Severe) Adverse Events, CGI-C Score=Clinical global impression of Change, CHOP-INTEND= Children's Hospital of Philadelphia Infant test of Neuromuscular Disorders, FU=Follow up, HINE-2=Hammersmith Infant Neurological Examination Section 2.

	Pane et al. 2021 * [39]	Pane et al.2023* [34]	Westrate et al.2022 [37]
Patients n **SMN2 copy n=2/3** **SMA1 subtype n**	**68** 48/17 2 pts with 1 copy, 1 pt with 4 copies Dubovitz score 1.1: 7 1.5: 36 1.9: 25	**48** 33/14 1 pt with 1 copy Dubovitz score 1.1: 5 1.5: 19 1.9: 24	**24** 17/6 1 pt unkown SMA1a: 3 patients 2/1 SMA1b: 9 patients 9/0 SMA1c: 12 patients 6/5
FU m	**24**	**48**	**24**
Loss to FU **n**	0 loss to follow up until 24m	5 changed treatment, 7 discontinued (3/7 lack of benefit and 4/7 side effects) 7 transferred 1 died	0
CHOP-INTEND **mean±SD or median**	**Baseline:** 18.09±14.22 **at 24m FU:** 26.75±19.45 **0-24m:** +8.66±9.35 p<0.001 across the whole cohort Age at treatment start <210 days: p=0.001 <2 years: p=0.001 2-54years: p=0.012 5 -11years: p=0.001 12-19 years: n.r Age was a predictive value for change whilst SMN2 copy number was not.	**Baseline:** 21±15 **at 48m FU:** n.r **0-48m:** +10.6±12.1, p<0.001 across the whole cohort Dubovitz 1.1: p=0.144 Dubovitz 1.5: p<0.001 Dubovitz 1.9: p<0.001 Age at treatment start: <210 days: p=0.017 <2 years: p=0.001 2-4years: p=0.010 5 -11years: p=0.655 12-19years: n.r SMN2 copy did not influence the magnitude of changes	**Baseline:** median =32 **at 24m FU:** median=42 **SMA 1a:** 2/3 improved **SMA 1b:** 6/9 improved **SMA 1c:** 8/12 improved
HINE-2 **median±SD**	**Baseline:** 0.88±1.33 **at 24m:** 3.5±4.96	**Baseline:** 1.3±2 **at 48m FU:** n.r	n.r

	0-24m: +2.62±4.39, p<0.001 Age at treatment start <210 days: p<0.001 <2 years: p=0.001 2-54years: p=0.039 5-11years: p=0.042 12-19 years: n.r Age was a predictive value for change whilst SMN2 copy number was not.	**0-48m:** +4.3±5.7 p<0.001 Dubovitz 1.1: p=0.655 Dubovitz 1.5: p<0.008 Dubovitz 1.9: p<0.001 Age at treatment start: <210 days: p=0.018 <2 years: p=0.001 2-4years: p=0.066 5-11 years: p=0.153 12-19years: n.r SMN2 copy did not influence the magnitude of changes.	
Motor Milestone criteria response **n (%)**	21/68 (31) **achieved sitting** 16/21 during first year of treatment 6/21 during second year Age at treatment start <210 days :7/7 (100) >210d<2y:11/23 (55) >2y<4y: 3/14(17.64)	**improvement on at least one item of HINE scale** 28/ 48 (58) **at least one milestone fully achieved** 23/28 (48) **at least one deterioration** 2/28 (7) **no change** 20/48 (41.6) most frequently achieved milestones were head control, stable sit and antigravity movements of lower limbs	n.r
Respiratory support Non invasive **n (%)**	**Baseline:** 7/68 (10.3) **FU 24m:** 8/68(11.7) all 7pts used NIV >16h/day	**Baseline:** 21/48(43.6) 1/48 (2.5) >16h 2/48 (4.2) >10h 18/48 (37.5) <10h **at 48m FU :** 28/48(56.2) 2/48(4.2) >16h 3/48 (6.3) >10h 23/48 (48%) <10h	**Baseline:** 13/24 (54) 7 nocturnal (29) 6 >16h/d (25) **at 24m FU:** 21/24 (88) 14 nocturnal (58) 5 >16h (21) **SMA 1a:** 3 /9(100) **SMA 1b:** 8 (89) **SMA 1c:** 10 (83)

Respiratory Support invasive n (%)	**Baseline:** 20/68(29.4) **at 24m FU:** 23/68(33.8) all pts had tracheostomies	**Baseline:** 13/48(27.1) **at 48m FU:** 13/48(27.1)	0 patients required IV
Nutritional support n (%)	**Baseline :** 36/68(52.9%) **at 24m FU:** 44/68(64.7%)	**Baseline:** 23/48(47.9) 5/46 NG 18/48 PG **at 48m FU:** 25/48(58.3)	**Baseline:** 14/24 (58) **SMA 1a:** 3/3 (100) 3/3 NG **SMA 1b:** 5/9 (55.5) 4 NG, 1 PG **SMA1c:** 6/12 (50) 4 NG, 2 PG **at 24m FU:** 20/24(83.3) **SMA 1a:** 3/3 (100) 2 NG, 1 PG **SMA 1b:** 9/9 (100) 9/9 PG **SMA 1c:** 8/12(67) 3NG, 5 PG
p-FOIS	n.r	n.r	**Baseline** **SMA 1a:** median=1 **SMA 1b:** median=3 **SMA 1c :** median=5 **at 24m FU:** **SMA 1a:** median=1 **SMA 1b:** median=2 **SMA 1c:** median=3
AEs /SAEs n (%)	n.r	**Headaches, Pain and Nausea in 10/48 (20.8%)**	n.r.

** Both Pane 2021 and 2023 describe the same cohort of patients* (30)(32)

Abbreviations: (S)AE=(Severe)Adverse Events, CHOP-INTEND= Children's Hospital of Philadelphia Infant test of Neuromuscular Disorders, FU=Follow up, HINE-2=Hammersmith Infant Neurological Examination Section 2, p-FOIS= The paediatric functional oral intake scale, RULM=Revised Upper Limb Module.

Table A- 11: Nusinersen in SMA 1+2

	Iwayama et al. 2022 [50]
Patients n **SMA type** **SMN copy nr 2/3**	**7** SMA1 4/7(57%). SMA2 3/7(43%) 1a= 1, 1c= 3* 2/2 0/3 * 3 participants were changed from SMA 2 to SMA 1c due to them not achieving sitting without support after detailed interview
FU y **median (range)**	3.55 1.78-4.52
Loss to FU n	no loss to FU
CHOP INTEND **median (range)**	**Baseline**: 5 (0-31) **at FU:** 21(0-39), p=0.1
HFSME **median (range)**	**Baseline:** 0 (0-3) **at FU:** 0 (0-5), p=0.346
RULM **median (range)**	**Baseline:** 1(0-20) **at FU:** 3(0-21), p=0.089
Motor Milestone criteria response **n/ (%)**	n.r
Respiratory support **noninvasive** **n (%)**	**Baseline total**: 4/7 (75) **SMA1**: 3/4 (75) night time only 1/4 all day 2/4 **SMA2**: 1/3 (33) night time only **at FU:** n.r
Respiratory **support** **invasive** **n (%)**	0 patients required IV
Nutritional support **n (%)**	**Baseline total**: 3/7 (75) **SMA1**: 3/4(75) **SMA2**: 0/3 (0) **at FU**: n.r
AEs/SAEs	n.r

Abbreviations: (S)AE=(Serious) Adverse Events, CHOP-INTEND= Children's Hospital of Philadelphia Infant test of Neuromuscular Disorders, FU=Follow up, HFSME=Hammersmith Functional Motor Scale Expanded, RULM=Revised Upper Limb Module.

Table A- 12: Nusinersen in SMA 2+3

	Darras et al. 2019 (ISIS-396443-CS2: NCT01703988, NCT02052791 [44]	**Montes et al 2019 (ISIS-396443-CS2: NCT01703988, NCT02052791** [45]	**Fainmesser et al. 2022 [52]**	**Pane et al. 2022 [52]**	**Pechman et al. 2022 [54]**
Patients n **SMA type** **SMN2copy n=1/2/3/≥4/unknown**	**28** SMA2:11 SMA3:17 0/1/21/6	**14** SMA2:1 SMA3: 13 0/0/ 9/5/0	**37** SMA2: 15 SMA3: 22 n.r	**111** SMA2: 46 SMA3:65 n.r	**256** **SMA 2:** 217 **SMA3:** 39 **SMA 2:** **Younger sitters:** 0/11/78/12/6 **Older sitters:** 1/5/37/11/19 **Lost ability to sit:** 0/2/23/3/9 **SMA 3:** **Lost ability to walk:** 0/0/26/6/7
Ambulant/Sitters (+non-sitters)*	28/13 **SMA2:** 0/11 **SMA3:** 15/17	7/1	7/30 **SMA2:**0/15 **SMA3 :**7/15	61/41 (+9 non-sitters) **SMA2:** 0/38(+8) **SMA3**: 41/23(+1)	no children were ambulatory **SMA 2:** **Young sitters <5y:**107 **Older sitters >5y:** 73 **Lost sitters:** 37 **SMA 3:** **Lost walkers :**39
FU m	**35**	**35**	**26-30**	**24**	**38**
Loss to FU n	4 pts discontinued. No patient discontinued treatment due to AEs.		1 pt discontinued due to adverse reaction to Lumbar puncture	1 pt (SMA3, walker) discontinued due to AE (LP headache)	13 discontinued 7/13 changed medication 6/13 no details 15 lost to FU – no details
Motor milestone criteria response n (%)	n.r		n.r	n.r	16/107 (14.9) of Young sitters and 1(1.3) of Older sitters achieved walking independently 14/17 (82.3%) by FU 14m

					4 lost sitters (10.8%) and 1 lost walker (also unable to sit) (2.6%) regained the ability to sit independently. **NO loss of motor milestones in any cohort.**
CHOP INTEND **mean ± SD**	n.r		n.r	n.r	n.r
RULM **mean ± SD**	ULM** Baseline: SMA 2: (n=11): 11.9±0.9 SMA 3; (n=4): 16.0 ± 1.2 at 35m FU: overall +4 ±2.4 Clinically meaninful improvement (>2points) 5/9 (56%) by last predefined study day 1050	n.r	n.r	**Total Baseline:** 28.5 (16.75-36) (n=80) **(median and 1st-3rd quartile)** **Total at FU:** n.r **SMA2** **Baseline:** 14.2±7.3 (n=26) **Sitters:** 17.1± 5.1 (n=20) **Non-sitters:** 4.5±4.7 (n=6) **at 24m FU:** +1.6±3.1, **p=0.018** **Sitters:** +1.7±3.5 **p=0.036** **Non-sitters:** +1.3 ± 2.5 p=0.276 **SMA3** **Baseline:** 31.5±7.2 (n=54) **Ambulant:** 34.5±3.6 (n=33) **Non-Ambulant:** 26.818.9 (n=21) **at 24m FU:** +0±2.1, p>0.05 **Ambulant:** +0.1±1.6, p>0.05 **Non-Ambulant:** -0.3±2.8,p>0.05	**Young sitters** **Baseline Score:** 16.2±7.1 (n=26) **at 38m FU:** +9.1 (n=32) **Older sitters** **Baseline Score** 19.0±7.5 (n=51) **at 38m FU:** +2.2 (n=28) **Lost sitters** **Baseline Score** 12.8±7.1 (n=18) **at 38m FU:** +7.3 (n=8) **Lost walkers** **Baseline Score** 26±6.1 (n=29) **at 38m FU:** +3.3 (n=14) **Clinically Meaningful changes:** 83/256 (32.4) **Young sitters** 30/107 (28) **Older sitters** 30/73 (41.1) **Lost sitters** 8/37 (21.6) **Lost walkers** 15/39 (38.5)

				No statistically significant improvement detected in total cohorts or age, functionality or severity stratified groups.	Inferential analysis showed that Improvements were observed continuously during FU and that higher baseline score was associated with smaller score improvements.
MMT using MRC Scale (0-100) median (IQR)	**n.r**	**n.r**	**Baseline :** (n=34): 66 (44.5-80.5) **at 26m FU:** (n=16): **75**(62.5-84), p=0.09 adjusted baseline 70 (61.5-85.7) **SMA2** **Baseline:** (n=15) **45** (38-59) **at 26m FU: 63** (42-77.2), p=0.254 (n=4): adjusted baseline 54.4 (41-68.7) **SMA3** **Baseline: 80**(68-85) (n=19) **at 26m FU: 80**(68.2-84.7) p=0.41 (n=12) baseline 75 (68.5-87.5)	n.r	n.r
6MWT mean ±SD	**(In walkers n=13)** **Baseline:** 253.3 ±50.7 **At 35m (1050 d) FU:** + 92 ±21.5 2/4 children who lost the ability to walk before study start, regained it.	Baseline total: (n=14): 235.2 ±188.2) Pts <11y: 259.8 ±155.5 Pts > 11y: 190.0 ± 250.9 At 35m FU (1050d): +98m (median) Median fatigue associated with the 6MWT reduced by –3.87% at end of FU.	**n.r**	n.r	n.r

	Clinically meaningful improvements (>30m increase from baseline): 8/8 (100) 1 SMA 2 child gained the ability to walk				
HFSME or RHS (Revised HFSME) **median (IQR) or mean ± SD**	**Total Baseline: (n=28)** 38 **± 3.3** **Total Follow-up:** nr. **SMA2:**Baseline: 21.3±2.9 At 35m FU: +10.08±2.9 Clinically meaninful improvements (>3 points): 7/9 (78) at last predefined study visit day 1050 **SMA3:** Baseline: 48.9±3 At 35m FU: +1.8 ±0.9 Clinically meaningful improvements (>3 points) 4/11 (36) at last predefined study visit day 1050 Walkers (n=13) Baseline: 54.8 ± 1.5 At 35m FU: + 2.6± 0.8 Clinically meaningful improvements (>3 points) 4/9 (44) at last predefined study visit day 10:50	**n.r**	**RHS** **Baseline:** 14 (5-30) (n=35): **at 26m FU:** 23.5 (11.5-48.5), p=0.82 (n=16) adjusted baseline 25.5 (13.2-44) **SMA2** **Baseline:** 5 (2-10) (n=15) **at 26m FU:** 9.5 (2.7-31.2), p=0.5 (n=4) adjusted baseline 9.5 (2-23) **SMA3** **Baseline:** 28..5 (16.2-44.2) (n=20) **at 26m FU:** 32.5 (13.25-49.7), p=0.46 (n=12) adjusted baseline 33.5(117.2-45.7)	**Total Baseline (n=111):** 24 (9.4-46) **Total at FU:** n.r. **SMA 2** **Baseline:** 10.6±9 (n=46) **FU 24m:** +1.9±4.6, **p=0.019** **Sitters:** +2.2±5, **p=0.020** **Non-Sitters:** +1.8±4, p=0.577 **SMA3** **Total Baseline:** 39.5±17 **at 24m FU:** +1.5±4.8, p=0.017 **Ambulant:** +2.5±5, **p=0.004** **Non-Ambulant:**-0.3±2.8, p>0.05	**Young sitters** **Baseline Score** 20.7±11.4 (n=52) **at 38m FU:** +7 (n=29) **Older sitters** **Baseline Score** 15.7±12.4 (n=47) **at 38m FU :** +0.1 (n=19) **Lost sitters** **Baseline Score** 13.7±14.4 (n=15) **at 38m FU: n.r** **Lost walkers** **Baseline Score** 29.9±9.1 (n=33) **at 38m FU:** +2.9 (n=9) **Clinically meaningful changes (³3 points):** 63/254 (24.6) **Young sitters:** 37/107(34.6) **Old sitters:** 11/73 (15.1) **Lost sitters:** 5/37 (13.5)

					Lost walkers: 10/39 (25.6) **Inferential analysis showed SMN2 copy nr influencing HFSME score and lower baseline scores were associated with smaller improvements.**
ALSFR-R (0-48) median (IQR)	n.r		**Baseline:** 36 (30-41) (n=34) **at 26m FU:** 40(34.2-43.7), p=0.66 (n=16) adjusted baseline 40 (34.7-44) **SMA2** **Baseline:** 31(29-35) (n=15) **at 26m FU:** 36 (29.5-41.2) p=0.37 (n= 4) adjusted baseline 36(27.5-40) **SMA3** **Baseline:** 41 (36-44) (n=19) **at 26m FU:** 41.5 (35.7-44), p=0.86 (n=12) adjusted baseline 41 (37.2-44.7)	n.r	n.r
Respiratory support Non invasive n (%)	n.r		n.r	n.r	**patients required <16h/day** **Baseline:** 39/256 (15.2) **at FU 38m:** 61/256 (23.8) * 23 started additionally, 1 able to discontinue **Younger sitters:** **Baseline:** 12/107**(**11.2) **at FU 38m:** 14/107 (13)

				Older sitters: **Baseline:** 16/73(21.9) **at FU 38m:** 27 /73(38.3) **Lost sitters:** **Baseline:** 9/37(24,3) **at FU 38m:** 15/37(40.5) **Lost walkers:** **Baseline:** 2/39(5.1) **at FU 38m:** 5/39(12.8) no details on hours of use, but no children used permanent NIV**.**
Respiratory Support invasive n (%)	n.r	n.r	n.r	0 patients required invasive ventilation
Nutritional support n (%)	n.r			**Baseline:** 14/256 (5.5) **FU:** 18/256 (7) **Younger sitters:** **Baseline:** 4/107(3.7) **At 38m FU:** 5*107**(**5.6) *one patient that initiated tube feeding could discontinue after 4 m **Older sitters:** **Baseline:** 5/73(6.8) **at 38m FU:** 6/73(8.2) **Lost sitters:** **Baseline:** 5/37**(**13.5) **at 38m FU:** 7/37**(**18.9)

Hospitalisations	n.r		n.r	n.r	**122 hospitalisations due to AE in 64 patients**
AEs/SAEs n (%)	≥1 AE: 28/28 (100) most common AEs: LP syndrome 16/28(57) headache 13/28 (46) nasopharyngitis:12/28(43) URTI: 12/28 (43) puncture site pain:11/28 (39) scoliosis: 8/28 (29) pyrexia: 7/28 (25) joint contracture: 6/28(21) rhinorrhea: 6/28 (21) vomiting: 6/28 (21). SAEs: in 5/28 (18) post-LP syndrome: 2/5, LRTI, respiratory distress, and viral pneumonia: 1/5 acute respiratory failure, RSV pneumonia: 1/5 vesicoureteral reflux and pye-lonephritis: 1/5		3/37 (8) post lumbar headache increased appetite, weight gain 1 Crohn's disease, 1 Pre-Diabetes not considered drug related	n.r	**144 AE (in 64 patients)** **0 confirmed drug-related AE** **31 (25.4) possibly related** 45.8: respiratory infection 20.8: gastroenteritis 9: post LP syndrome 8.3: infections, other 4.1: fractures 4.2 respiratory distress 3.5 pain 1.4: abdominal symptoms 2.8: others (non specified)

**Pane et al.*(48) *Included 9 non-sitters in their study (8 with SMA 2 and 1 with SMA 3). It is unclear if those are patients who lost the ability to sit during disease progress or if they were wrongly labelled as never gaining the ability to sit precludes diagnosis of SMA type 2 or 3.*

*** only assessed in non-ambulatory SMA2 and 3 patients*

Abbreviations: AE=Adverse Events, ALSFRS-R= Revised Amyotrophic Lateral Sclerosis Functional Rating Scale, CHOP-INTEND= Children's Hospital of Philadelphia Infant test of Neuromuscular Disorders, FEV1= Forced Expiratory Volume in 1 second, FU=Follow up, MMT= Manual Muscle Test, MRC= Medical Research Council, HFSME=Hammersmith Functional Motor Scale Expanded, RHS =Revised Hammersmith Functional Motor Scale, RULM=Revised Upper Limb Module, RSV- respiratory syncytial virus,U/L RTI=Upper/Lower Respiratory Tract Infection

Table A- 13: Nusinersen in SMA 3

	Pechman et al 2023 [55]
Patients n **SMN2copy 1/2/3/4+/unkown**	**231** **Paediatric walker 114** **Adult walker 117** 0/10/35/57/12 2/4/24/67/20
FU time	**38m**
Loss to FU m	3 patients stopped treatment (2 changed to Risidiplam) 14 lost to follow up after 12 m
RULM **mean and CI**	**Paediatric walker** **Adult walker** **Baseline:** (n=70/101) 32.4 (30.8-34.2) 34.7(33.7-5.9) **at FU 38m**:* 35.1 34.1 (n=33/43) **relative changes** **at FU 38m:** +2.8 -0.5 **Clinically meaningful** **improvement n (%)** **>2 points** **during FU** 27/114(23.7) 17/117(14.5) Inferential analysis showed lower baseline scores having a statistically significant influence on score improvement.
HFSME **mean and CI**	**Paediatric walker** **Adult walker** **Baseline:** (n=88/105) 51.1 (48.6-53.7) 46.2 (43.2-49.5) **at FU: 38m*** 44 56 (n=37/43) **relative changes** **at FU 38m:** +5.3 -1.4 **Clinically meaningful** **improvement n (%)** **>3points during FU:** 38/114(33.3) 42/117(35.9)

	Inferential analysis showed lower baseline scores having a statistically significant influence on score improvement.
6MWT **mean and CI**	**Paediatric walker** **Adult walker** **Baseline:** (n=50/84) 329 (264.9-393.6) 353.8 (312.5-403.7) **at 38m FU:*** 360m 365m **relative changes** **at FU 38m:** +39.3 m +24.4 **Clinically meaningful improvement n (%):** **> 30m during FU:** 31/114 (27.2) 31/117(26.5) **by FU 26m:** 11(13.1) 8(9.9) **by FU 38m:** 7 (12.7) 3(5.5) Inferential analysis showed higher SMN copy nr having statistically significant influence on the improvement.
Respiratory support **noninvasive** **n (%)**	**Paediatric walkers** **Adult walkers** **Baseline:** 0 0 **FU 38m:** 0 3/117 (2.56)
Respiratory support **Invasive** **n (%)**	0 patients required invasive support at baseline or follow up
Nutritional support	0 patients required support at baseline. 1 paediatric walker required temporary support through tube feeing.
Fatigue **n (/%)**	**Baseline:** (n=231) 69 (29.8) **at FU:** (n=110) 10 (9.1) **Paediatric Walkers** **Adult Walkers** **Baseline:** 27 (23.7) 42 (35.9) (n=114/117) **at FU 38m:** 2 (3.6) 8 (14.5) **(**n=55/55)
Hospitalisation	32 hospitalisations from AE.

AEs/SAEs **n (%)**	50 AE in 40 patients :32 (64%) hospitalisation and 18 (36%) without Post LP syndrome: 26% Infectious Diseases; 16% Fractures/accidents: 36% Cardiac symptoms: 6% Pain: 2% Other: 14% 16/50 (32) possibly related to drug treatment

**Since exact numbers are not reported, numbers are based on estimations from Figures 1 and 3 in* (50)

Abbreviations: AE=Adverse Events, FEV1= Forced expiratory volume in 1 second, FU=Follow up, HFSME=Hammersmith Functional Motor Scale Expanded, RULM=Revised Upper Limb Module, 6-MWT=6m Walk Test.

Table A- 14: Nusinersen in SMA 1-3

	Tscherter et al. 2022 [56]
Patients n **SMA type** **SMN2copy 2/3/^{3}4**	**44** SMA1 n=11 SMA 2 n=21 SMA 3 n=12 6 walkers/6 non-walkers 5/4/0 1/16/3 1/3/6
FU time y **median (min-max)**	**SMA 1:** 2.1 (0.8-3.4) **SMA 2:** 1.8 (0.5-2.9) **SMA 3:** 1.9 (0.6-2.6)
Loss to FU n	**no patients died** **3 pts discontinued** (2xSMA1, 1xSMA2**)** due to inclusion in another trial, difficulties with LP due to scoliosis and increased opening pressure during LP. all patients switched treatment to another DMT.
CHOP INTEND **median and range**	**SMA 1** (n=11) **Baseline:** 25 (2-29) **at FU:** +25 (2-42) < under 18 m: +29.5 (25-42) >18m: +5 (2-8) Correlation between age at treatment initiation and disease duration before treatment start (p=0.002) but no correlation with SMN copy nr. **SMA 2+SMA 3:** n.r
RULM **median and range**	**SMA 2** (n=12) **Baseline:** 14 (0-24) **at FU:** 5 patients + 1-5 points 5 patients + 1-3 points 2 patients unchanged **SMA 3** (n=5): **Baseline:** 31 (18-37) **FU:** 2 patients +4-6 points

	2 patients unchanged 1 patient -2 pts
HFSME **median and range**	**SMA 2** (n=16): **Baseline**: 5.5 (0-25) **at FU**: 5 patients +1-15 pts 4 patients -1 –5 pts 7 patients unchanged **SMA 3** (n=11): **Baseline:** 41 (6-62) **at FU:** 53 (6-64) No correlation detected between age at treatment start and HFSE score improvement. Some evidence for correlation between SMN2 Copy nr and motor improvement. (contradictory to finding for CHOP-INTEND)
6MWT **median and range**	**SMA 3** (n=5): **Baseline:** 387m (169-576) **at FU:** 466m relative increase (+72-146)
Motor milestone achievements	**SMA1** (n=11) 8 patients gained (holding head up, rolling onto one side, sitting without support, standing with support, raising hands, reaching overhead, useful function of hands) and 1 patient lost motor abilities (raising hands) **SMA 2** (n=21) 8 patients gained (5 standing with assistance, 2 walking with and 1 walking without assistance) and 1 patient lost motor abilities (holding head up and raising hands) No patients lost the ability to sit. **SMA 3** (n=12) None of the ambulatory patients lost the ability to walk but none gained any more function. In the nonambulatory patients, one gained the ability to walk, 2 gained the ability to walk more than 10m and 2 achieved climbing stairs. One patient achieved reaching overhead from sittig.
Respiratory support **non invasive** **n (%)**	**SMA 1** < 18m at treatment start (n=6): **Baseline:** 0

	at FU: 3 nocturnal NIV <16h/d **SMA 1**>18m at treatment start (n=5): **Baseline:** 4 **at FU:** 4 **SMA 2:** n.r **SMA 3**: n.r
Respiratory support invasive n (%)	0 patients required invasive ventilation at baseline or FU.
Nutritional support n	**SMA 1**< 18m at treatment start (n=6): **Baseline**: 0 **at FU:** 4 (PG) **SMA 1**>18m at treatment start (n=5): **Baseline**: 4 **at FU:** n.r. **SMA 2** and **SMA 3** : n.r
AEs/SAEs n (%)	15/44 (34) patients had at least one side effect unrelated to lumbar puncture 6 (14) Proteinuria 7 (16) Thrombocytosis 1 (2) Thrombocytopenia 2 (5) Coagulation disorder 2 (5) ECG changes 6 (14) LP related issues 2 (5) other AE/SAE not specified.

Abbreviations: AE=Adverse Events, CHOP-INTEND= Children's Hospital of Philadelphia Infant test of Neuromuscular Disorders, DMT= Disease Modifying Treatment, FU=Follow up, HFSME=Hammersmith Functional Motor Scale, LP= lumbar puncture, RULM=Revised Upper Limb Module, 6-MWT=6m Walk Test.

Table A- 15: Nusinersen in SMA 1-4

	Bjelica et al. 2023 [49]
Patients n **SMA type** **SMN2copy <4/>4**	**38** SMA 1: 1 SMA 2: 14 SMA 3: 21(3a:7,3b:14) SMA 4: 2 <4:18 >4:20
FU time m	**30**
Loss to FU	unclear
Ambulatory	11 (28.9)
RULM, **mean and SD**	**Baseline:** 22.1±13.2 (n=33) **at FU 30m:** +0.2±4.8 (n=17)
HFSME, **mean and SD**	**Baseline:** 24.7±23.6 (n=29) **Relative Improvement** **at FU30m:** -0.2±5.6, p>0.05 (n=15)
6MWT	n.r
Respiratory support **non invasive** **n (%)**	**Baseline:** 7/38 (18.4) **at FU:** n.r
Respiratory support **Invasive** **n (%)**	**Baseline:** 0/38(0) **at FU:** n.r
Nutritional support, n	**Baseline:** 2/38 (PG) **at FU:** n.r
Fatigue FSS **mean difference and SD**	**Baseline**: 40.1±11.9 (n=24) **at FU30m**: +3.4±8.3 (n=24) Changes in PEF at FU 30 m showed negative correlation with FSS at FU 10m and 22 m (p<0.05 and <0.01 respectively)
Quality of Life SF36, **mean difference and SD**	**Baseline:** 58.6±12.0 (n=24) **at 30m FU:** -4.8±15.3

	(n=17) Total score did not show statistically significant change related to changes in pulmonary function.
Hospitalisation	n.r
AEs /SAEs	n.r

**Since exact numbers are not reported in Bjelica et al 2023 the numbers are based on estimations from Figure 2 in* (52)

Abbreviations: (S)AE=(Serious)Adverse Events, FSS= Krupp's Fatigue Severity Scale, FCV= forced capacity volume, FEV1= forced expiratory volume in 1 second, PEF= peak expiratory flow FU=Follow up, HFSME=Hammersmith Functional Motor Scale, RULM=Revised Upper Limb Module, 6-MWT=6m Walk Test, SF-36=36 Short Item Health Survey.

Table A- 16: Onasemnogene abeparvovec in SMA 1

	Al-Zaidy et a.l 2019a [42] NCT02122952	**Al-Zaidy et al 2019 b [46]** NCT02122952	**Lowes et al 2019 [47]** NCT02122952	**Mc Grattan et al. 2023 [38]**
Patients n **SMN2copy**	**12** all patients had 2 SMN2 copies	**12** SMA1 pts **16** untreated SMA 1 pts **27** healthy children All patients had 2 SMN2 copies	**12** Early dosing/low motor group: 3 Late dosing group: 6 Early dosing/high motor group: 3 all patients had 2 SMN2 copies	**11 (START cohort)*** all patients had 2 SMN copies
FU time m	**24**			**24**
Loss to FU n	0 loss to FU	0 loss to FU in treatment group 15/16 death or loss to FU in un-treated group Healthy cohort: n.r	0 loss to FU	0 loss to FU
Survival **n (%)**	12/12 (100)	12/12 (100) in treatment group 8/16 (50) in untreated group Healthy cohort : n.r	12/12 (100)	n.r
CHOP INTEND **mean and SD**	n.r	**Baseline:** AVXS-101 group: 28.2 (12.3) Untreated SMA1 group:20.3(7.3) Healthy group: 51.1 (8.9) **At FU:** AVXS-101 group: (n=12): 56.5 Untreated SMA1 group: (n=3): 5.3 Healthy group: n.r ≥4 points improvement: AVXS-101 group: 12/12 (100) ≥40 points achieved and sustained by 11/12 (92) Untreated SMA1 group: 0/16 (0) Healthy group: n.r.	**Baseline:** Early dosing/low motor group: 15.7 (1.53) Late dosing group: 26.5 (7.66) Early dosing/high motor group: 44.0 (7.94) **At FU:** Early dosing/low motor group: 50.7 (5.77) Late dosing group: 49.8 (16.64) Early dosing/high motor group: 60.3 (6.35)	n.r

Motor milestone response n (%)	11/12 (92) achieved head control and ability to sit unassisted sitting > 5 sec : 11/12 (92) sitting >10 sec: 10/12(83) sitting >30 sec: 9/12 (75) beyond 2y FU : 2 more children could sit >30s(92) 9/12 (75) achieved rolling 4/12(33) achieved standing with support 2/12 (17) achieved crawling, pull and stand and walking	**AVXS-101 group:** (n=12 at FU) Motor milestone response as recorded in Al-Zaidy et al. A **Untreated SMA1 group:** (n=10 at FU) **0 (0)** Motor milestones not formally assessed but deduction of function from CHOPINTEND scores suggests no infants in the untreated group achieved any of the relevant milestones.	Total sit without support for ≥5 s: 11/12 (92) Including 3/3 (100) of those in early dose/low motor group 2/12 standing without support in the early dose/ high motor group	
Respiratory support noninvasive >16h/day n (%)	**Baseline**: 2/12 (16.6) **at FU:** 5/12 (41.6) all remained stable	**Baseline:** AVXS-101 group: 2/12 (17) Untreated SMA1 group: 6/16 (37) Healthy group: 2/27 (7) **At FU:** n.r.	**Baseline:** Early dosing/low motor group: 0/3 (0) Late dosing group: 2/6 (33.3) Early dosing/high motor group: 0/3 (0) **At FU:** Early dosing/low motor group: 3/3 (100%) Late dosing group: n.r.** Early dosing/high motor group: n.r.	n.r
Respiratory support invasive n (%)	**Baseline:** 0/12 (0) **at FU:** 0/12 (0) no patients required tracheostomies	n.r	n.r	n.r
Respiratory stability (no aspiration/pneumonia) n (%)	n.r.	n.r	n.r	**Baseline:** 11/11 (100) **at FU:** 8/11 (73)
Nutritional support, n (%)	**Baseline :** 5/12 (42) **at FU:** 6/12(50) only 1 patient required support, all patients who had been exclusively fed at baseline, (6/7) continued to do so.	**Baseline:** AVXS-101 group: 5/12 (42) Untreated SMA1 group: 7/12 (44) Healthy group: 1/12 (4)	**Baseline:** Early dosing/low motor group: 3/3 (100) Late dosing group: 2/6 (33.3) Early dosing/high motor group: 0/3 (0)	**Baseline:** 4/11 (36) **at FU:** 5/11(45)

		At FU: n.r.	**At FU:** Early dosing/low motor group: 0/3 (0) Late dosing group: n.r. Early dosing/high motor group: n.r.	
Swallow function/Bulbar function **n (%)**	Safe swallow **liquids:** **Baseline:** 4/12 (33.3) **at FU:** 10/12 (83) Safe swallow to allow **Baseline**: 7/12 (58) **partial oral feeding:** **at FU:** 11/12 (92)	n.r	n.r	Baseline: 4/11 (36) FU: 11/11(100)
Communication ability **n (%)**	n.r	n.r	n.r	**Baseline**: n.r **at FU:** 4/4 (100) communication was only assessed for n=4 before the end of study time in START
Hospitalisation rates	1.4 hospitalisation /year (0-4.8) 10/12 (83) for respiratory illness, but none led to respiratory endpoint of invasive ventilation mean annualized hospitalisation rate: 2.1 (0-7,6) mean Length of Stay/ hospitalisation: 6.7 d (range 3-12.1)	n.r	n.r	n.r
AEs/SAEs **n (%)**	n.r	275 AEs in 12/12 (100) pts, 53 SAEs in 10/12 (83) pts AEs considered related to treatment: 4 in 3 pts Most frequent other AEs: URTI: 28 (83) Pyrexia: 12 (58), Vomiting: 11 (67) Pneumonia: 14 (58) Constipation:8 (50) Nasal congestion 8 (50)	n.r	n.r

**Mc Grattan et al.* (53) *utilised data from phase 1 of START NCT02122952 and two phase 3 trials, (STRIVE-US NCT 03306277, STRIVE-EU NCT03461289) for a post hoc analysis. We only inlcuded data of the START trial in our analysis because only those patients had FU >12 m*

*** assuming still 2/3 since in Al Zaidy et al.*(34)*describe 5/12 requiring NIV at follow up.*

Abbreviations: FU=Follow Up.

Table A- 17: Risdiplam in SMA 1

	Darras et al. 2021 (FIREFISH NCT02913482) [48]	**Masson et al.2022** (FIREFISH NCT02913482) [14]
Patients n **SMN2copy**	**41** all patients had 2 SMN2 copies	
FU time m	**12**	**24**
Loss to FU n	3 patients died	
BSID III (item 22) **Sitting> 5 sec** **n (%, CI)**	**Baseline:** 0/41(0) **at 12 m FU:** 12/41 (29; CI 16-14) statistically significant difference to the performance criterion of 5% from natural history data p<0.001 **at 24mFU:** 25/41 (61) not in included in 24m statistical hierarchy	
BSID III (item 22) **Sitting > 30 sec** **n (%, CI)**	Baseline: 0/41 FU12m: 7/41(17; 8-30) FU 24m: 18/41 (44; 31-58) statistically significant difference to the performance criterion of 5% from natural history data p<0.001	
BSID III (item 40 **Standing alone** **n (%, CI)**	Baseline: 0 (0-7) FU 12m: 0 (0-7) FU 24m: 0 (0-7)	
BSID III (item 42) **walking** **n (%, CI)**	Baseline: 0 (0-7) FU 12m: 0 (0-7) FU 24m: 0 (0-7)	
CHOP INTEND	(median and range): **Baseline:** 22.0 (8.0-37.0) **at 12m FU:** 42.0 (13.0-57.0) ≥**40 pts total** n (% and CI) : 23/41 (56; CI 40-72) statistically significant difference to the performance criterion of 17% from the natural history data p<0.001 ≥**4 pts improvement:** n (% and CI) 37/41(90; CI 77-97) statistically significant difference to the performance criterion of 17% from the natural history data p<0.001	

	(median and IQR): **Adjusted Baseline:** 22.0 (15.0-28.0) **at 24m FU:** n.r ≥**40 pts total** n (% and CI):31/41(76;62-86) not included in 24m statistical hierarchy ≥**4 pts improvement** n (% and CI)**:** 37/41 (90;79-97) not included in 24m statistical hierarchy	
HINE-2 milestone responses median and IQR n (% and CI)	**Baseline:** 1.0 (0.0-5.0) **at 24m FU:** median n.r 32/41 (78, CI 77-97) had response* statistically significant difference to performance criterion 12% from the natural history data p<0.001 **Baseline:**1.0 (0.0-1.0) **at 24m FU:** median n.r 35/41(85; 73-93) had response	
Respiratory support NIV and IV n (%, CI)	**Baseline:** 12/41 (29) **at 12 m FU**: 31/41 (75.6) **at 24m FU:** 33/41 (80)	
Nutritional support, n (%, CI)	**Baseline:** **At 12 m FU:** 6/41 (15%) **At 24 m FU:** 7/41 (17%)	
survival, n (%, CI)	38/41 (93, 82;87)	
event free survival, n (%, CI)**	**Baseline:** 29 (71) **at 12m FU:** 35/41(85, 70-93) statistically significant difference to performance criterion 42% from the natural history data p<0.001 **at 24m FU:** 34/41 (85, 73-2) not included in 24m statistical hierarchy	
AE/SAE n (%)	254 total AE during 12 months during FU period ≥1: 41 /41 (100) most common AE:	356 total AE during 24 m FU period ≥1: 41 /41 (100%) most common AE:

	URTI 28(68) Pneumonia. 16(39) Pyrexia 16(39) Diarrhea 4(10) Rash 4 (10) 48 total SAEs in 41 patients ≥1: 24/41 (59) fatal: 3(7)- considered due to SMA-related respiratory complications most common SAE: Pneumonia: 13 (32) Bronchiolitis: 2 (5) Hypotonia: 2 (5) Respiratory failure: 2(5)	URTI 22(54) Nasopharyngitis 7(17) Pneumonia. 19(46) Bronchitis 6(15) Pyrexia 18(44) Diarrhoea 6(15) Constipation 12(29) Treatment related AE: 7 (17) 68 total SAEs in 28 patients after 24 m FU most common SAE: Pneumonia 16(39) Respiratory distress 3 (7) Other 2 (5)

** HINE-2 improvement was defined as an increase of at least 2pts in the ability to kick (or maximum score), or an increase of at least 1 pt in head control, rolling, sitting, crawling, standing or walking. Worsening was defined as a decrease of at least 2 pts in the ability to kick (or lowest score), or a decrease of at least 1 pt. in head control, rolling, sitting, crawling, standing or walking.*

*** Event free survival was defined as alive with no permanent ventilation (no tracheostomy, or BIPAP for > 16h/day continuously for >21 consecutive days or continuous intubation for >21 days, in the absence of, or following the resolution of, an acute reversible event.*

Abbreviations: (S)AE=(Serious)Adverse Events, BSID III=Bayley Scales of Infant and Toddler development, CHOP-INTEND=Children's Hospital of Philadelphia Infant test of Neuromuscular Disorders), FU=Follow Up, HINE-2= Section 2 Hammersmith Infant Neurological Examination,

Table A- 18: Risdiplam in SMA 2+3

	Mercuri et al. 2022 NCT02913482 [15]	**Oskoui et al. 2023 NCT02913482 (open label, part 2)** [51]
Patients n **SMA type *** **SMN2copy 2/3/4/unknown**	**180** Risdiplam: 120 SMA 2:84(70) SMA 3: 36(30) 2(3) / 107(89) / 10(8) / 0	 Placebo/Crossover: 60 SMA 2: 44(73) SMA 3:16/(27) 1(2) / 50(83)/8(13) / 1(2)
FU time m	12	24
Loss to FU n	Risdiplam group: 3, Placebo/crossover group: 1 discontinued to start commercially approved treatments	2 patients discontinued Data available for n=164 with complete 24 m FU (Covid 19 restrictions complicated FU)
MFM32, **baseline mean± SD** **changes from baseline** **mean (95% CI)**	**Baseline:** **Risidiplam group:** **Placebo group:** 45.48 ±12.09 47.35±10.12 **at 12 m FU:** least squares mean change, **Risdiplam group:** **Placebo group:** n=115 n=59 1.36 (0.61-2.11) -0.19 (-1.22-0.84) mixed model repeated measure analysis estimated a statistically significant treatment difference: 1.55 (0.30-2.81) p=0.016	1. Comparison Risdiplam group and Crossover group (receiving 24 and 12m of Risidiplam,respectively) **Baseline:** ***Risidiplam group:*** ***Crossover group:*** 45.48 ±12.09 47.14±10.87 **at 24 m FU:** **(after 12 m treatment for crossover group)** mean change from baseline in MFM32 total: **Risdiplam group:** **Crossover group:** +1.8 (0.7-2.9) + 0.3(-0.7-1.3) mean change in MFM32 individual scores***: **Risdiplam group:** **Crossover group:** D1 0.4 (-0.1-1.0) 0.1(-0.7-0.8) D2 1.1 (-0.8-3.0) -0.3 (-2.2-1.5) D3 6.3 (4.2-8.3) 2.0 (0.4-3.5) **2. Comparing changes between Risdiplam group and External Comparator** **Baseline:**

		Risdiplam: **External comparator** MFM20 total: 47.2± 12.3 47.1±12.9 MFM20(< 6y) 51±10.7 49.1±12.6 MFM32(>6y) 45.5±12.7 46.2±13.0 **at 24m FU:** least squares mean change, **Risdiplam group:** **External comparator:** +1.4 (-0.2-3.1) -1.7(-3.4-0.0) Clinically** significant treatment difference: 3.1 (1.7-4.6) p<0.0001
MFM32** **n (%) of patients with score change ³ 3 points from baseline**	**at 12m FU, n (%):** **Risdiplam group:** **Placebo group:** 44/115 (38) 12/59 (24) Odds ratio : 2.35	1. Comparison Risdiplam group and Crossover group: **at 24 m FU, % (95% CI)** **Risdiplam group:** **Crossover group:** n=103 n=50 32 (23.8-41.5) 16 (7.4-27.4) 2. Comparison Risdiplam group and External Comparator **At 24 m FU, % (95% CI)** **Risdiplam group:** **External comparator:** **weighted n= 115.0** **weighted n= 114.0** 34 16 odds ratio: 2.5 (1.1 -5.6) p=0.0253
MFM32 **% of patients with score change ³ 0 points from baseline (stabilisation)**	**Risdiplam group: 80/115 (80)** **Placebo group: 32/59 (54)**	1. Comparison Risdiplam group and Crossover group: **at 24 m FU, % (95% CI)** **Risdiplam group:** **Crossover group:** n=103 n=50 58 (48.7-67.4) 59 (44.9-71.4) 2. Comparison Risdiplam group and External comparator: **at 24 m FU, % (95% CI)** **Risdiplam group:** **External comparator:**

		weighted n= 115.0 **weighted n= 114.0** 63 40 statistically significant odds ratio: 2.7 (1.4-5.1) p=0.0029
RULM **baseline mean± SD** **changes from baseline** **mean (95% CI)**	**Baseline:** **Risdiplam group:** **Placebo group:** n=119 n=58 19.65±7.22 20.9±6.41 **at 12 m FU:** least squares mean change **Risidiplam group:** **Placebo group:** n=119 n=58 1.61(1.00-2.22) 0.02 (-0.83-0.87) clinically significant treatment difference:1.59 (0.55-2.62) p=0.047	1. Comparison Risidiplam group and Crossover group: **Baseline:** **Risdiplam group:** **Crossover group:** n=119 n=59 19.65±7.22 20.41±6.40 **at 24m FU:** mean change (95% CI) **Risdiplam group:** **Crossover group:** n=105 n=53 2.8 (1.9-3.6) 0.9 (0.1-1.6) 2. Comparison Risidiplam group and External Comparator: n.r
HFSME **baseline mean ±SD** **changes from baseline** **mean (95% CI)**	**Baseline:** **Risdiplam group:** **Placebo group:** n=120 n=60 16.10±12.46 16.62±12.09 **at 12 m FU:** least squares mean change **Risdiplam group:** **Placebo group:** n=120 n=60 0.95 (0.29-1.61) 0.37(-0.54-1.28) no clinically significant treatment difference p=0.39	1. Comparison Risidiplam group and Crossover group: **Baseline:** **Risdiplam group:** **Crossover group:** n=120 n=58 16.10±12.46 16.76 ±11.54 **at 24m FU:** mean change (95% CI) **Risdiplam group:** **Crossover group:** n=106 n=9 2.2 (1.1-3.1) 0.0 9(-1.0-1.1) 2. Comparison Risidiplam group and External Comparator: n.r
Pulmonary care, n (%) ****	**Baseline:** **Risdiplam group (n=120):** **Placebo group (n=60):** 40 (33) 30 (50) **at 12m FU:** n.r	**Baseline:** **Risdiplam group:** **Placebo group:** 40 (33) 30 (50) **at 24 m FU:** n.r
	Baseline:	**Baseline:**

Nutritional support, n (%) *****	**Risdiplam group (n=120):** **Placebo group (n=60):** 2 (2) 0 (0) **at 12m FU:** n.r	**Risdiplam group:** **Placebo group:** 2(2) 0(0) **at 24 m FU:** n.r
SMAIS-ULM	**Baseline:** **Risdiplam group:** **Placebo group:** n.r n.r **Caregiver reported SMAIS:** **at 12 m FU:** least squares mean change **Risdiplam group:** **Placebo group:** n=116 n=60 1.65(0.66-2.63) -0.91(-2.23-0.42) Differences not statistically significant p=0.39 **Patient reported SMAIS**: change from baseline **Risdiplam group:** **Placebo group:** n=43 n=23 +1.04 (-0.26-2.5) -0.40 (-2.13-1.32)	1. Comparing changes between Risdiplam group and Crossover group: **Caregiver reported SMAIS:** **at 24m FU:** **mean change (95% CI)** **Risdiplam group:** **Crossover group:** n=103 n=53 2.7 (1.7-3.7) 1.6 (0.4- 2.8) **Patient reported SMAIS:** **Risdiplam group:** **Crossover group:** n=39 n=24 0.8 (-0/8-2.4) 0.6 (-1.0-2.2) 2. Comparison Risdiplam group and External Comparator: n.r
CGI-C **% of patients rated as "improved"**	**Baseline:** **Risdiplam group:** **Placebo group:** n.r n.r **at 12 m FU:** **Risdiplam group:** **Placebo group:** 57/120 (48) 24/60 (40) Differences not statistically significant p=0.39	**at 24m FU:** n.r
AE + SAE, n (%)	**Risdiplam group:** **Placebo group:** Total AEs: 789 354 ≥1 AE: 111/120 (93) 55/60 (92) ≥1 SAE: 24/120 (20) 11/60 (18)	**during 12-24 m FU** **Risdiplam group:** **Crossover group** Total AEs: 506 242 ≥1 AE: 110/120 (91.7) 48/60 (80) ≥1 SAE: 25/120 (20.8) 3/60 (5)

	treatment related AE: 16/120 (13) 6/120 (10) AE with incidences of ≥5% difference between groups: Pyrexia: 25/120 (21) 10/60 (17) Diarrhea: 20/120 (17) 5/60 (8) Rash: 20/130 (17) 1/60 (2) Mouth ulcers: 8/120 (7) 0 UTI: 8/120 (7) 0 Arthralgia: 6/120 (5). 0 SAEs with incidences of ≥5% difference between groups: Pneumonia: 9 /120 (8) 1/60 (2) Deaths: 0/120 (0) 0/120 (0) AEs leading to dose modification or interruption: 0/120 (0) 0/120 (0)	treatment related AE: 0/0 (0) 0/0 (0) most common AEs: URTI: 19/120 (15.8) 10/60 (16.7) Nasopharyngitis: 26/120 (21.7) 6/60 (10) Pyrexia: 16/120 (13.3) 6/60(10) Headache: 12/120 (10) 10/60 (16.7) Diarrhea: 9/120 (7.5) 6/60 (10) Vomiting: 14/120 (11.7) 8/60 (13.3) Cough: 12/120 (10) 5/60 (8.3) most common SAEs: Pneumonia: 8(6.7) 0 (0) Death: 0/120 (0) AEs leading to dose modification or interruption: 0/120 (0)

** Inclusion criteria: non-ambulant (unable to walk unassisted for ≥10m) but able to sit independently for more than 5 secs (≥1 on item 9 of MFM 32 and ≥2 on item A of RULM).*
*** no clinically meaningful change estimate has been established so far, authors used ≥3 points improvement as the threshold.*
**** individual MFM32 scores: D1: standing, transfers, ambulation, D2: proximal and axial function, D3: distal function*
*****includes cough assist or BiPAP, 0 patients had a tracheostomy.*
******gastrostomy*
Abbreviations: (S)AE=(Serious)Adverse Events, CGI-C =Clinical Global Impressions Scale- clinician rated, SMAIS-ULM=SMA Independence Scale Upper Limb Module,FCV= forced capacity volume, FU=Follow up, HFSME=Hammersmith Functional Motor Scale, MFM 20/32= Motor Function Measure, RULM=Revised Upper Limb module,

Combination therapies

Table A- 19: Onasemogene abeparvovec + nusinersen in SMA 1

	Mendell et al.2021 [43]
Patients n **SMN2 copy nr.**	**13** n=3: low dose n=10: therapeutic dose all patients had 2 SMN2 copies
concomitant nusinersen treatment, n (%)	7/13(53) low dose cohort: 3/3(100) therapeutic dose cohort: 4/10 (40)
FU time, median (range) y	5.2 (4.6-6.2)
Loss to FU, n	0
Motor milestone achievements, * n (%)	Therapeutic dose cohort: Maintenance since completion of START trial: 8/10 (100) New milestones: 2/10 (20) (standing with assistance) low dose cohort: n.r
Survival, n (%)	13/13 (100)
Event free survival n (%)**	low dose cohort :2/3 (66.6) therapeutic dose cohort :10/10 (100)
Respiratory support, NIV, n (%)	therapeutic dose cohort: **Baseline:** 4/10 (40) **at FU:** 4/10 (40) low dose cohort: n.r
Respiratory support, IV, n (%)	therapeutic dose cohort: **Baseline:** 0/13 (0) **at FU:** 0/13 (0) low dose cohort: **Baseline:** 0/3 (0) **at FU:** 1/3 (33.3) ***
Nutritional support n (%)	n.r

Adverse events, n (%) **Any AE** **SAE**	Nr of any AE total: n.r. Patients with SAE: 8/13 (62) most frequent SAEs: acute respiratory failure; 4/13 (31) pneumonia: 4/13 (31) dehydration: 3/13 (23) respiratory distress: 2/13 (15) bronchiolitis: 2/13 (15) all SAEs were considered to be unrelated to disease modifying therapy no SAEs led to discontinuation

** classified as WHO multicentre growth study definitions or Bayley Scales of Infant and Toddler Development.*
***free from permanent ventilation *** requiring permanent (invasive) ventilation*
Abbreviations: (S)AE= (Serious) Adverse Event, AESI= Adverse Event of Special Interest, FU=Follow Up.

Table A- 20: Risdiplam + nusinersen, onesamnogene abeparvovec, olesoxime OR RG7800 in SMA 1-3

	Chiriboga et al. 2023 [33] **J**EWELFISH study (NCT03032172)
Patients n **SMA type** **SMN2copy 1/2/3/4/unknown**	**174** SMA 1: 15(9) SMA2: 108 (62) SMA3: 51 (29) 1 (1) / 12 (7) / 136 (78) / 22 (13) / 3(2)
Non-sitters*/Sitters/Walkers, n (%)**	59 (34) / 99 (57) / 16 (9)
FU time, m	17±7.1 (0.9-47)
Loss to FU, n	1 patient withdrew due to issues with blood access prior to receiving treatment 8 patients withdrew during FU (all patient decision): 5/8 in the first 12m (3 cause unknown, 1 lack of improvement, 1 IBS/Panic attacks), 3/8 after 12 m (2 cause unknown, 1 covid safety concerns)
Previous Treatment	Olexosime: 71/174 (41) MOONFISH (RG7800): 13/174 (7.4) -3/13 had received placebo Nusinersen: 76/174 (43.6) -3/76 had also received olexosime Onasemnogene abeparvovec: 14/174 (8) -1/14 had received nusinersen prior to OA
HFSME total score <10	n=168 age 2-60 **Baseline Total:** 105/168 (63) **at FU:** n.r
Pulmonary care (NIV/IV/BiPAP)	**Baseline** **Total:** 93/174 (53) Olexosime: 39/71 (55) MOONFISH (RG780): 1/13 (8) Nusinersen: 43/76(57) Onasemnogene abeparvovec: 10/14 (71) **at FU:** n.r
Nutritional support	**Baseline** **Total:** 11/174 (7) requiring NG tube or PG tube Olexosime: 2/71 (3) MOONFISH (RG780): 0/13 (0) Nusinersen: 8/76 (10) Onasemnogene abeparvovec: 1/14 (7) **at FU:** n.r
	Baseline total: 139/168 (83)

Scoliosis	**>40% curvature:** 66/174 (39) **at FU:** n.r.
AE, SAE, n (%)	AE total: 923 Patients with ³1 AE: 159/173 (92) most common AE (reported in ³14 patients) URTI: 30/173 (17) Diarrhoea: 19/173 (11) Pyrexia: 30/173 (17) Nasopharyngitis: 17/173 (10) Headache: 28/173 (16) Vomiting: 14/173 (8) Nausea: 20/173 (12) Patients with ≥1 treatment related AE: 33/173 (19) SAE total: n.r. Patients with ≥1 SAE: 24/173 (14) most common SAEs (reported in ≥3 patients): Pneumonia: 4/173 (4) LRTI: 3/173 (2) URTI: 3/173 (2) Respiratory failure: 3/173 (2) SAE leading to treatment interruption or modification: 6/173 (4) Patients with treatment related SAE: 1/173 (1.3) (tachycardia) Death: 0

**Defined as score 0 on MFM32, ** defined as having a score ≥1 on MFM32 and unable to walk for ≥10m unassisted*

Abbreviations: (S)AE= (Severe) Adverse Effect, FU= Follow Up, BiPAP=Bilevel positive airway pressure,IBS= Irritable Bowel Syndrome, HFSME=Hammersmith Functional Motor Scale, U/L RTI= upper/lower respiratory tract infection

Table A- 21: Risdiplam + nusinersen in SMA 2

	Nungo-Garzon et al. 2023 [31] NCT04256265
Patients n **SMN2copy 1/2/3/4**	**6** 1/0/4/1
FU time, m	**12**
Loss to FU, n	no loss to FU
Sitters/Non-Sitters, n	0/6
Previous nusinersen	2/6
Nutritional Support **n (%)**	**Baseline:** 3/6 oral support **at FU:** 3/6
RULM*	**Baseline: M**ean: 3.16 Median (range) : 0.5 (10) **at FU:** +(>2pts): 2/6
Respiratory Support **noninvasive** **n (%)**	**Baseline:** 4/6 (67) **at FU:** 4/6 (67)
Respiratory Support **invasive** **n (%)**	**Baseline:** 0/6 (0) **FU:** 0/6 (0)
ALSFRS-R*	**Baseline:** Mean:18.6 **at FU:** Mean: 22 Mean change: 3.8 +(>2pts): 3/6** (50)
EK2*	**Baseline:** Mean: 31.5 **at FU:** Mean: 27.5 Mean change: 4 +(2pts): 5/6**(83)
C-GIC	**Baseline:** n.r **FU:** +1 (mild improvement)in 6/6 (100)
P-GIC	**Baseline:** n.r **at FU:** 4 pts reported mild improvement (+1), 1 moderate improvement (+2) and 1 no change
GAS*	**Baseline:** n.r **at FU:** min 1/3 predefined individual goals achieved: 4/6** patients
AEs /SAEs **n (%)**	1/6 (16.6) (headache and GI symptoms) leading to withdrawal but after restart at later date no recurrence.

**Clinically meaningful changes were defined as ≥2 points for RULM, EK2, ALSFR-R and changes of ≥ 5% in BMI and FVC.*
*** for EK2, ALSFRS-R and GAS, 2/5, 2/3 and 2/4 displaying clinically meaningful changes were the patients that had been on nusinersen for 9 and 3 months, respectively.*
Abbreviations: (S)AE=Severe adverse effects, ALSFR-R=The Revised Amyotrophic Lateral Sclerosis Functional Rating Scale, C -GIC= Clinical Global Improvement scale, EK-2=Egen Klassification,
FEV1= Forced Expiratory Volume in 1 second, GAS=Global Attainment Scale, RULM=Revised Upper Limb Module, P-GIC- Patient global Improvement Scale

7.2 Search strategies

Cochrane

Search Name: SMA-Therapies (Update 2023)

Last Saved: 06/07/2023 18:01:02

Comment: DG 060723

ID	Search
#1	MeSH descriptor: [Muscular Atrophy, Spinal] explode all trees
#2	(spin* musc* atroph*) (Word variations have been searched)
#3	MeSH descriptor: [Muscular Disorders, Atrophic] this term only
#4	(Kugelberg NEAR Welander) (Word variations have been searched)
#5	(Werdnig NEAR Hoffmann) (Word variations have been searched)
#6	(SMA):ti,ab,kw
#7	#1 OR #2 OR #3 OR #4 OR #5 OR #6 (Word variations have been searched)
#8	(Nusinersen*) (Word variations have been searched)
#9	(spinraza*) (Word variations have been searched)
#10	(biib 058) (Word variations have been searched)
#11	(biib058) (Word variations have been searched)
#12	(ionis smnrx) (Word variations have been searched)
#13	("isis 396443") (Word variations have been searched)
#14	(isis396443) (Word variations have been searched)
#15	("isis smnrx") (Word variations have been searched)
#16	(Onasemnogene*) (Word variations have been searched)
#17	("avxs 101") (Word variations have been searched)
#18	(avxs101) (Word variations have been searched)
#19	(Risdiplam*) (Word variations have been searched)
#20	(evrysdi*) (Word variations have been searched)
#21	("7 (4, 7 diazaspiro [2.5] oct* 7 yl) 2 (2, 8 dimethylimidazo [1, 2 b] pyridazin 6 yl) 4h pyrido [1, 2 a] pyrimidin 4 one") (Word variations have been searched)
#22	("rg 7916") (Word variations have been searched)
#23	(rg7916) (Word variations have been searched)
#24	(ro 7034067) (Word variations have been searched)
#25	(ro7034067) (Word variations have been searched)
#26	#8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 (Word variations have been searched)
#27	#7 AND #26 (Word variations have been searched)
#28	#7 AND #26 with Cochrane Library publication date Between Jun 2021 and Jul 2023 (Word variations have been searched)
#29	#7 AND #26 with Publication Year from 2021 to 2023, in Trials (Word variations have been searched)
#30	#28 OR #29 (Word variations have been searched)
#31	(conference proceeding):pt
#32	(abstract):so
#33	(clinicaltrials OR trialsearch OR ANZCTR OR ensaiosclinicos OR Actrn OR chictr OR cris OR ctri OR registroclinico OR clinicaltrialsregister OR DRKS OR IRCT OR Isrctn OR rctportal OR JapicCTI OR JMACCT OR jRCT OR JPRN OR Nct OR UMIN OR trialregister OR PACTR OR R.B.R.OR REPEC OR SLCTR OR Tcr):so
#34	#31 OR #32 OR #33
#35	#30 NOT #34
	14 Hits

Embase

	Session Results	
	No. Query Results	Results
#75	#73 NOT #74	138
#74	#73 AND 'Conference Abstract'/it	162
#73	#72 AND ([english]/lim OR [german]/lim)	300
#72	(#31 OR #67 OR #68 OR #70) AND [11-06-2021]/sd	304
	NOT [07-07-2023]/sd	
#71	#31 OR #67 OR #68 OR #70	701
#70	#30 AND #69	189
#69	('meta analysis'/exp OR 'systematic review'/exp	1,621,356
	OR ((meta NEAR/3 analy*):ab,ti) OR	
	metaanaly*:ab,ti OR review*:ti OR overview*:ti OR	
	((synthes* NEAR/3 (literature* OR research* OR	
	studies OR data)):ab,ti) OR (pooled AND	
	analys*:ab,ti) OR (((data NEAR/2 pool*):ab,ti)	
	AND studies:ab,ti) OR medline:ab,ti OR	
	medlars:ab,ti OR embase:ab,ti OR cinahl:ab,ti OR	
	scisearch:ab,ti OR psychinfo:ab,ti OR	
	psycinfo:ab,ti OR psychlit:ab,ti OR psyclit:ab,ti	
	OR cinhal:ab,ti OR cancerlit:ab,ti OR	
	cochrane:ab,ti OR bids:ab,ti OR pubmed:ab,ti OR	
	ovid:ab,ti OR (((hand OR manual OR database* OR	
	computer*) NEAR/2 search*):ab,ti) OR ((electronic	
	NEAR/2 (database* OR 'data base' OR 'data	
	bases')):ab,ti) OR bibliograph*:ab OR 'relevant	
	journals':ab OR (((review* OR overview*) NEAR/10	
	(systematic* OR methodologic* OR quantitativ* OR	
	research* OR literature* OR studies OR trial* OR	
	effective*)):ab)) NOT ((((retrospective* OR	
	record* OR case* OR patient*) NEAR/2	
	review*):ab,ti) OR (((patient* OR review*) NEAR/2	
	chart*):ab,ti) OR rat:ab,ti OR rats:ab,ti OR	
	mouse:ab,ti OR mice:ab,ti OR hamster:ab,ti OR	
	hamsters:ab,ti OR animal:ab,ti OR animals:ab,ti	
	OR dog:ab,ti OR dogs:ab,ti OR cat:ab,ti OR	
	cats:ab,ti OR bovine:ab,ti OR sheep:ab,ti) NOT	
	('editorial'/exp OR 'erratum'/de OR 'letter'/exp)	
	NOT (('animal'/exp OR 'nonhuman'/exp) NOT	
	(('animal'/exp OR 'nonhuman'/exp) AND	
	'human'/exp))	
#68	#30 AND ([cochrane review]/lim OR [systematic	63
	review]/lim OR [meta analysis]/lim)	
#67	#30 AND #66	554
#66	#51 NOT #65	5,551,363
#65	#52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR	4,298,966
	#59 OR #60 OR #61 OR #62 OR #63 OR #64	
#64	'animal experiment'/de NOT ('human experiment'/de	2,548,253
	OR 'human'/de)	
#63	(rat:ti,tt OR rats:ti,tt OR mouse:ti,tt OR	1,213,336
	mice:ti,tt OR swine:ti,tt OR porcine:ti,tt OR	
	murine:ti,tt OR sheep:ti,tt OR lambs:ti,tt OR	

	pigs:ti,tt OR piglets:ti,tt OR rabbit:ti,tt OR	
	rabbits:ti,tt OR cat:ti,tt OR cats:ti,tt OR	
	dog:ti,tt OR dogs:ti,tt OR cattle:ti,tt OR	
	bovine:ti,tt OR monkey:ti,tt OR monkeys:ti,tt OR	
	trout:ti,tt OR marmoset*:ti,tt) AND 'animal	
	experiment'/de	
#62.	(databases NEAR/5 searched):ab	64,903
#61	'update review':ab	136
#60	'we searched':ab AND (review:ti,tt OR review:it)	48,107
#59	review:ab AND review:it NOT trial:ti,tt	1,096,857
#58	('random cluster' NEAR/4 sampl*):ti,ab,tt	1,562
#57	'random field*':ti,ab,tt	2,890
#56	nonrandom*:ti,ab,tt NOT random*:ti,ab,tt	18,764
#55	'systematic review':ti,tt NOT (trial:ti,tt OR	251,304
	study:ti,tt)	
#54	'case control*':ti,ab,tt AND random*:ti,ab,tt NOT	21,202
	('randomised controlled':ti,ab,tt OR 'randomized	
	controlled':ti,ab,tt)	
#53	'cross-sectional study' NOT ('randomized	374,658
	controlled trial'/exp OR 'controlled clinical	
	trial'/de OR 'controlled study'/de OR 'randomised	
	controlled':ti,ab,tt OR 'randomized	
	controlled':ti,ab,tt OR 'control group':ti,ab,tt	
	OR 'control groups':ti,ab,tt)	
	#52. ((random* NEXT/1 sampl* NEAR/8 ('cross section*'	3,095
	OR questionnaire* OR survey OR surveys OR	
	database OR databases)):ti,ab,tt) NOT	
	('comparative study'/de OR 'controlled study'/de	
	OR 'randomised controlled':ti,ab,tt OR	
	'randomized controlled':ti,ab,tt OR 'randomly	
	assigned':ti,ab,tt)	
#51	#32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR	6,284,222
#39	OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR	
#46	OR #47 OR #48 OR #49 OR #50	
#50	trial:ti,tt	400,976
#49	'human experiment'/de	634,522
#48	volunteer:ti,ab,tt OR volunteers:ti,ab,tt	281,855
#47	(controlled NEAR/8 (study OR design OR	452,681
	trial)):ti,ab,tt	
#46	. assigned:ti,ab,tt OR allocated:ti,ab,tt	483,206
#45	((assign* OR match OR matched OR allocation)	451,621
	NEAR/6 (alternate OR group OR groups OR	
	intervention OR interventions OR patient OR	
	patients OR subject OR subjects OR participant OR	
	participants)):ti,ab,tt	
#44	crossover:ti,ab,tt OR 'cross over':ti,ab,tt	123,496
#43	(parallel NEXT/1 group*):ti,ab,tt	31,734
#42.	'double blind procedure'/de	208,623
#41.	((double OR single OR doubly OR singly) NEXT/1	273,033
	(blind OR blinded OR blindly)):ti,ab,tt	
#40	(open NEXT/1 label):ti,ab,tt	106,955
#39	(evaluated:ab OR evaluate:ab OR evaluating:ab OR	2,731,229

	assessed:ab OR assess:ab) AND (compare:ab OR	
	compared:ab OR comparing:ab OR comparison:ab)	
#38	compare:ti,tt OR compared:ti,tt OR 621,636 6 Jul 2023	
	comparison:ti,tt	
#37	placebo:ti,ab,tt 362,298 6 Jul 2023	
#36	'intermethod comparison'/de 299,733 6 Jul 2023	
#35	'randomization'/de 97,568 6 Jul 2023	
#34	random*:ti,ab,tt 1,943,815 6 Jul 2023	
#33	'controlled clinical trial'/de 440,254 6 Jul 2023	
#32	'randomized controlled trial'/exp 774,858 6 Jul 2023	
#31	#6 AND #29 AND ([randomized controlled trial]/lim 108 6 Jul 2023	
	OR 'controlled clinical trial'/de)	
#30	#6 AND #29 2,163 6 Jul 2023	
#29	#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 2,494 6 Jul 2023	
	OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21	
	OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28	
#28	ro7034067 39 6 Jul 2023	
#27	'ro 7034067' 5 6 Jul 2023	
#26	rg7916 68 6 Jul 2023	
#25	'rg 7916' 19 6 Jul 2023	
#24	'7 (4, 7 diazaspiro [2.5] oct* 7 yl) 2 (2, 8 6 Jul 2023	
	dimethylimidazo [1, 2 b] pyridazin 6 yl) 4h	
	pyrido [1, 2 a] pyrimidin 4 one'	
#23	evrysdi 105 6 Jul 2023	
#22	'risdiplam'/exp 444 6 Jul 2023	
#21	charisma:tn 4 6 Jul 2023	
#20	avxs101	189
#19	'avxs 101'	228
#18	zolgensma*	299
#17	onasemnogene*	812
#16	'onasemnogene abeparvovec'/exp	765
#15.	'isis smnrx'	17
#14	isis396443	
#13	'isis 396443'	15
#12	'ionis smnrx'	1
#11	biib058	
#10	'biib 058'	
#9.	spinraza*	380
#8.	nusinersen*	1,839
#7	'nusinersen'/exp	1,709
#6.	#1 OR #2 OR #3 OR #4 OR #5	109,173
#5	sma:ti,ab	44,362
#4	werdnig NEAR/1 hoffmann	1,559
#3	kugelberg NEAR/1 welander	855
#2	. 'spin* musc* atroph*'	13,615
#1	'spinal muscular atrophy'/exp	69,569
	Date: 6. Jul 2023	

Medline

Database: Ovid MEDLINE(R) ALL <1946 to July 05, 2023>

Search Strategy:

1	exp Muscular Atrophy, Spinal/ (6404)
2	spin* musc* atroph*.mp. (7309)
3	exp Muscular Disorders, Atrophic/ (30994)
4	(Kugelberg adj Welander).mp. (195)
5	(Werdnig adj Hoffmann).mp. (310)
6	SMA.ti,ab. (27620)
7	1 or 2 or 3 or 4 or 5 or 6 (63371)
8	Nusinersen*.mp. (683)
9	spinraza.mp. (127)
10	"biib 058".mp. (0)
11	biib058.mp. (0)
12	"ionis smnrx".mp. (2)
13	"isis 396443".mp. (5)
14	isis396443.mp. (0)
15	"isis smnrx".mp. (6)
16	Onasemnogene*.mp. (169)
17	zolgensma.mp. (118)
18	"avxs 101".mp. (37)
19	avxs101.mp. (0)
20	Risdiplam*.mp. (124)
21	evrysdi.mp. (24)
22	"7 (4, 7 diazaspiro [2.5] oct* 7 yl) 2 (2, 8 dimethylimidazo [1, 2 b] pyridazin 6 yl) 4h pyrido [1, 2 a] pyrimidin 4 one".mp. (0)
23	"rg 7916".mp. (2)
24	rg7916.mp. (5)
25	"ro 7034067".mp. (0)
26	ro7034067.mp. (3)
27	8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26 (864)
28	7 and 27 (793)
29	limit 28 to clinical trial, all (33)
30	((randomized controlled trial or controlled clinical trial).pt. or randomi#ed.ab. or placebo.ab. or drug therapy.fs. or randomly.ab. or trial.ab. or groups.ab.) not (exp animals/ not humans.sh.) (4993418)
31	28 and 30 (404)
32	limit 28 to (meta analysis or "systematic review") (23)
33	(((comprehensive* or integrative or systematic*) adj3 (bibliographic* or review* or literature)) or (meta-analy* or metaanaly* or "research synthesis" or ((information or data) adj3 synthesis) or (data adj2 extract*))).ti,ab. or (cinahl or (cochrane adj3 trial*) or embase or medline or psyclit or (psycinfo not "psycinfo database") or pubmed or scopus or "sociological abstracts" or "web of science").ab. or ("cochrane database of systematic reviews" or evidence report technology assessment or evidence report technology assessment summary).jn. or Evidence Report: Technology Assessment*.jn. or ((review adj5 (rationale or evidence)).ti,ab. and review.pt.) or meta-analysis as topic/ or Meta-Analysis.pt. (697664)
34	28 and 33 (36)
35	29 or 31 or 32 or 34 (417)
36	limit 35 to dt=20210611-20230706 (176)
37	limit 35 to ed=20210611-20230706 (234)
38	36 or 37 (248)
39	limit 38 to (english or german) (240)
07.07.2023	

INAHTA

Search step # Search query,"Hits","Searched At"

4 ((((ro7034067) OR (ro 7034067) OR (rg7916) OR (rg 7916) OR ("7 (4 7 diazaspiro [2.5] oct* 7 yl) 2 (2 8 dimethylimidazo [1 2 b] pyridazin 6 yl) 4h pyrido [1 2 a] pyrimidin 4 one") OR (evrysdi*) OR (Risdiplam*) OR (charisma) OR (avxs101) OR (avxs 101) OR (Onasemnogene*) OR (isis smnrx) OR (isis396443) OR (isis 396443) OR (ionis smnrx) OR (biib058) OR (biib 058) OR (spinraza*) OR (Nusinersen*)) OR (ro7034067) OR (ro 7034067) OR (rg7916) OR (rg 7916) OR ("7 (4 7 diazaspiro [2.5] oct* 7 yl) 2 (2 8 dimethylimidazo [1 2 b] pyridazin 6 yl) 4h pyrido [1 2 a] pyrimidin 4 one") OR (evrysdi*) OR (Risdiplam*) OR (charisma) OR (avxs101) OR (avxs 101) OR (Onasemnogene*) OR (isis smnrx) OR (isis396443) OR (isis 396443) OR (ionis smnrx) OR (biib058) OR (biib 058) OR (spinraza*) OR (Nusinersen*)) FROM 2021 TO 2023) AND (English OR German)[Language],"12","2023-07-06T16:21:47.000000Z"
3 (((ro7034067) OR (ro 7034067) OR (rg7916) OR (rg 7916) OR ("7 (4 7 diazaspiro [2.5] oct* 7 yl) 2 (2 8 dimethylimidazo [1 2 b] pyridazin 6 yl) 4h pyrido [1 2 a] pyrimidin 4 one") OR (evrysdi*) OR (Risdiplam*) OR (charisma) OR (avxs101) OR (avxs 101) OR (Onasemnogene*) OR (isis smnrx) OR (isis396443) OR (isis 396443) OR (ionis smnrx) OR (biib058) OR (biib 058) OR (spinraza*) OR (Nusinersen*)) OR (ro7034067) OR (ro 7034067) OR (rg7916) OR (rg 7916) OR ("7 (4 7 diazaspiro [2.5] oct* 7 yl) 2 (2 8 dimethylimidazo [1 2 b] pyridazin 6 yl) 4h pyrido [1 2 a] pyrimidin 4 one") OR (evrysdi*) OR (Risdiplam*) OR (charisma) OR (avxs101) OR (avxs 101) OR (Onasemnogene*) OR (isis smnrx) OR (isis396443) OR (isis 396443) OR (ionis smnrx) OR (biib058) OR (biib 058) OR (spinraza*) OR (Nusinersen*)) FROM 2021 TO 2023,"16","2023-07-06T16:21:17.000000Z"
2 (((ro7034067) OR (ro 7034067) OR (rg7916) OR (rg 7916) OR ("7 (4 7 diazaspiro [2.5] oct* 7 yl) 2 (2 8 dimethylimidazo [1 2 b] pyridazin 6 yl) 4h pyrido [1 2 a] pyrimidin 4 one") OR (evrysdi*) OR (Risdiplam*) OR (charisma) OR (avxs101) OR (avxs 101) OR (Onasemnogene*) OR (isis smnrx) OR (isis396443) OR (isis 396443) OR (ionis smnrx) OR (biib058) OR (biib 058) OR (spinraza*) OR (Nusinersen*)) OR (ro7034067) OR (ro 7034067) OR (rg7916) OR (rg 7916) OR ("7 (4 7 diazaspiro [2.5] oct* 7 yl) 2 (2 8 dimethylimidazo [1 2 b] pyridazin 6 yl) 4h pyrido [1 2 a] pyrimidin 4 one") OR (evrysdi*) OR (Risdiplam*) OR (charisma) OR (avxs101) OR (avxs 101) OR (Onasemnogene*) OR (isis smnrx) OR (isis396443) OR (isis 396443) OR (ionis smnrx) OR (biib058) OR (biib 058) OR (spinraza*) OR (Nusinersen*)) FROM 2021 TO 2023,"16","2023-07-06T16:20:46.000000Z"
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